Rheumatology, 2025, **64**, 1400–1408
https://doi.org/10.1093/rheumatology/keae185
Advance access publication 20 March 2024
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Incidence of systemic vasculitides after *Mycobacterium tuberculosis* infection: a population-based cohort study in Korea

Minkyung Han[1,‡], Jang Woo Ha[2,‡], Inkyung Jung [3], Chi Young Kim[4,*,§], Sung Soo Ahn [2,*,§]

[1]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Division of Rheumatology, Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Gyeonggi-do, Republic of Korea
[3]Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

*Correspondence to: Chi Young Kim, Division of Pulmonology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Eonju-ro Gangnam-gu, 06229 Seoul, Republic of Korea. E-mail: cykim@yuhs.ac; Sung Soo Ahn, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Yongin Severance Hospital, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 16995, Republic of Korea. E-mail: saneth@yuhs.ac

‡M.H. and J.W.H. contributed equally.

§C.Y.K. and S.S.A. contributed equally.

Abstract

Background: Tuberculosis (TB) is a highly prevalent disease associated with significant morbidity and mortality globally and is reported to be associated with the onset of autoimmunity. This study investigated the association between TB and the incidence of systemic vasculitides (SV).

Methods: Data were obtained from the South Korean National Claims database to identify patients with TB and controls (who had undergone appendectomy). The overall occurrence of SV and disease subtypes during the observation period was compared between the two groups. Adjusted Cox proportional hazards regression and Kaplan–Meier analysis were performed to identify the relationship between TB and SV and to compare SV incidence.

Results: We identified 418 677 patients with TB and 160 289 controls. The overall SV incidence rate was 192/1 000 000 person-years during a mean follow-up of 7.5 years and was higher in patients with TB than controls. Cox regression revealed that the risk of SV was elevated in the TB group independently (adjusted hazard ratio [aHR]: 1.72, 95% confidence interval [CI]: 1.45–2.05). Furthermore, the risk of SV was significantly higher in extrapulmonary TB (aHR: 4.28, 95% CI: 3.52–5.21) when the TB group was categorized into pulmonary and extrapulmonary TB. The findings remained identical even after applying a stabilized inverse probability of treatment weighting analysis.

Conclusions: Patients with TB have an increased risk of SV, which is prominent in extrapulmonary TB. As well as confirming TB is associated with an increased incidence of immune-related vasculitis, our findings highlight the need for clinical vigilance for early diagnosis and initiation of treatment.

Keywords: tuberculosis, systemic vasculitides, risk, incidence, extrapulmonary tuberculosis.

Rheumatology key messages

- Patients with tuberculosis have an increased incidence of systemic vasculitides than controls.
- This risk peaked in the initial three months of tuberculosis diagnosis, especially for extrapulmonary tuberculosis.
- Clinical vigilance is required in patients with tuberculosis for early diagnosis and initiation of treatment.

Introduction

Tuberculosis (TB) is an infectious disease that usually affects the lower respiratory tract and is primarily transmitted through the inhalation of respiratory droplets [1]. TB can be categorized into two forms: i) pulmonary disease that predominantly affects the lungs, and ii) extrapulmonary disease, involving infections in organs outside the lungs, of which pulmonary TB is more common [2]. According to a 2020 Global Tuberculosis Report, the estimated global incidence of TB was ∼10 million and 1.4 million people having TB-related deaths, respectively, in 2019 [3]. Although substantial efforts and progress have been made in the management of TB in recent years, it remains a major global health concern and is responsible for substantial morbidity and mortality. After *Mycobacterium tuberculosis* infection, a

Received: 14 November 2023. **Accepted:** 15 March 2024

complex immune reaction occurs in the adaptive and innate immunity to facilitate the elimination of the infection [4–6]. Although this is an essential part of host immunity for the efficient control of TB, excessive inflammation may arise, resulting in dysregulation of the immune system and the development of autoimmune diseases [7, 8].

Systemic vasculitides (SV) are a group of rare autoimmune disorders characterized by the development of sterile inflammation within the blood vessels [9]. SV can be classified according to the size of the affected vessels, organs involved, pathological features of the tissues, and the presence of associated etiologies [10]. In SV, an abnormal immune response promotes inflammation that damages vessel walls and leads to the disease manifestations [11]. SV is a potentially life-threatening disorder, because suboptimal treatment leads to organ damage that is associated with increased morbidity and mortality [12]. Known risk factors for SV include genetic predisposition, environmental triggers including infection, and medications [13, 14]. As infections, including TB, can disrupt the immune system and promote systemic inflammation [15], it is possible that TB is associated with an increased risk of SV; however, such an association has not been established. The objective of this study was to evaluate the relationship between TB and SV by using data from a nationwide cohort of patients with TB.

Methods

Patient data source and operational definition of TB and controls

The data source was the Health Insurance Review and Assessment Service (HIRA) database of South Korea (data access approval number: M20230414001), from 2009 to 2021. Information on patients who receive hospital care in either an outpatient or inpatient setting covered by the National Health Insurance (NHI) system is collected in the HIRA database. As the majority of residents in South Korea (>50 million people) are registered with the NHI and their healthcare utilization patterns are documented in the HIRA database, it is a valuable resource for epidemiological investigations [16]. Briefly, patient details, including the birth date of an individual, sex, insurance type, prescription of medications, disease-associated procedures, and diagnostic codes based on the 10th revised version of the International Classification of Diseases (ICD-10), are accessible via the HIRA database.

For the TB group, we retrieved data of patients with the ICD-10 code for TB (A15-19) from the HIRA database for the calendar years 2009–2021. After selecting patients who were prescribed at least two first-line TB drugs (isoniazid, ethambutol, rifampin/rifampicin, and pyrazinamide) at initial diagnosis [17, 18], a one-year washout period was applied, and those with diagnostic codes for SV before the diagnosis of TB were excluded. The control group included patients who underwent appendectomy (procedural code of Q2860-2863) in 2010 or 2011 [19, 20]), excluding patients assigned the ICD-10 code for TB and at least two of first-line TB drugs between 2009 and 2021 and those with the diagnostic codes for SV before appendectomy (Supplementary Fig. S1, available at *Rheumatology* online). The selection of patients who had undergone appendectomy as a control group was because, in the HIRA database, only the healthcare utilization of a certain individual is recorded.

Follow-up started on the date of being diagnosed with TB and starting treatment with more than two first-line TB drugs or undergoing appendectomy (designated index date for each group) and ended on the date of diagnosis of SV, the end of 2021, or to the date of death, whichever occurred first. The study was approved by the Institutional Review Board of Severance Hospital (IRB: 4–2023-0288) and adhered to the guidelines specified in the Declaration of Helsinki. Owing to the retrospective nature and use of de-identified patient data, the requirement for obtaining informed consent was waived.

Definition of systemic vasculitis, systemic vasculitis subgroups, and patient variables

The definition of SV and the ICD-10 codes included antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (M31.3, M31.7, M30.1), Takayasu arteritis (M31.4), giant cell arteritis (M31.6), polyarteritis nodosa (PAN) (M30.0), and Behçet disease (M35.2). In order to increase the accuracy of the diagnosis, only patients who were diagnosed with SV as inpatients or who visited an outpatient department at least twice within one month were included as having the corresponding disorder.

The patient variables collected included age, sex, insurance type at diagnosis of TB or appendectomy, and comorbidities of hypertension (HTN), diabetes mellitus (DM), dyslipidaemia, ischemic heart disease, heart failure, moderate/severe liver disease, and renal disease within one year of the index date. Patient comorbidities were investigated according to the ICD-10 codes assigned as: HTN: I10-15; DM: E10-14; dyslipidaemia: E78; ischemic heart disease: I20-25; heart failure: I50; moderate/severe liver disease: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, and K76.5–K76.7; and renal disease: N18, N19, I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N25.0, Z49.0–Z49.2, Z94.0, and Z99.2 [21–23]. In addition, information was collected on whether TB was pulmonary (A15, A16, and A19) or extrapulmonary (A17 and A18) in patients with TB.

Statistical analysis

Continuous and categorical variables were reported as means ± standard deviations, and frequency with percentages, respectively, and Student's t-tests and χ^2 tests, respectively, were used to compare groups. The incidence of SV was calculated and compared between patients with TB and controls, and according to the time intervals by calculating the incidence rate per 1 000 000 person-years (IR/1 000 000 PY) and the incidence rate ratios (IRRs). In addition, variables associated with the occurrence of SV were evaluated using multivariable Cox proportional hazards regression, and testing of proportional hazard assumption was done by the Grambsch and Therneau test. In an alternative analysis, a Cox proportional hazard model was applied for the primary endpoint according to the augmented backward elimination algorithm proposed by Dunkler *et al.* [24]. As the first step, all potential prognostic variables were included in a step-wise backward elimination model using a likelihood-ratio test with a significance level of $a > 0.2$ for exclusion. In a second step, all primarily excluded variables were re-entered separately and kept in the model in case of a change-in-estimate of >5% to identify relevant confounders. As a result, the following variables were included in the model 3: sex, insurance type, HTN, DM, dyslipidaemia, renal disease, and group (TB group *vs* control group) and model 4: sex, insurance type, dyslipidaemia, and group (extrapulmonary TB *vs* pulmonary TB *vs* control group). As for a sensitivity analysis, we also conducted a stabilized inverse probability of treatment

Table 1. Baseline characteristics of the patients in the TB and control groups

Variables	Total $n = 578,966$	Patients with TB $n = 418,677$	Controls $n = 160,289$	*P* value
Age, years	49.99±22.27	56.19±20.07	33.78±19.36	<.001
Distribution of patient age				
0–14	33505 (5.8)	3068 (0.7)	30437 (19.0)	<.001
15–34	131187 (22.7)	72128 (17.2)	59059 (36.9)	
35–54	158528 (27.4)	113481 (27.1)	45047 (28.1)	
55–74	155086 (26.8)	134247 (32.1)	20839 (13.0)	
≥75	100660 (17.4)	95753 (22.9)	4907 (3.1)	
Sex, *n* (%)				
Male	325259 (56.2)	241100 (57.6)	84159 (52.5)	<.001
Female	253707 (43.8)	177577 (42.4)	76130 (47.5)	
Insurance type, *n* (%)				
National Health Insurance	535294 (92.5)	382950 (91.5)	152344 (95.0)	<.001
Medical Aid	43672 (7.5)	35727 (8.5)	7945 (5.0)	
Type of TB, *n* (%)				
Extrapulmonary TB		56052 (13.4)		
Pulmonary TB		362625 (86.6)		
Underlying disease, *n* (%)				
Hypertension	159809 (27.6)	141672 (33.8)	18137 (11.3)	<.001
Diabetes mellitus	112887 (19.5)	103918 (24.8)	8969 (5.6)	<.001
Dyslipidemia	154547 (26.7)	138079 (33.0)	16468 (10.3)	<.001
Ischemic heart disease	46950 (8.1)	42296 (10.1)	4654 (2.9)	<.001
Heart failure	22682 (3.9)	21723 (5.2)	959 (0.6)	<.001
Moderate/severe liver disease	3386 (0.6)	2913 (0.7)	473 (0.3)	<.001
Renal disease	14653 (2.5)	13867 (3.3)	786 (0.5)	<.001

Data are presented as the mean (± standard deviation) or frequency (%).
TB: tuberculosis.

Table 2. Incidence rate of systemic vasculitides (per 1,000,000 person-years) among patients with TB and controls

	Total $n = 578,966$	Patients with TB $n = 418,677$	Controls $n = 160,289$	Crude IRR (95% CI)	*P* value
Overall SV	192	237	125	1.90 (1.63–2.22)	<.001
Disease subgroups					
ANCA-associated vasculitis	30	46	6	7.35 (3.96–13.62)	<.001
Takyasu arteritis	7	10	3	3.61 (1.39–9.37)	0.008
Giant cell arteritis	5	5	5	1.00 (0.41–2.45)	0.997
Polyarteritis nodosa	6	7	4	1.62 (0.67–3.91)	0.281
Behçet disease	144	169	107	1.58 (1.33–1.88)	<.001

ANCA: anti-neutrophil cytoplasmic antibody, IRR: incidence rate ratio, SV: systemic vasculitides, TB: tuberculosis.

weighting (sIPTW) analysis to balance the differences in baseline characteristics between the TB and control groups. The cumulative incidence of SV in patients with pulmonary and extrapulmonary TB and controls was compared using Kaplan–Meier analysis and the log-rank test with Bonferroni correction for multiple comparisons. All statistical analyses were performed using the SAS 9.4 Enterprise Guide (SAS Institute, Inc., Cary, NC, USA) and R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), and two-tailed *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics of patients with TB and controls and the incidence of systemic vasculitis

Of the 578 966 patients included in the study, 418 677 and 160 289 were included in the TB and control groups, respectively. The mean age of the patients was 50.0 years and 56.2% were male, and the proportion of pulmonary TB was 86.6% in the TB group. A comparison of the baseline characteristics between the two groups revealed significant differences in the investigated variables. Notably, compared with the control group, patients with TB were older, more likely to be male, to have medical aid as the insurance type, and to have comorbidities (all $p < 0.001$) (Table 1).

During the mean follow-up of 7.5 years, the incidence rate of SV was 192/1 000 000 PY overalls; 237/1 000 000 PY in the TB group and 125/1 000 000 PY in the control group, and the IRR in the TB group compared with the control group was 1.90 (95% CI: 1.63–2.22). Among disease subgroups, the risk of AAV (IRR: 7.35, 95% CI: 3.96–13.62), Takayasu arteritis (IRR: 3.61, 95% CI: 1.39–9.37), and Behçet disease (IRR: 1.58, 95% CI: 1.33–1.88) were all significantly higher in the TB group than in the controls (Table 2).

Factors associated with the development of systemic vasculitis

The unadjusted Cox regression analysis found that age, female sex, underlying disease of dyslipidaemia, and TB were associated with an increased risk of SV. Both extrapulmonary and pulmonary TB were associated with a significantly increased risk of developing SV (Table 3). In addition, Kaplan-Meier

Table 3. Clinical factors associated with incident systemic vasculitides during the observation period

	Unadjusted analysis		Adjusted analysis (Model 1)		Adjusted analysis (Model 2)		Adjusted analysis (Model 3)[c]		Adjusted analysis (Model 4)[c]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.00 (1.00–1.01)	0.021	0.99 (0.99–1.00)	0.357	1.00 (0.99–1.01)	0.831				
Sex										
Male	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Female	1.51 (1.31–1.73)	<0.001	1.53 (1.33–1.75)	<0.001	1.36 (1.18–1.56)	<0.001	1.52 (1.32–1.74)	<0.001	1.35 (1.18–1.55)	<0.001
Insurance type										
National Health Insurance	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Medical Aid	0.77 (0.57–1.04)	0.093	0.73 (0.54–1.00)	0.052	0.78 (0.57–1.05)	0.100	0.73 (0.54–1.00)	0.051	0.77 (0.57–1.04)	0.087
Underlying disease										
Hypertension	1.09 (0.93–1.28)	0.278	0.90 (0.74–1.11)	0.328	0.89 (0.72–1.09)	0.245	0.87 (0.72–1.04)	0.135		
Diabetes mellitus	1.06 (0.89–1.27)	0.519	0.87 (0.71–1.08)	0.211	0.92 (0.75–1.14)	0.451	0.87 (0.70–1.07)	0.180		
Dyslipidaemia	1.41 (1.21–1.64)	<0.001	1.39 (1.16–1.67)	<0.001	1.32 (1.10–1.58)	0.003	1.38 (1.16–1.65)	<0.001	1.25 (1.07–1.46)	0.004
Ischemic heart disease	1.20 (0.93–1.55)	0.159	1.09 (0.82–1.44)	0.557	1.10 (0.83–1.46)	0.508				
Heart failure	1.02 (0.68–1.55)	0.910	0.83 (0.54–1.28)	0.401	0.84 (0.55–1.31)	0.447				
Moderate/severe liver disease	1.18 (0.49–2.85)	0.710	1.13 (0.47–2.74)	0.782	1.11 (0.46–2.67)	0.822				
Renal disease	1.53 (0.99–2.33)	0.050	1.42 (0.92–2.21)	0.118	1.23 (0.79–1.91)	0.369	1.42 (0.92–2.20)	0.116		
Group[a]										
TB group	1.67 (1.43–1.96)	<0.001	1.72 (1.45–2.05)	<0.001			1.68 (1.43–1.97)	<0.001		
Control group	1.00 (ref)		1.00 (ref)				1.00 (ref)			
Group[b]										
Extrapulmonary TB	4.60 (3.81–5.54)	<0.001			4.28 (3.52–5.21)	<0.001			4.27 (3.53–5.16)	<0.001
Pulmonary TB	1.19 (1.00–1.41)	0.045			1.19 (0.99–1.43)	0.069			1.17 (0.99–1.39)	0.072
Control	1.00 (ref)				1.00 (ref)				1.00 (ref)	

[a] Included in Models 1 and 3.
[b] Included in Models 2 and 4.
[c] An augmented backward elimination method was applied for Models 3 and 4.
TB: tuberculosis.

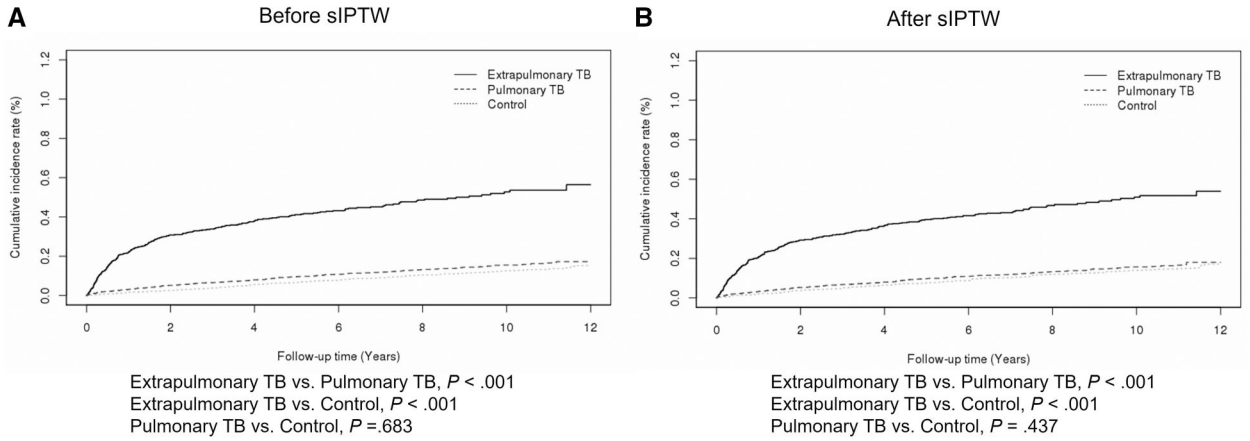

Figure 1. Cumulative incidence of systemic vasculitides in patients with pulmonary and extrapulmonary TB and the control group. Patients with extrapulmonary TB had the highest incidence of SV compared with patients with pulmonary TB and controls, and patients with pulmonary TB had comparable incidence of SV with the control group. Kaplan-Meier analysis showing the cumulative incidence of SV (A) before and (B) after sIPTW

Table 4. Comparison of incidence rates of systemic vasculitides according to the elapsed time after the index date

	Total			
Elapsed time for SV diagnosis after index date	**Number of patients**	**IR/1 000 000 PY (95% CI)**	**Crude IRR (95% CI)**	**Age and sex-adjusted IRR (95% CI)**
SV < 3 months	96	687 (558–833)	4.66 (3.75–5.79)	4.63 (3.73–5.76)
3 months ≤ SV <9 months	114	420 (348–502)	2.66 (2.18–3.26)	2.64 (2.16–3.24)
9 months ≤ SV < 15 months	77	292 (232–362)	1.74 (1.37–2.21)	1.72 (1.36–2.19)
SV ≥ 15 months	547	149 (137–162)	1.00 (ref)	1.00 (ref)

IR: incidence rate; IRR: incidence rate ratio; PY: person-year; SV: systemic vasculitides.

analysis revealed that patients with extrapulmonary TB had the greatest risk of SV, which did not differ significantly between the pulmonary TB group and controls (extrapulmonary TB *vs* pulmonary TB: $p < 0.001$, extrapulmonary TB *vs* controls: $p < 0.001$, and pulmonary TB *vs* controls: $p = 0.683$) (Figure 1A).

After adjustment for variables that were shown to be significant in the unadjusted analysis, female sex (adjusted hazard ratio [aHR]: 1.53, 95% CI: 1.33–1.75), dyslipidaemia (aHR: 1.39, 95% CI: 1.16–1.67), and TB (aHR: 1.72, 95% CI: 1.45–2.05) were associated with SV in model 1 in which patients were categorized into TB and control groups. Furthermore, in model 2 in which patients were categorized into extrapulmonary TB, pulmonary TB, and control groups, patients with extrapulmonary TB (aHR: 4.28, 95% CI: 3.52–5.21), but not pulmonary TB (aHR: 1.19, 95% CI: 0.99–1.43) had an increased risk of developing SV compared with controls. Selection of variables according to the augmented backward elimination algorithm yielded consistent results, in which TB (aHR: 1.68, 95% CI: 1.43–1.97) (model 3) and extrapulmonary TB (aHR: 4.27, 95% CI: 3.53–5.16) (model 4) were associated with incident SV. These findings were demonstrated identically even when patients with TB having the index date between 2010–2011 were only selected (Supplementary Table S1, available at *Rheumatology* online).

In a subgroup analysis, AAV showed a significant association with TB (aHR: 4.73, 95% CI: 2.47–9.08) in model 1, and for both extrapulmonary (aHR: 4.74, 95% CI: 2.45–9.15) and pulmonary (aHR: 4.70, 95% CI: 2.16–10.26) TB in model 2. Similarly, while it was shown that TB increased the risk of Behçet disease in model 1, only extrapulmonary TB (aHR: 4.60, 95% CI: 3.72–5.68), but not pulmonary TB, was statistically significant in model 2 (Supplementary Tables S2 and S3, available at *Rheumatology* online).

Risk of systemic vasculitis according to time since the index date and sensitivity analysis using stabilized inverse probability of treatment weighting

To evaluate whether there is a difference in SV incidence according to the time since the index date, the time to onset of SV was categorized as:< 3 months, 3 to < 9 months, 9 to < 15 months, and ≥15 months. Compared with ≥ 15 months, the incidence rate of SV was significantly higher in the < 3 months, 3 to < 9 months, and 9 to < 15 months intervals, and was the highest in the < 3 months interval (age and sex-adjusted IRR: 4.63, 95% CI: 3.73–5.76) (Table 4).

Given the considerable differences in patient characteristics in the TB and control groups, we performed an sIPTW analysis to minimize confounding due to differences in patient characteristics between groups. In the weighted analysis, the standardized mean difference (SMD) of the baseline variables was < 0.1 for all variables, indicating that the groups were balanced after sIPTW (Table 5). After sIPTW, the Kaplan-Meier analysis revealed that the risk of SV was higher in the extrapulmonary TB group than in the pulmonary TB and control groups (extrapulmonary TB *vs* pulmonary TB: $p < 0.001$, extrapulmonary TB *vs* controls: $p < 0.001$, and pulmonary TB *vs* controls: $p = 0.437$) (Figure 1B).

Table 5. Comparison of patient characteristics before and after weighting by sIPTW

Variables	Before sIPTW				After sIPTW			
	Total $n = 578\,966$	Patients with TB $n = 418\,677$	Controls $n = 160\,289$	Before sIPTW SMD	Total $n = 703\,664$	Patients with TB $n = 451\,511$	Controls $n = 252\,153$	After sIPTW SMD
Age, years	49.99 ± 22.27	56.19 ± 20.07	33.78 ± 19.36	1.136	50.12 ± 23.82	50.52 ± 22.37	49.40 ± 27.23	0.045
Sex, n (%)								
Male	325 259 (56.2)	241 100 (57.6)	84 159 (52.5)	0.102	383 542 (54.5)	250 491 (55.5)	133 051 (52.8)	0.054
Female	253 707 (43.8)	177 577 (42.4)	76 130 (47.5)		320 122 (45.5)	201 020 (44.5)	119 102 (47.2)	
Type of insurance, n (%)								
National Health Insurance	535 294 (92.5)	382 950 (91.5)	152 344 (95.0)	0.143	650 366 (92.4)	417 612 (92.5)	232 754 (92.3)	0.007
Medical Aid	43 672 (7.5)	35 727 (8.5)	7945 (5.0)		53 298 (7.6)	33 899 (7.5)	19 399 (7.7)	
Underlying disease, n (%)								
Hypertension	159 809 (27.6)	141 672 (33.8)	18 137 (11.3)	0.559	191 210 (27.2)	125 890 (27.9)	65 320 (25.9)	0.045
Diabetes mellitus	112 887 (19.5)	103 918 (24.8)	8969 (5.6)	0.556	135 483 (19.3)	88 884 (19.7)	46 600 (18.5)	0.031
Dyslipidaemia	154 547 (26.7)	138 079 (33.0)	16 468 (10.3)	0.574	186 029 (26.4)	121 925 (27.0)	64 104 (25.4)	0.036
Ischemic heart disease	46 950 (8.1)	42 296 (10.1)	4654 (2.9)	0.295	55 719 (7.9)	37 029 (8.2)	18 690 (7.4)	0.029
Heart failure	22 682 (3.9)	21 723 (5.2)	959 (0.6)	0.276	24 907 (3.5)	17 847 (4.0)	7061 (2.8)	0.064
Moderate/severe liver disease	3386 (0.6)	2913 (0.7)	473 (0.3)	0.057	4068 (0.6)	2657 (0.6)	1411 (0.6)	0.004
Renal disease	14 653 (2.5)	13 867 (3.3)	786 (0.5)	0.208	16 620 (2.4)	11 535 (2.6)	5085 (2.0)	0.036

Data are presented as mean (±SD) or frequency (%) for numbers before sIPTW and in weighted values after sIPTW.
sIPTW: stabilized inverse probability of treatment weighting analysis; SMD: standardized mean difference; TB: tuberculosis.

Discussion

Traditionally reported risk factors for TB include increased age, poverty, exposure to *Mycobacterium tuberculosis* after contact with patients with active disease, illicit drug use, alcohol use, and an immunocompromised state [25]. Notably, the advent of an aging society, a widening gap in social disparity, an increased number of immunocompromised individuals within the general population, and the spread of drug-resistant TB, have made TB difficult to control in recent decades [26]. Although South Korea has recently made substantial progress in reducing the incidence of TB, it continues to be an important public health problem as it is still prevalent in the general population and poses a significant risk to vulnerable populations [27]. In this study, we aimed to establish whether TB is associated with the subsequent diagnosis of SV. Patients with TB had a higher incidence rate of SV than the control group, which was consistent across the subgroups of AAV, Takayasu arteritis, and Behçet disease. Intriguingly, patients with extrapulmonary TB had a higher incidence rate of SV than the pulmonary TB group, which remained identical in the sIPTW analysis. Taken together, these findings suggest that patients with TB have an increased risk of developing SV and underscore the need for greater clinical attention.

In this study, the increased incidence of SV following the diagnosis of TB can be attributed to several potential immunological factors. First, in SV, neutrophils and macrophages play crucial roles in disease pathogenesis as they release inflammatory mediators and reactive oxygen species to expedite injury to blood vessel walls and compromise vascular integrity [28, 29]. In addition, the pathogenic expansion of T cells observed in SV, characterized by an increase in the helper T 1 and 17 subsets and a decrease in the number of regulatory T cells, is thought to contribute to sustaining vascular inflammation [30]. A complex immune response involving both innate and adaptive immune components has been described in patients with TB [31]. Failure to restore immune homeostasis after TB could lead to paradoxical immune reactions, potentiate immune dysregulation, and influence the development of SV. Next, the molecular mimicry between TB and proteins in the blood vessels, either at a molecular or structural level, could provoke an abnormal immune response [32]. The cross-reactive immune response induced by the structural similarity between pathogenic antigens and host vascular proteins is thought to cause autoimmune responses targeting vascular tissues and inadvertently promotes the development of vasculitis. Finally, a chronic inflammatory state triggered by TB could contribute to the development of altered immunity owing to the loss of immune tolerance, persistent activation of autoreactive immune cells, and overproduction of pro-inflammatory cytokines [33, 34]. Therefore, the collective effect of TB on the immune system may increase susceptibility to SV. Further research is required to elucidate the relevant molecular pathways and genetic factors in TB leading to the development of SV.

Epidemiologic studies indicate SV is an uncommon disorder showing a wide disparity in its incidence according to investigated geographic regions and ethnic groups [35]. Of note, we observed that the incidence of AAV and Takayasu arteritis appeared to be similar to the numbers reported in our previous investigations [36, 37], even though the incidence of Behçet disease was lower [38]. On the other hand, we found that the incidence of AAV and giant cell arteritis was lower than the reports from Europe and the USA, while Behçet disease and Takayasu arteritis were more common, and were similar for PAN [39, 40]. In the meantime, although consistent results were found even when patients with TB with the index date of 2010–2011 were used to compare the risk of SV with controls, the decreasing global incidence of TB, as well as changes in the epidemiology of SV (especially for the decrease of PAN and increase of AAV [41–43]) in the recent years should be also taken into account when interpreting our findings. Finally, given that differences in the methods to define SV could also lead to discrepant results, it is apparent that additional research is mandated to better understand the epidemiology of SV.

A comparison of the incidence of SV in patients with TB and controls revealed that the IR was 1.90 times higher in the TB group. Notably, a subset analysis of SV demonstrated that this risk was consistent for AAV, Takayasu arteritis, and Behçet disease. The IRR of AAV was particularly high following TB diagnosis, whereas the incidence of giant cell arteritis and PAN was comparable between the TB group and control group, suggesting that the association between TB and SV could differ according to the specific SV subtype, even though the pathophysiological mechanism by which TB may differentially predispose to different SV subtypes could not be delineated in this study. This indicates that the possibility of SV should be considered and a thorough evaluation should be conducted if patients with TB develop signs and symptoms suggestive of SV. In addition, when the incidence rate of SV was calculated according to the time since TB diagnosis, it was observed that the risk of SV was highest in the first 3 months after TB diagnosis. Taken together, these findings highlight a need for greater vigilance for SV following TB diagnosis, which could potentially contribute to early SV diagnosis and early initiation of treatment potentially resulting in better clinical outcomes. However, compared with the Cox analysis, there was a restraint that only adjustment with age and sex could be done in elucidating the time-dependent difference of SV incidence after TB.

Clinically, TB can be classified into pulmonary and extrapulmonary subtypes, and extrapulmonary TB accounts for ~15–20% of TB cases [44]. Consistent with this finding, our analysis indicated that the proportion of patients with pulmonary TB was 86.6%, which was much higher than that of patients with extrapulmonary TB. Interestingly, our results showed that patients with extrapulmonary TB had the highest risk of SV, with a significantly elevated cumulative incidence, even when compared with those with pulmonary TB. The unusually high rate of SV in patients with extrapulmonary TB, highlights the need for greater awareness, and might be related to the distinct mechanisms of infection transmission in pulmonary and extrapulmonary TB. Whereas pulmonary TB is generally transmitted via the respiratory tract, extrapulmonary TB is disseminated by a lymphatic or hematogenous spread [45]. Therefore, the higher bacterial burden of TB within the circulatory system may lead to a greater likelihood of inducing unexpected immunological responses and triggering the development of autoimmunity within the vasculature.

Although this nationwide analysis included a large number of patients with TB and controls, this study also has some limitations. First, because this study had a retrospective design, the effects and duration of TB treatment and the

incidence of SV could not be estimated. Second, the variables investigated comprised baseline patient data at the time of TB diagnosis or surgery for appendectomy, so we were unable to assess changes in the covariates that might have influenced the onset of SV. Third, information on occupational factors, alcohol consumption, smoking habits, and individual laboratory test results were not recorded in the HIRA database and were thus unavailable. Fourth, since the usage of healthcare resources of an individual is only reported in the HIRA database, information on healthy controls was not available and a direct comparison of SV incidence could not be done with patients with TB. Fifth, as there is no gold standard to define SV in epidemiologic investigations, the incidence and outcomes could be affected when different criteria to identify SV are applied. Sixth, looking into the association between other variables and SV (beyond TB and SV) may not be methodologically ideal, as the main objective of this investigation was to elucidate the relationship between TB and SV. Further research is warranted to confirm that the incidence of SV is increased in patients with TB, which will expedite the development of effective diagnostic and therapeutic strategies.

In summary, this study found that the risk of developing SV is increased after a TB diagnosis, particularly among patients with extrapulmonary TB. In addition to identifying an association between TB and autoimmune disorders in a clinical setting, our findings have practical significance as they could facilitate early detection and management of SV among patients with TB.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data utilized in this study cannot be shared publicly in accordance with the South Korean regulations of the Personal Information Protection Act. The Korea National Health Insurance Sharing Service (contact via http://opendata.hira.or.kr; contact: +82–33-739–1087, 1088) has full authority to distribute data collected in the HIRA database to domestic researchers only for scientific studies after formal application.

Contribution statement

Conceptualization: M.H., J.W.H., C.Y.K., and S.S.A.; Methodology: M.H., J.W.H., C.Y.K., and S.S.A.; Software: M.H. and S.S.A.; Validation: M.H., I.J., and S.S.A.; Formal Analysis: M.H.; Investigation: M.H., J.W.H., C.Y.K., and S.S.A.; Resources: M.H., C.Y.K., and S.S.A.; Data Curation: M.H. and S.S.A.; Writing—Original Draft Preparation: M.H., J.W.H., C.Y.K., and S.S.A.; Writing—Review & Editing: M.H., J.W.H., I.J., C.Y.K., and S.S.A.; Visualization: M.H. and S.S.A.; Supervision: I.J. and S.S.A.; Project Administration: M.H., J.W.H., I.J., C.Y.K., and S.S.A.; Funding Acquisition: None.

Funding

No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

1. Pai M, Behr MA, Dowdy D *et al.* Tuberculosis. Nat Rev Dis Primers 2016;2:16076.
2. Zumla A, Raviglione M, Hafner R, von Reyn CF. Tuberculosis. N Engl J Med 2013;368:745–55.
3. Chakaya J, Khan M, Ntoumi F *et al.* Global Tuberculosis Report 2020 - reflections on the global TB burden, treatment and prevention efforts. Int J Infect Dis 2021;113(Suppl 1):S7–S12.
4. O'Garra A, Redford PS, McNab FW *et al.* The immune response in tuberculosis. Annu Rev Immunol 2013;31:475–527.
5. de Martino M, Lodi L, Galli L, Chiappini E. Immune response to mycobacterium tuberculosis: a narrative review. Front Pediatr 2019;7:350.
6. Chandra P, Grigsby SJ, Philips JA. Immune evasion and provocation by Mycobacterium tuberculosis. Nat Rev Microbiol 2022;20:750–66.
7. Belyaeva IV, Kosova AN, Vasiliev AG. Tuberculosis and autoimmunity. Pathophysiology 2022;29:298–318.
8. Starshinova A, Malkova A, Kudryavtsev I *et al.* Tuberculosis and autoimmunity: common features. Tuberculosis (Edinb) 2022;134:102202.
9. La Rocca G, Del Frate G, Delvino P *et al.* Systemic vasculitis: one year in review 2022. Clin Exp Rheumatol 2022;40:673–87.
10. Jennette JC, Falk RJ, Bacon PA *et al.* 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
11. Guillevin L, Dörner T. Vasculitis: mechanisms involved and clinical manifestations. Arthritis Res Ther 2007;9(Suppl 2):S9.
12. Bacchiega ABS, Ochtrop MLG, de Souza AWS. . Systemic vasculitis. In: Anaya J-M, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R, eds. Autoimmunity: from bench to bedside. Bogota, Colombia: Center for Autoimmune Diseases Research, School of Medicine and Health Sciences, El Rosario University, 2013:621–42
13. Acosta-Herrera M, González-Gay MA, Martín J, Márquez A. Leveraging genetic findings for precision medicine in vasculitis. Front Immunol 2019;10:1796.
14. Katz G, Wallace ZS. Environmental triggers for vasculitis. Rheum Dis Clin North Am 2022;48:875–90.
15. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol 2010;125:S3–23.
16. Kim HK, Song SO, Noh J, Jeong IK, Lee BW. Data configuration and publication trends for the korean national health insurance and health insurance review & assessment database. Diabetes Metab J 2020;44:671–8.
17. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. Am J Respir Crit Care Med 2011;183:675–8.
18. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. Eur Respir J 2012;40:143–51.
19. Eoh KJ, Han M, Kim EH, Jung I, Kim YT. Markedly increased risk of malignancies in women with endometriosis. Gynecol Oncol 2021;161:291–6.
20. Bae JM, Lee JH, Yun JS, Han B, Han TY. Vitiligo and overt thyroid diseases: a nationwide population-based study in Korea. J Am Acad Dermatol 2017;76:871–8.
21. Quan H, Sundararajan V, Halfon P *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.
22. Kim HW, Han M, Jung I, Ahn SS. New-onset atrial fibrillation in seropositive rheumatoid arthritis: association with disease-modifying anti-rheumatic drugs treatment. Rheumatology (Oxford) 2023;63:630–8.

23. Lee HH, Cho SMJ, Lee H *et al.* Korea Heart Disease Fact Sheet 2020: analysis of Nationwide Data. Korean Circ J 2021; 51:495–503.
24. Dunkler D, Plischke M, Leffondré K, Heinze G. Augmented backward elimination: a pragmatic and purposeful way to develop statistical models. PLoS One 2014;9:e113677.
25. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med 2013;2013:828939.
26. Mondoni M, Centanni S, Sotgiu G. New perspectives on difficult-to-treat tuberculosis based on old therapeutic approaches. Int J Infect Dis 2020;92s:S91–S99.
27. Min J, Kim HW, Kim JS. Tuberculosis: republic of Korea, 2021. Tuberc Respir Dis (Seoul) 2023;86:67–9.
28. Michailidou D, Mustelin T, Lood C. Role of neutrophils in systemic vasculitides. Front Immunol 2020;11:619705.
29. Tombetti E, Mason JC. Pathophysiology of vasculitis. In: Krams R, Bäck M, eds. The ESC textbook of vascular biology. Oxford: Oxford University Press, 2017: 253–72.
30. Lintermans LL, Stegeman CA, Heeringa P, Abdulahad WH. T cells in vascular inflammatory diseases. Front Immunol 2014;5:504.
31. Gupta N, Kumar R, Agrawal B. New players in immunity to tuberculosis: the host microbiome, lung epithelium, and innate immune cells. Front Immunol 2018;9:709.
32. Muñoz-Grajales C, Pineda JC. Pathophysiological relationship between infections and systemic vasculitis. Autoimmune Dis 2015; 2015:286783.
33. Wu J, Xie A, Chen W. Cytokine regulation of immune tolerance. Burns Trauma 2014;2:11–7.
34. Bluestone JA. Mechanisms of tolerance. Immunol Rev 2011; 241:5–19.
35. Watts RA, Robson J. Introduction, epidemiology and classification of vasculitis. Best Pract Res Clin Rheumatol 2018;32:3–20.
36. Ahn SS, Han M, Park YB, Jung I, Lee SW. Incidence, prevalence and risk of stroke in patients with Takayasu arteritis: a nationwide population-based study in South Korea. Stroke Vasc Neurol 2022; 7:149–57.
37. Ahn SS, Lim H, Lee CH *et al.* Secular trends of incidence, prevalence, and healthcare economic burden in ANCA-associated vasculitis: an analysis of the 2002-2018 South Korea National Health Insurance Database. Front Med (Lausanne) 2022;9:902423.
38. Lee YB, Lee SY, Choi JY *et al.* Incidence, prevalence, and mortality of Adamantiades-Behçet's disease in Korea: a nationwide, population-based study (2006-2015). J Eur Acad Dermatol Venereol 2018;32:999–1003.
39. Calamia KT, Wilson FC, Icen M *et al.* Epidemiology and clinical characteristics of Behçet's disease in the US: a population-based study. Arthritis Rheum 2009;61:600–4.
40. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol 2022;18:22–34.
41. Sönmez HE, Armağan B, Ayan G *et al.* Polyarteritis nodosa: lessons from 25 years of experience. Clin Exp Rheumatol 2019;37 (Suppl 117):52–6.
42. Kanecki K, Nitsch-Osuch A, Gorynski P *et al.* Polyarteritis nodosa: decreasing incidence in Poland. Arch Med Sci 2019; 15:1308–12.
43. Nilsen AT, Karlsen C, Bakland G *et al.* Increasing incidence and prevalence of ANCA-associated vasculitis in Northern Norway. Rheumatology (Oxford) 2020;59:2316–24.
44. Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. Expert Rev Respir Med 2021;15:931–48.
45. Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ. Extrapulmonary tuberculosis: pathophysiology and imaging findings. Radiographics 2019;39:2023–37.

Rheumatology, 2025, 64, 1400–1408
https://doi.org/10.1093/rheumatology/keae185
Original Article