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Risk of Gout Among Patients With Tuberculosis: A Nationwide Cohort Study in South Korea

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ABSTRACT

Aim: Medications used for tuberculosis (TB) treatment are thought to increase uric acid levels and influence the occurrence of gout. The objective of this study was to evaluate the risk of gout in patients with TB.

Methods: We searched the South Korean National Health Claims database for incident cases of TB. After identifying patients diagnosed with gout within 6 months of TB diagnosis, the risk compared to the general population was estimated by calculating the standardized incidence ratios (SIRs). A nested case–control analysis among patients with TB was performed by matching subjects diagnosed with and without gout in a 1:5 ratio to identify the risk factors for gout.

Results: Of the 3848 patients with gout, the proportions of males, patients aged ≥ 70 years, and those with a diagnosis within the first 2 months were 70.2%, 33.0%, and 52.8%, respectively. The incidence of gout in patients with TB was significantly higher than in the general population (overall SIR: 1.42, sex-adjusted SIR: 1.32, age-adjusted SIR: 1.04). Conditional logistic regression analysis indicated that hypertension (odd ratio [OR] 1.43, 95% confidence interval (CI) 1.31–1.58), heart failure (OR 1.19, 95% CI 1.01–1.39), chronic kidney disease (OR 2.47, 95% CI 1.99–3.06), and use of pyrazinamide (OR 1.02, 95% CI 1.02–1.02) and ethambutol (OR 1.00, 95% CI 1.00–1.01) were associated with gout.

Conclusion: The increased risk of gout in patients with TB and the association between comorbidities and TB medications underscore the need for higher clinical awareness in this population.

1 | Introduction

Gout is one of the most common forms of inflammatory arthritis in adults and is characterized by the deposition of monosodium urate crystals in the joints—usually in the foot, ankle, and knee—or the periarticular tissues, causing intense pain, swelling, redness, and warmth [1]. Although acute attacks of gout are mostly self-limiting and resolve within 2 weeks [2], if left untreated, recurrent episodes of pain can progress to the chronic phase of the disease. Progression of the disease to chronic gout, represented by the formation of tophi, can destroy the involved joints and lead to substantial functional impairment [3]. Gout frequently affects men and older patients, with its incidence and prevalence growing continuously in recent decades [4]. Although gout was previously considered more common in Europe and the Americas than in Asia, epidemiological studies have demonstrated that the number of patients with gout is rapidly increasing, even in Eastern populations [5]. Thus, the increasing global burden of gout underscores the importance of identifying high-risk populations prone to developing this potentially debilitating disease.

Tuberculosis (TB) is a highly prevalent infection worldwide and a significant public health concern [6]. It is the leading cause of death attributed to an infectious agent [7], and while there has been substantial progress in decreasing the global burden of TB, eliminating it is still challenging. Transmitted primarily through the respiratory tract, TB affected 10.6 million individuals in 2022, with 1.3 million succumbing to the disease [8]. These data underscore the need for increased clinical attention to understand the complications associated with TB. Patients with TB are typically prescribed a combined regimen of isoniazid (INH), ethambutol (ETB), rifampin (RFP), and pyrazinamide (PZA). Since PZA and ETB impact uric acid levels in the circulation by decreasing the clearance of uric acid in the kidneys [9], it could be hypothesized that patients with TB are at an increased risk of developing gout. However, to our knowledge, the incidence of gout in patients with TB has not been described in the literature. Therefore, the main objective of this study was to identify the risk of gout in patients with TB using the Health Insurance Review & Assessment (HIRA) database, focusing on the drugs used for TB treatment and comorbid diseases.

2 | Methods

2.1 | Data Acquisition

We performed a retrospective analysis by searching the HIRA database for the calendar years 2009–2021 (data acquisition approval number: M20230414001). The HIRA database, an organization run by the South Korean government, collects records of hospital care usage covered by the National Health Insurance (NHI). Since NHI is the sole insurer approved in South Korea, and hospitals requesting financial reimbursement from the government must record the treatment provided to the patient, the healthcare usage patterns of most residents (> 50 million individuals) are included in the HIRA database, making it an optimal source for epidemiologic studies [10]. This study was approved by the Institutional Review Board of Severance Hospital (IRB approval no: 4–2023-0288). As the HIRA database only provides deidentified data to prevent the extrusion of personal information, the requirement for obtaining informed consent from the patients was waived.

2.2 | Study Design and Definition of TB, Gout, and Comorbidities

First, we extracted patients with TB in the database who were diagnosed as TB between 2009 and 2021 using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code A15-19 [11]. After identifying those prescribed ≥ 2 first-line TB drugs (INH, ETB, RFP, and PZA) upon initial diagnosis and applying a two-year washout, those prescribed with TB drugs for > 6 months were selected. Finally, when patients diagnosed with gout prior to the TB diagnosis were excluded, the total number of patients was 228 744. The index date for the TB group was set as the initial date of TB diagnosis and the prescription of two or more first-line TB drugs.

We defined patients as having gout when the ICD-10 code of M10 (either in a principal or first–fifth additional diagnosis) was assigned and the patient was admitted to the hospital or visited the outpatient department on more than two occasions within 1 month. Considering that the standard regimen for TB treatment is prescribed for 6 months, only cases of gout occurring within 6 months of TB diagnosis were evaluated, and a total of 3848 patients with gout were identified (Figure 1). The patients' comorbidities included hypertension (I10–15), diabetes mellitus (E10–14), dyslipidemia (E78), ischemic heart disease (I20–25), heart failure (I50), chronic kidney disease (N18), and moderate/severe liver disease (I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, and K76.5–76.7) within 1 year of the TB index date.

2.3 | Nested Case–Control (NCC) Analysis

To identify the effect of comorbidities and TB medications on the onset of gout, we performed an NCC analysis by matching age, sex, TB index date, TB type (extrapulmonary [A17 and A18] or pulmonary [A15, A16, and A19]), and follow-up duration after TB diagnosis in a 1:5 ratio in patients diagnosed with and without gout (Figure 1). The use of TB medications was categorized into ETB and PZA users and nonusers to evaluate the effects of these drugs on the incidence of gout. As INH and RFP are core drugs used for treating TB [12], they were not included as covariates in the NCC analysis.

2.4 | Statistical Analysis

Data of continuous variables are presented as means ± standard deviations, and the differences were compared using the student's t-test; categorical variables are presented as frequencies and proportions and compared using the chi-square test. The relative risk of gout in patients with TB compared to that in the general population was estimated by calculating the incidence rate (IR) and crude and adjusted standardized incidence ratios (SIRs). The incidence of gout in the general population was adopted from the numerical estimates in 2015, as previously described [13]. Moreover, factors associated with the occurrence of gout in the NCC-matched population were estimated using conditional logistic regression. Statistical analyses were performed using either the SAS 9.4 Enterprise Guide (SAS Institute Inc., Cary, NC, USA) or R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), with a two-tailed p value < 0.05 considered significant.

3 | Results

3.1 | Age and Sex Distribution of Patients With Gout and TB and the Risk of Gout Compared to the General Population

Among patients with TB affected by gout, the proportions of male and female individuals were 70.2% and 29.8%. The incidence of gout in patients > 70 years old was the highest (33.0%), followed by 21.0% in the 50–59-year age group and 17.7% in the 60–69-year age group. The proportions of patients who developed gout

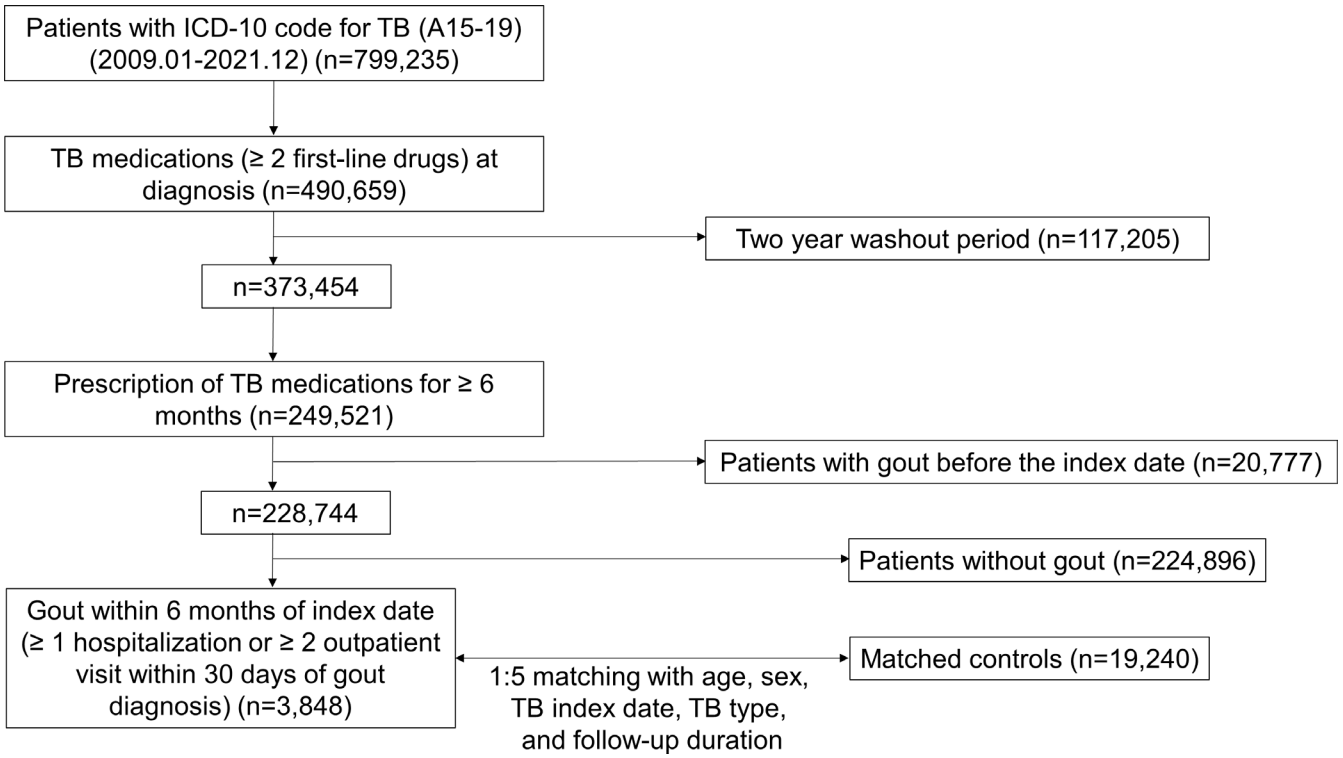

FIGURE 1 | A flowchart illustrating the selection of eligible patients for this study. TB, tuberculosis.

at < 2 months, between 2–4 months, and > 4 months were 52.8%, 29.4%, and 17.8%, respectively (Figure 2).

The overall IR of gout in patients with TB was 2.74/1000 person-years, and the IR of gout in patients with TB was higher in male than in female patients and was the highest in the ≥ 70-years age group. The risk of gout in the study population was significantly higher than that in the general population (overall and sex- and age-adjusted SIRs: 1.42, 95% confidence interval [CI] 1.37–1.46; 1.32, 95% CI 1.28–1.37; and 1.04, 95% CI 1.01–1.08; respectively). This heightened risk of gout remained consistent in male and female patients and the 0–29-year and 50–59-year age groups when the patients were categorized according to sex and age (Table 1).

3.2 | Comparison of Baseline Characteristics Among Patients With TB With and Without Gout After Matching

Upon comparing the characteristics of patients diagnosed with and without gout after matching, we found that the insurance type was comparable between the groups ($p = 0.120$). Underlying diseases such as hypertension, dyslipidemia, ischemic heart disease, heart failure, and chronic kidney disease were more prevalent in patients with gout. Regarding TB medication, INH, RFP, PZA, and ETB were more frequently prescribed to patients with gout than to those without gout during the follow-up (all $p < 0.001$) (Table 2).

3.3 | Factors Associated With Gout

Unadjusted conditional logistic regression analysis indicated that underlying diseases of hypertension, dyslipidemia, ischemic heart disease, heart failure, and chronic kidney disease and PZA and ETB use were associated with gout in patients with TB. When the factors were adjusted, hypertension (odd ratio [OR] 1.43, 95% CI 1.31–1.58), heart failure (OR 1.19, 95% CI 1.01–1.39), chronic kidney disease (OR 2.47, 95% CI 1.99–3.06), and PZA (OR 1.02, 95% CI 1.02–1.02) and ETB (OR 1.00, 95% CI 1.00–1.01) use were revealed to influence the occurrence of gout (Table 3).

4 | Discussion

The rapid increase in the number of patients with gout in Eastern countries could be ascribed to the introduction of Western lifestyle measures and dietary patterns, the rise of obesity within the general population, an aging society, and the widespread use of medications influencing uric acid levels. The increase in gout in the public community has important societal implications, as it could influence patients' quality of life, decrease work productivity, and result in greater healthcare expenditures [14]. Patients with TB experience elevated serum uric acid levels due to the effects of therapeutic agents; however, the specific risk of developing gout in this population is unknown. Furthermore, although a previous investigation identified putative factors for gout during TB, the incidence of gout in patients with TB was not elucidated [15]. In the present study, analysis of the HIRA database revealed that patients with TB had a significantly higher risk of developing gout than the general population. Intriguingly, in patients with TB, underlying diseases such as hypertension, heart failure, and chronic kidney disease and PZA and ETB contributed to the incidence of gout.

Hyperuricemia, defined as a serum uric acid level > 7 mg/dL in men and > 6 mg/dL in women, is a typical laboratory finding

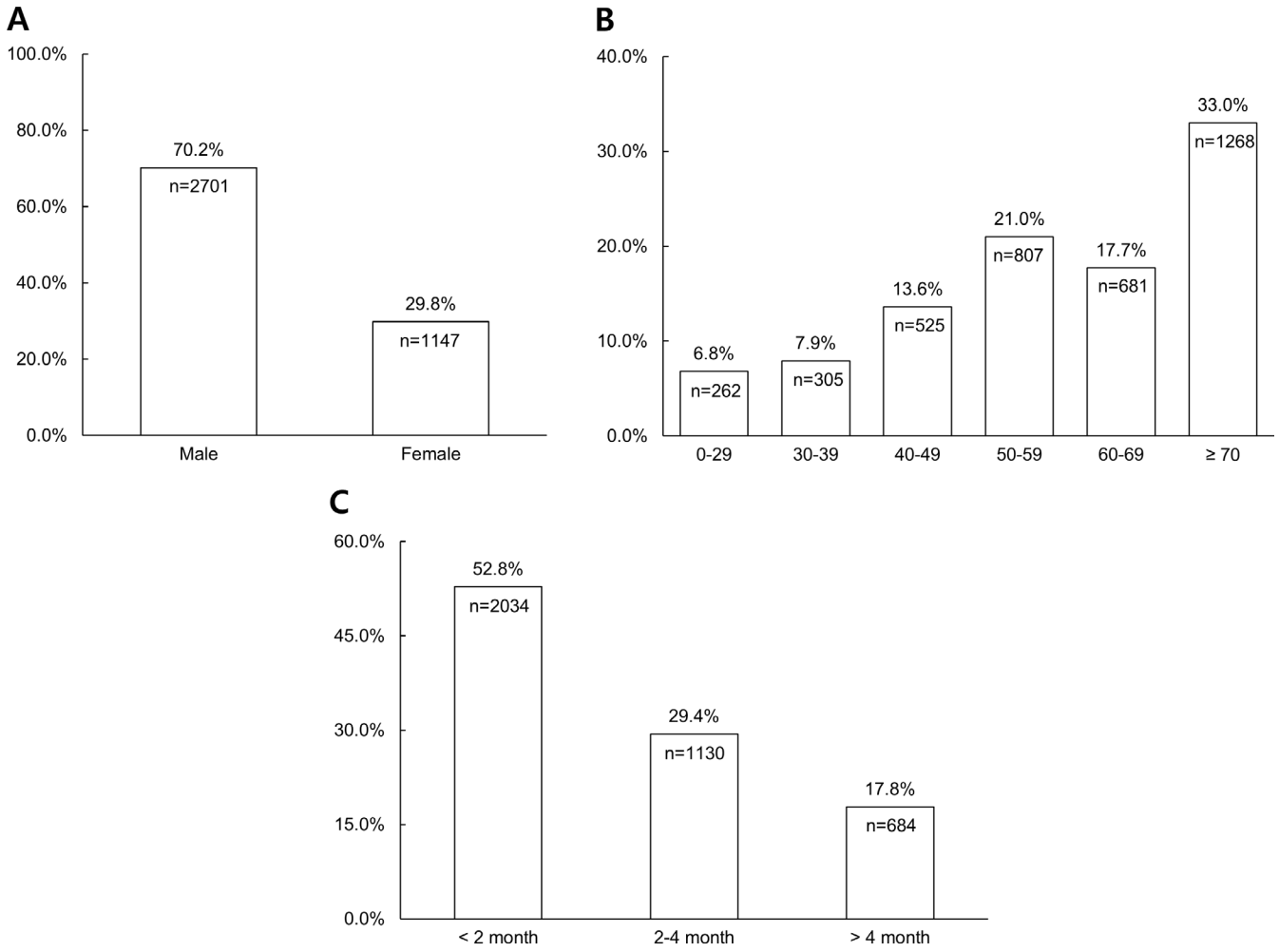

FIGURE 2 | Demographic characteristics of TB patients with gout. The proportion of patients is presented according to (A) sex, (B) age distribution, and (C) the period of gout diagnosis after TB. TB, tuberculosis.

TABLE 1 | Incidence rate of gout in the TB group compared to the general population.

	IR/1000 PY (95% CI)	SIR (95% CI)	Expected	Observed
Overall population	2.74 (2.65–2.82)	1.42 (1.37–1.46)	2711.58	3848
Sex		1.32 (1.28–1.37)[a]	2907.83	3848
Male	3.46 (3.33–3.59)	1.08 (1.04–1.13)	2490.39	2701
Female	1.83 (1.73–1.94)	2.75 (2.59–2.91)	417.44	1147
Age		1.04 (1.01–1.08)[b]	3688.83	3848
0-29	1.18 (1.04–1.32)	1.44 (1.27–1.62)	182.51	262
30–39	1.65 (1.47–1.84)	0.80 (0.72–1.00)	379.09	305
40–49	2.41 (2.21–2.62)	1.09 (0.99–1.19)	481.95	525
50–59	3.16 (2.95–3.39)	1.20 (1.12–1.28)	673.14	807
60–69	3.49 (3.23–3.76)	1.05 (0.97–1.13)	647.80	681
≥ 70	3.84 (3.63–4.05)	0.96 (0.91–1.01)	1324.34	1268

Abbreviation: TB, tuberculosis.
[a]The value indicates the sex-adjusted standardized incidence ratio.
[b]The value indicates the age-adjusted standardized incidence ratio.

TABLE 2 | Baseline characteristics of TB patients with and without gout after matching.

Variables	Total ($n = 23\,088$)	Patients with gout ($n = 3848$)	Patients without gout ($n = 19\,240$)	p
Age, years	59.14 ± 17.45	59.14 ± 17.45	59.14 ± 17.45	—
Distribution of patient age				
0–29	1572 (6.8)	262 (6.8)	1310 (6.8)	—
30–39	1830 (7.9)	305 (7.9)	1525 (7.9)	
40–49	3150 (13.6)	525 (13.6)	2625 (13.6)	
50–59	4842 (21.0)	807 (21.0)	4035 (21.0)	
60–69	4086 (17.7)	681 (17.7)	3405 (17.7)	
≥ 70	7608 (33.0)	1268 (33.0)	6340 (33.0)	
Sex, *n* (%)				
Male	16 206 (70.2)	2701 (70.2)	13 505 (70.2)	—
Female	6882 (29.8)	1147 (29.8)	5735 (29.8)	
Type of TB, *n* (%)				
Extrapulmonary TB	2982 (12.9)	497 (12.9)	2485 (12.9)	—
Pulmonary TB	20 106 (87.1)	3351 (87.1)	16 755 (87.1)	
Insurance type, *n* (%)				
National Health Insurance	21 277 (92.2)	3522 (91.5)	17 755 (92.3)	0.120
Medical Aid	1811 (7.8)	326 (8.5)	1485 (7.7)	
Underlying disease, *n* (%)				
Hypertension	8607 (37.3)	1654 (43.0)	6953 (36.1)	< 0.001
Diabetes mellitus	6324 (27.4)	1038 (27.0)	5286 (27.5)	0.539
Dyslipidemia	8481 (36.7)	1505 (39.1)	6976 (36.3)	< 0.001
Ischemic heart disease	2450 (10.6)	451 (11.7)	1999 (10.4)	0.016
Heart failure	1270 (5.5)	259 (6.7)	1011 (5.3)	< 0.001
Chronic kidney disease	528 (2.3)	150 (3.9)	378 (2.0)	< 0.001
Moderate/severe liver disease	160 (0.7)	29 (0.8)	131 (0.7)	0.696
TB medication, *n* (%)				
Isoniazid	21 061 (91.2)	3825 (99.4)	17 236 (89.6)	< 0.001
Rifampicin	21 225 (91.9)	3812 (99.1)	17 413 (90.5)	< 0.001
Pyrazinamide	20 079 (87.0)	3787 (98.4)	16 292 (84.7)	< 0.001
Ethambutol	19 161 (83.0)	3372 (87.6)	15 789 (82.1)	< 0.001

Abbreviation: TB, tuberculosis.

observed in patients with gout [16]. Since excess uric acid is responsible for the formation of urate crystals and their evolution into symptomatic disease [1], the development of hyperuricemia is indispensable in gout, although hyperuricemia may not occur in some patients [17]. Uric acid is endogenously produced in the liver as the final product of purine metabolism, in which purines derived from dietary sources or endogenous synthesis are broken down into xanthine and further converted into uric acid by the enzyme xanthine oxidase. Under normal circumstances, uric acid is transported in the bloodstream and filtered through the kidneys, with approximately 70%–80% excreted in the urine and the remainder eliminated through the gastrointestinal tract [18]. The elevation of uric acid levels is largely understood to be a consequence of two main factors. First, increased uric acid production can result from the consumption of purine-rich diets, excessive alcohol consumption, or the presence of metabolic disorders. Second, decreased renal excretion of uric acid may be attributed to renal insufficiency, medications, or genetic abnormalities that affect uric acid transporters in the kidneys [19]. Since PZA and ETB increase uric acid levels in the

TABLE 3 | Conditional logistic regression analysis associated with the incidence of gout.

Variables	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Insurance type				
National Health Insurance	1.00 (ref)		1.00 (ref)	
Medical Aid	1.11 (0.98–1.26)	0.111	1.07 (0.94–1.22)	0.319
Underlying disease				
Hypertension	1.47 (1.35–1.59)	< 0.001	1.43 (1.31–1.58)	< 0.001
Diabetes mellitus	0.97 (0.90–1.06)	0.508	0.84 (0.76–1.00)	0.051
Dyslipidemia	1.15 (1.07–1.24)	< 0.001	1.08 (0.99–1.18)	0.081
Ischemic heart disease	1.16 (1.03–1.30)	0.011	0.96 (0.84–1.09)	0.502
Heart failure	1.32 (1.14–1.53)	< 0.001	1.19 (1.01–1.39)	0.038
Chronic kidney disease	2.05 (1.69–2.49)	< 0.001	2.47 (1.99–3.06)	< 0.001
Moderate/severe liver disease	1.11 (0.74–1.66)	0.621	1.34 (0.87–2.05)	0.186
TB medication usage				
Pyrazinamide/day	1.02 (1.02–1.03)	< 0.001	1.02 (1.02–1.02)	< 0.001
Ethambutol/day	1.01 (1.01–1.01)	< 0.001	1.00 (1.00–1.01)	< 0.001

Abbreviation: OR, odds ratio.

circulation, the elevated incidence of gout in patients with TB in the present study is principally explained by the effect of anti-TB medications.

Our NCC analysis indicated that PZA and ETB use increased the odds of developing gout, supporting the fact that drugs are crucial factors contributing to the occurrence of gout in patients with TB. Nonetheless, TB infection itself could be proposed as a risk factor for gout because it can increase the production of uric acid and may affect urate solubility by altering acid–base homeostasis following infection [20]. Given that these processes facilitate the nucleation and growth of monosodium urate crystals in the human body [21], it can be inferred that TB is associated with a greater onset of gout. However, an increase in uric acid level alone is not sufficient to diagnose gout, as a suggestive clinical episode is required. Notably, previous studies have demonstrated that toll-like receptor 2/4 signaling, nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome activation, and the subsequent release of interleukin-1, a crucial cytokine responsible for inducing inflammation in gout [22, 23], are enhanced in TB. Therefore, the simultaneous activation of pertinent pathways for gout attack during TB infection suggests a potential association between TB and an elevated risk of gout.

Analysis of the South Korean National Health Claims database indicated that the incidence of gout per 1000 person-years was 1.52 in 2009 and 1.94 in 2015 [13]. In the present study, the number of patients who developed gout was 2.74/1000 person-years among patients with TB, and the overall, sex-, and age-adjusted SIR for gout was significantly higher in patients with TB than in the general population. In addition to the use of PZA and ETB, the comorbid risk factors hypertension, heart failure, and chronic kidney disease were significantly associated with gout incidence in patients with TB, suggesting that greater caution and active evaluation are required among these patients when clinical signs and symptoms that raise the possibility of gout occur. In particular, as most gout events occur within the first 2 months of TB treatment, it is advisable for attending physicians to pay more attention during this period.

This study had some limitations. First, although the number of included patients was high, this study was performed retrospectively using the HIRA database. Furthermore, an analysis stratifying according to uric acid levels and glomerular filtration rate could not be performed because the database does not include laboratory data on uric acid level and renal function. Second, although the duration of usage and selection of TB medication could vary according to drug susceptibility, the site involved, and side effects, such data could not be investigated. Third, data on lifestyle patterns, including alcohol ingestion, smoking, and the frequency and intensity of exercise, which may potentially influence serum uric acid levels, were unavailable in the HIRA database, and adjustment for these factors was not possible [24]. Fourth, given that the incidence of gout was defined according to the ICD-10 code alone, cases of gout may have been overestimated, although further specification was performed to increase diagnostic accuracy. Fifth, it should be taken into account that hypertension and chronic kidney disease—which were identified as risk factors for gout in TB—are also related to TB occurrence in the general population and might have affected data interpretation. Thus, additional studies are required to overcome the limitations of the present study and elucidate the risk of gout in patients with TB.

In conclusion, the present study's results indicate that the risk of gout is higher in patients with TB than in the general population. Underlying diseases such as hypertension, heart failure, chronic kidney disease, and PZA and ETB use were associated with the occurrence of gout in patients with TB, underscoring the need for higher vigilance for gout in this patient group.

Author Contributions

Conceptualization: Ha J.W., Kim C.Y., and Ahn S.S.; data curation: Han M.; formal analysis: Han M. and Jung I.; funding acquisition: none; Investigation: Han M., Ha J.W., Kim C.Y., and Ahn S.S.; methodology: Han M., Ha J.W., Kim C.Y., and Ahn S.S.; project administration: Han M., Ha J.W., Kim C.Y., and Ahn S.S.; resources: Han M., Ha J.W., and Ahn S.S.; Software: Han M. and Jung I.; supervision: Jung I.; validation: Han M. and Ahn S.S.; Visualization: Han M., Ha J.W., Kim C.Y., and Ahn S.S.; writing – original draft: Han M., Ha J.W., Kim C.Y., and Ahn S.S.; writing – review and editing: Han M., Ha J.W., Jung I., Kim C.Y., and Ahn S.S.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was approved by the Institutional Review Board of Severance Hospital, and the requirement for informed consent from the patients was waived, as the HIRA only provides de-identified data to prevent the extrusion of personal information (IRB approval no: 4–2023-0288).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The dataset generated and analyzed for this study cannot be publicly shared according to the Personal Information Protection Act of South Korea. The Korea National Health Insurance Sharing Service (contact via https://nhiss.nhis.or.kr; contact: +82-33-736-2432, 2433) is responsible for distributing HIRA data for scientific research to researchers after obtaining formal approval.

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