Effectiveness of tuberculosis preventive treatment in patients with rheumatic diseases: a global systematic review and meta-analysis

Beiming Wang,[a,e] Shi Chen,[b,e] Xiaoqing Liu,[b,c,d,**] and Lifan Zhang[b,c,d,*]

[a]4+4 Medical Doctor Program, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[b]Division of Infectious Diseases, Department of Internal Medicine, State Key Laboratory of Complex Severe and Rare Disease, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[c]Clinical Epidemiology Unit, Peking Union Medical College, International Clinical Epidemiology Network, Beijing, China
[d]Center for Tuberculosis Research, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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Summary

Background Patients with rheumatic disease (RD) are particularly vulnerable to progressing to tuberculosis disease (TBD). The effectiveness of tuberculosis preventive treatment (TPT) in this high risk group needs systematic assessment.

Methods We conducted a systematic review and meta-analysis by searching PubMed, Embase, the Cochrane Library, Web of Science, Scopus, and China National Knowledge Internet (CNKI) for relevant cohort studies from inception through January 2025. Eligible studies evaluated the incidence of TBD and/or the effectiveness of TPT in patients with RD. Two authors independently reviewed and extracted summary data from published reports. Pooled incidence rate (IR), risk ratio (RR) and their 95% confidence interval (CI) were calculated as the primary effect measure. Prospero registration number is CRD42023473966.

Findings 64 studies with 116,015 patients with RD were included to evaluate effectiveness of TPT. TPT decreased the overall risk of TBD in patients with RD (RR: 0.76, 95% CI 0.63–0.91). TPT showed better effectiveness in high tuberculosis (TB) burden countries/regions (RR: 0.46, 95% CI 0.27–0.77). Using isoniazid (INH) monotherapy for 9–12 months was effective (RR: 0.54, 95% CI 0.35–0.85). Taking tuberculin skin test (TST) combined with interferon gamma release assays (IGRA) as tuberculosis infection (TBI) screening methods might maximize the benefits of TPT (RR: 0.58, 95% CI 0.39–0.88). TPT showed optimal protective effects in patients with RD in TBI positive status (RR: 0.11, 95% CI 0.04–0.32). Compared with patients with RD receiving biologics, TPT showed better effects in patients with RD only receiving traditional treatment (RR: 0.44, 95% CI 0.27–0.73). And TPT performed more effectively in systematic lupus erythematosus (SLE) than arthritis.

Interpretation TPT decreased the risk of TBD in patients with RD, especially in TB high burden countries/regions. When using isoniazid monotherapy, extending the treatment course might have better protection. TST combined with IGRA might be optimal when screening the TBI. More types of RDs, short-course regimens containing rifamycins and high-quality randomized controlled trials (RCT) should be the focus of future research.

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Keywords: Rheumatic disease; Tuberculosis; Prevention; Screening; Meta-analysis

*Corresponding author. Division of Infectious Diseases, Department of Internal medicine, State Key Laboratory of Complex Severe and Rare Disease, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
**Corresponding author. Division of Infectious Diseases, Department of Internal medicine, State Key Laboratory of Complex Severe and Rare Disease, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
E-mail addresses: zhanglifan@pumch.cn (L. Zhang), liuxq@pumch.cn (X. Liu).
[e]Co-first author.

Research in context

Evidence before this study

We conducted a comprehensive search of PubMed, Embase, the Cochrane Library, Web of Science, Scopus, and CNKI for publications related to TB prevention in patients with RD up to January 2025. Eligible study types included RCTs and cohort studies, with no language restrictions. A total of 64 articles were identified and included in the single-rate meta-analysis. Of these, 46 studies included control groups and were incorporated into the traditional meta-analysis. Our search revealed no systematic reviews published on this topic during the period covered.

Added value of this study

This systematic review revealed that the use of TPT can reduce the overall risk of TBD in patients with RD. TPT was more effective in patients with RD in high TB burden countries/regions, when using INH for more than 9 months and receiving a combined TST and IGRA screening strategy for TBI. Additionally, RD-related drug use, RD type, and TBI status of the control group were important factors influencing TPT effectiveness. Although most studies lacked control of the TBI status variable, our correction suggested that TPT performed better than initially expected.

Implications of all the available evidence

Although extensive clinical practice has been conducted on the use of TPT in patients with RD, systematic evaluations of the effectiveness of TPT in this population remain scarce. Additionally, we found that no studies had been conducted on other types of RD beyond SLE and arthritis. RCTs were also extremely limited. Our findings combined with previous studies could help guide healthcare professionals in improving the effectiveness of TPT in patients with RD.

Introduction

Tuberculosis (TB) is an infectious disease with a long history, having taken millions of lives. Although four commonly used TB drugs including isoniazid (INH), rifampin (RIF), pyrazinamide, ethambutol were sequentially invented in 1950s and 1960s, the global TB burden is still great with 25%–33% population have tuberculosis infection (TBI), resulting in 7.5 million new TB cases and 1.4 million deaths annually.[1,2]

Rheumatic disease (RD) is a group of autoimmune systemic disease characterized by disorders of connective tissue, which lead to damage to joints, muscles, bones, and organs as the disease progresses. It is estimated that 9.8%–33.2% of people suffering from RD globally. Both the traditional treatments, including glucocorticoids and disease modifying antirheumatic drugs (DMARDs), as well as biologic agents developed in recent decades, further compromise the immune system of patients with RD.[3–5]

Thus, the patients with RD become a vulnerable group to infectious, especially the tuberculosis disease (TBD), which has a large population with TBI as defined as a status of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TBD.[6,7] And the involving of biologic agents worsened this situation, since tumor necrosis factor-alpha (TNF-α) is not only a cytokine involved in pathogenesis of RD but also an important role in infectious diseases control.[8,9] As many research reported, patients with RD may have a risk of TB of 2–10 times greater compared to general population and in any case the usage of tumor necrosis factor (TNF) inhibitors will increase the risk 2 to 30 times greater.[10,11] Even the usage of traditional DMARD in these patients increases the risk of TBD 2 to 11 times higher.[12,13]

However, although the problem of TBD in immune compromised population such as HIV patients or in TB contact population has been noticed and TPT has been proposed by lots of organizations, leading by world health organization (WHO), for many years, the effectiveness of TPT in patients with RD still lack of strong evidence.[14] What's more, the WHO currently recommends six regimens of TPT composed mainly of INH and/or rifamycins, and the shorter (1–3 months) rifamycins-based regimens have rapidly grown to 1 million out of a total of 4.7 million people receiving TPT. However, a systemic evaluation of the effectiveness of different TPT regimens in patients with RD is still lacking.[15]

Therefore, we conducted a systematic review and meta-analysis, with over 100,000 patients from global cohort studies to determine the extent to which TPT can reduce the risk ratio (RR) of TBD in patients with RD, and the differences between specific subgroups regarding local TB disease burden, TBI screening methods, types of rheumatic disease, anti-rheumatic disease treatment and TPT regimens.

Methods

Study design

We strictly followed the PRISMA guidelines to conduct our systematic review and meta-analysis about the effectiveness of TPT in patients with RD (Appendix and PRISMA checklist).[16] This study is registered with PROSPERO (CRD42023473966).

Search strategy

We systematically searched literature in the PubMed, Embase, Cochrane Library, Web of Science, Scopus, and China National Knowledge Internet (CNKI) from

inception through January 2025. The search strategy focused on the effectiveness of TPT in patients with RD, no specific countries/regions or language was restricted. The specific search strategies are described in Appendix.

Selection criteria

Eligible studies were required to (1) be cohort studies to be able to calculate RR of TBI in patients with RD; (2) include patients over 18; (3) include patients to be diagnosed with rheumatic diseases (see specific diseases in Appendix); (4) include patients who received TPT. We excluded case reports and reviews, as well as studies involving patients without RD, under 18 years old, or not receiving TPT. In addition, patients who failed to complete the TPT process were excluded from the analysis.

Study selection and data extraction

ENDNOTE X9 was used to manage the literature search records. Two researchers (B.M.W. and S.C.) independently reviewed the titles and abstracts of all the retrieved studies using the predefined criteria. All citations of searched meta-analysis were evaluated. Then the data of study type, study countries/regions, author, journal, publication time, follow-up time, sample size, patient information, disease, TBI screening method, TBI status, TPT regiments, usage of anti-rheumatic drugs, number of patients in experiment or control groups, TBD diagnostic criteria and developed TBD or not were extracted from final selected articles (Appendix). Any discrepancies were settled by consensus or a third more experienced researcher.

Statistical analysis

First, we conducted a single-rate meta-analysis to determine the incidence rate (IR) of TBD in patients with RD whether they received TPT or not in different specific subgroups, including local TB disease burden, TNF inhibitors usage and disease type. We compared untransformed IR with logit or arcsine-square-root transformed IR and found that transformed IR did not fulfill the normality assumption or decrease the overall heterogeneity, so we chose to show the final result with original IR, all data and precise p value was shown in Supplementary Table S1.

Then traditional meta-analysis was conducted to evaluate the effectiveness of TPT on the risk of TBD in all patients with RD and compare it between different subgroups including local TB burden, TPT regimens, TBI screening methods, TBI status of control group, biologic agents usage and specific RD type. The outcome was presented as RR with 95% confidence intervals (CI), and the final pooled RR was calculated from the crude RR value extracted from studies' original data as no studies provided adjusted RR and only three studies provided hazard ratio (HR).

Single-rate meta-analysis and traditional meta-analysis were conducted using Review Manager 5.3 and "meta" package on R 4.3.0 software. p value < 0.05 was considered statistically significant. The heterogeneity of included studies was assessed by using I^2 statistic and fixed-effect model (common effect model) was used when I^2 < 50%, otherwise the random-effects model would be chosen. And when there were subgroups with less than 5 studies in random-effects model, Hartung-Knapp-Sidik-Jonkman method was adopted.[17] When the overall heterogeneity was significant, a sensitivity analysis using the sequential elimination method was conducted for each study in the group, and meta-regression was conducted to analyze the contribution of different covariates to effect size and heterogeneity. Quality of observational studies were evaluated using the Newcastle–Ottawa Scale (NOS) and studies with a total score of over 5 were considered of good quality (Appendix). Publication bias of traditional meta-analysis and single-rate meta-analysis was assessed by visualization of funnel plot (Supplementary Figure S1), with Egger and Peters tests (Appendix).[18,19] No publication bias was observed.

Ethics statement

The study utilized publicly available data that did not include any confidential or personally identifiable information and therefore does not constitute human subjects research. Institutional review board approval and informed consent were waived.

Role of funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study selection and characteristics

We identified 7825 publications from six databases: 465 from PubMed, 35 from Cochrane Library, 2309 from Web of Science, 2598 from Embase, 2293 from Scopus and 125 from CNKI. As shown in Fig. 1, after screening, 64 studies reported 116,015 cases were included in single-rate meta-analysis, 46 studies with 113,238 cases were included in traditional meta-analysis.[20–5051–83] 18 studies with 2777 patients were only included in single-rate meta-analysis, because lack of control group or unable to conduct traditional meta-analysis. All the included studies came from 17 countries/regions, covering the four important continents on earth (Fig. 2). The characteristics of the included studies in single-rate meta-analysis and meta-analysis were summarized in Table 1.

Overall there were 1884 TBD cases in single-rate meta-analysis, accounting for 1.6% of all RD cases, with 169 in TPT group and 1715 in control group. As for traditional meta-analysis, there were 1870 TBD cases, accounting for 1.7% of all RD cases, with 155 in TPT

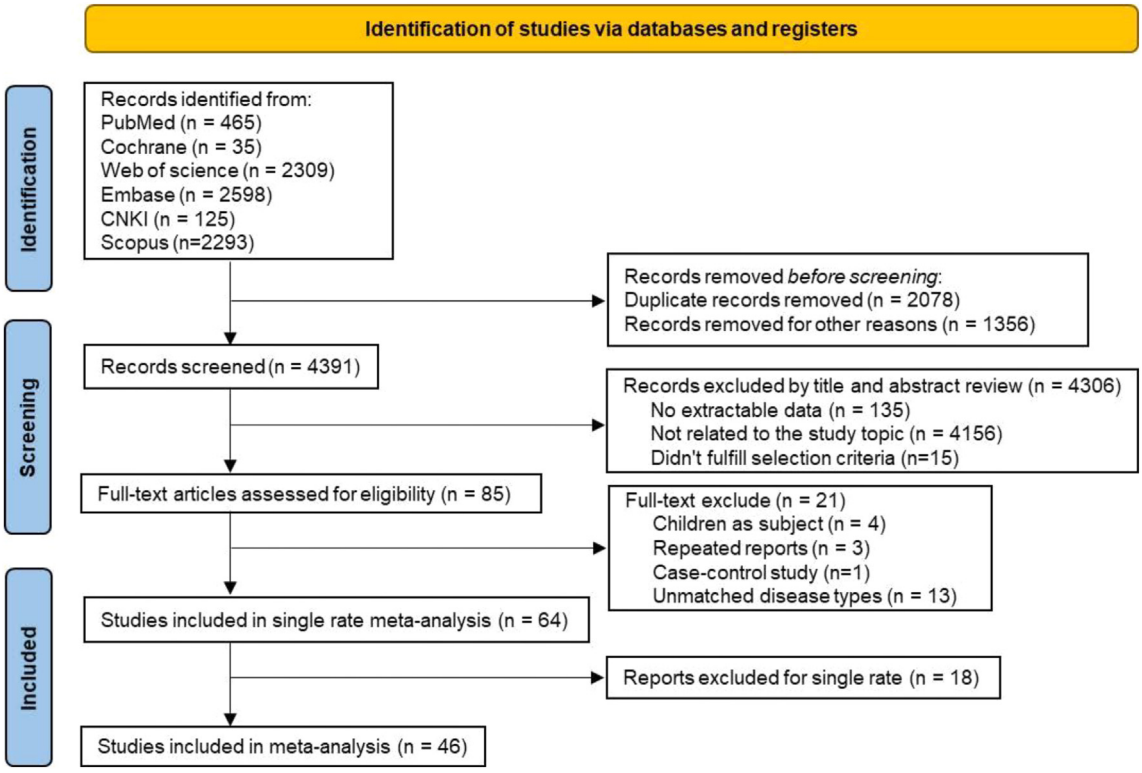


***Fig. 1:* Summary of database search and paper selection protocol**. 7825 publications were screened from six databases: 465 from PubMed, 35 from the Cochrane Library, 2309 from Web of Science, 2598 from Embase, 2293 from Scopus and 125 from CNKI. After screening, 64 studies were included in single-rate meta-analysis, 46 studies were included in traditional meta-analysis.

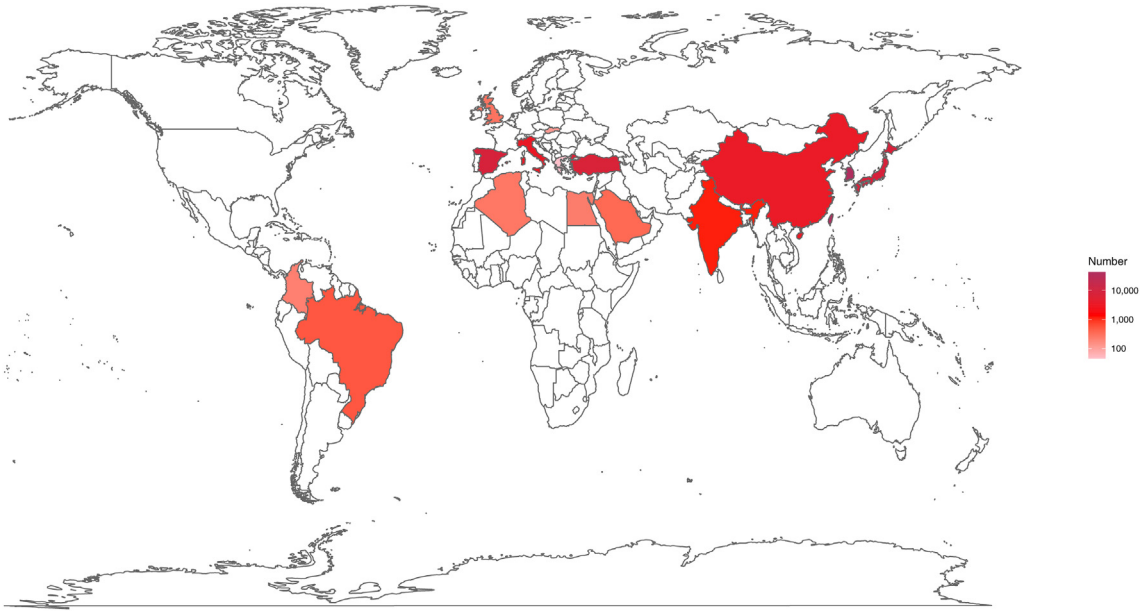


***Fig. 2:* Distribution of all cases included in this study**. 17 countries/regions included in this study: Algeria, Brazil, Chinese mainland, Colombia, Egypt, Greece, India, Italy, Japan, Saudi Arabia, Slovakia, South Korea, Spain, Taiwan, China, Hong Kong, China, Turkey and United Kingdom (UK).

	Results
Meta-analysis	
Number of studies, n	46
Number of cases, n	113,238
Age, median [25%,75%][a]	45.00 [40.68, 51.00]
Sex, male%[b]	26.89
Follow-up duration[c]	
Month, median [25%,75%]	27.40 [21.25, 41.10]
High burden country (Region), n (%)	4326 (3.74)
Brazil, n (%)	535 (0.47)
Chinese mainland, n (%)	2656 (2.35)
India, n (%)	1135 (1.00)
Other country (Region), n (%)	108,912 (96.18)
Algeria, n (%)	270 (0.24)
Hong Kong, China, n (%)	172 (0.15)
Taiwan, China, n (%)	42,607 (37.63)
Colombia, n (%)	221 (0.20)
Egypt, n (%)	235 (0.21)
Greece, n (%)	45 (0.04)
Italy, n (%)	1135 (1.00)
Japan, n (%)	7740 (6.84)
Saudi Arabia, n (%)	365 (0.32)
Slovakia, n (%)	124 (0.11)
South Korea, n (%)	39,829 (35.17)
Spain, n (%)	7911 (6.99)
Turkey, n (%)	6081 (5.37)
United Kingdom, n (%)	299 (0.26)
TPT strategy, n	75,689
INH, n (%)	73,051 (96.51)
0–9 months usage, n (%)	5248 (7.18)
9–12 months usage (including 9 months), n (%)	57,651 (78.92)
Including RIF, n (%)	2638 (3.49)
Screening method, n	74,299
TST, n (%)	12,871 (17.32)
IGRA, n (%)	7211 (9.71)
TST + IGRA, n (%)	54,217 (72.97)
Control group status, n	111,802
TBI +, n (%)	546 (0.49)
TBI -, n (%)	43,489 (38.90)
TBI + -, n (%)	67,767 (60.61)
Drug usage, n	113,238
Biologic agents, n (%)	108,768 (96.05)
TNF-α inhibitors majority (>80%), n (%)	47,792 (42.20)
Without biologic agents, n (%)	4470 (3.95)
DMARD, n (%)	288 (0.25)
Glucocorticoids, n (%)	3076 (2.72)
DMARD + Glucocorticoids, n (%)	1106 (0.98)
Disease type, n	101,935
SLE, n (%)	625 (0.61)
Arthritis majority (>80%), n (%)	101,310 (99.39)
RA majority (>80%), n (%)	77,990 (76.51)
PS and PsA majority (>80%), n (%)	118 (0.12)
Single-rate meta-analysis	
Number of studies, n	64

(Table 1 continues on next column)

	Results
(Continued from previous column)	
Number of cases, n	116,015
Age, median [25%,75%][d]	45.10 [41.00,51.45]
Sex, male%[e]	30.69
Follow-up duration[f]	
Months, median [25%,75%]	26.40 [18.60, 39.05]
High burden country (Region), n (%)	4944 (4.26)
Brazil, n (%)	535 (0.46)
Chinese mainland, n (%)	3206 (2.76)
India, n (%)	1203 (1.04)
Other country (Region), n (%)	111,071 (95.74)
Algeria, n (%)	270 (0.23)
Hong Kong, China, n (%)	172 (0.15)
Taiwan, China, n (%)	42,607 (36.73)
Colombia, n (%)	221 (0.19)
Egypt, n (%)	235 (0.20)
Greece, n (%)	45 (0.04)
Italy, n (%)	3395 (2.93)
Japan, n (%)	7932 (6.84)
Saudi Arabia, n (%)	365 (0.31)
South Korea, n (%)	40,191 (34.64)
Spain, n (%)	7941 (6.84)
Turkey, n (%)	7279 (6.27)
United Kingdom, n (%)	299 (0.26)
Drug Usage, n	102,096
Majority TNF-α inhibitors (>80%), n (%)	49,547 (48.53)
Not majority TNF-α inhibitors, n (%)	52,549 (51.47)
Disease type, n	104,277
SLE, n (%)	693 (0.66)
Arthritis majority (>80%), n (%)	103,584 (99.34)
RA majority (>80%), n (%)	78,627 (75.40)
PS and PsA majority (>80%), n (%)	935 (0.90)

[a]Short of specific age information from Huang 2018, Wu 2017, Xie 2009 and Zheng 2018. [b]Short of specific sex information from Wu 2017, Xie 2009, Zheng 2018. [c]Short of specific follow-up information from Ipek 2023, Sichletidis 2006, Song 2021, Yagmur 2021, Kyung 2014, Jungsil 2017 and Pinar 2014. [d]Short of specific age information from Huang 2018, Wu 2017, Xie 2009, Zheng 2018 and Qiu 2010. [e]Short of specific sex information from Wu 2017, Xie 2009, Zheng 2018 and Qiu 2010. [f]Short of specific follow-up information from Sema 2014, Sichletidis 2006, Song 2021, Yagmur 2021, He 2013, Ideguchi 2010, Jungsil 2017, Qiu 2010, Pinar 2014 and Ece 2024. Majority defined as over 80% of all people. We extracted the median and quartile again from the mean or median follow-up time and age provided by all studies.

Table 1: **Characteristics of included studies.**

group and 1715 in control group. 4326 cases including 116 TBD cases were distributed in 12 studies in TB high burden counties/regions. Only 2636 cases with 49 TBD cases in 4 studies clearly received RIF-based TPT. 54217 cases with 1254 TBD cases in 12 studies underwent tuberculin skin test (TST) and interferon gamma release assays (IGRA) combined screening method; 12,871 cases with 133 TBD cases in 17 studies only received TST screening method; 7211 cases with 60 TBD cases in 6 studies only received IGRA screening method. 89,972 cases with 1750 TBD cases in 37 studies received

biologic agents; 4470 cases with 120 TBD cases in 10 studies received only traditional treatments. 635 cases with 46 TBD cases in 5 studies were Systematic Lupus Erythematosus (SLE) and arthritis accounted for the majority of all the studies with 31 studies, 101,310 cases and 1717 TBD cases. In terms of TBI status, only 4 studies containing 546 and 22 TBD cases controlled for this variable in the control and TPT groups.

Single-rate meta-analysis

Sixty-four studies provided TBD IR data in patients with RD. We investigated the overall IR of TBD in patients with RD and found that TPT could significantly decrease the IR of TBD by 60% (TPT IR: 0.004, 95% CI: 0.003–0.006; Supplementary Figure S2; without TPT IR: 0.010, 95% CI: 0.007–0.013; Supplementary Figure S3).

In the subgroup of TB high burden countries/regions, TBD IR was 2.7%, about three times higher than other countries/regions in patients with RD without TPT (high burden countries/regions: IR: 0.027, 95% CI: 0.013–0.040; other countries/regions: IR: 0.009, 95% CI: 0.007–0.013; subgroup difference: p = 0.012; Supplementary Figure S4), but with the application of TPT the difference became unconspicuous (high burden countries/regions: IR: 0.004, 95% CI: 0.000–0.012; other countries/regions: IR: 0.004, 95% CI: 0.003–0.006; subgroup difference: p = 0.97; Supplementary Figure S5).

Another important factor affecting TBD IR in patients with RD was the use of biologic agents, especially TNF-α inhibitors. However, TBD IR did not decrease in the group of patients with RD without TNF-α inhibitors (for the majority using TNF-α inhibitors: IR: 0.008, 95% CI: 0.005–0.010; for those not primarily using TNF-α inhibitors: IR: 0.021, 95% CI: 0.010–0.033; subgroup difference: p = 0.025; Supplementary Figure S6). Even after TPT, the IR of TBD in patients with RD without TNF-α inhibitors was still 100% higher than that in the group using TNF-α inhibitors (with TNF-α inhibitors: IR: 0.004, 95% CI: 0.002–0.005; without TNF-α inhibitors: IR: 0.008, 95% CI: 0.005–0.012; subgroup difference: p = 0.0043; Supplementary Figure S7).

Last but not least, different types of RD affect differently on immune system, leading to various TBD IR. Among two main groups of RD we classified, SLE held the highest TBD IR with 9.5%, significantly higher than arthritis group with IR of 1.0% (SLE: IR: 0.095, 95% CI: 0.045–0.145; arthritis: IR: 0.010, 95% CI: 0.006–0.013; subgroup difference: p = 0.00083; Supplementary Figure S8). TPT showed significant protective effect in two groups, which decreased the IR of SLE to 0.4% and decreased the IR of arthritis to 0.7% (SLE: IR: 0.004, 95% CI: 0.000–0.013; arthritis: IR: 0.007, 95% CI: 0.005–0.008; subgroup difference: p = 0.56, Supplementary Figure S9). We specifically investigated the TBD IR in patients with different arthritis and found that the IR in patients with Rheumatoid Arthritis (RA) was 1.5%, but that in patients with PsA (Psoriatic Arthritis) was almost 0% (PsA with TPT: IR: 0.000, 95% CI: 0.000–0.006, RA with TPT: IR: 0.009, 95% CI: 0.007–0.011, subgroup difference: p = 0.0087, Supplementary Figure S10; PsA without TPT: IR: 0.000, 95% CI: 0.000–0.002, RA without TPT: IR: 0.015, 95% CI: 0.002–0.028, subgroup difference: p = 0.016, Supplementary Figure S11).

The heterogeneity of single-rate meta-analysis mainly came from the control groups of each study, which were addressed with random-effects model in final analysis. Then, a meta-regression analysis was conducted with five covariables as predictors including log study size, TBI status, countries/regions, TNF-α antagonists use and whether arthritis that we could explicitly obtained from each study to determine their contribution to heterogeneity and effect size. In meta-regression we used log odds in control group as response variable and all five covariables explained 42.33% of the total heterogeneity. And our meta-regression truly impacted the effect size of log odds in control group with p value of test of moderators of 0.0004 with log study size (beta coefficient: –0.38, 95% CI: –0.55 to –0.22, p < 0.0001) (Supplementary Table S2, Supplementary Figure S13).

Overall effectiveness of TPT in patients with RD

Overall, 46 studies were included in the traditional meta-analysis. The risk of developing TBD in patients with RD who received TPT was significantly decreased by 24% (RR: 0.76, 95% CI: 0.63–0.91; Fig. 3).

Effectiveness of TPT in TB high burden and other countries/regions

Then we stratified all the patients into two groups (the countries/regions with high TB burden and the other countries/regions). According to the global tuberculosis report of WHO in 2024, we regarded the following countries/regions in our studies as TB high burden countries/regions: Brazil, China, India. And the effectiveness of TPT performed significantly better in high burden countries/regions of 12 studies (RR: 0.46, 95% CI: 0.27–0.77; Fig. 4) then in other countries/regions of 34 studies (RR: 0.82, 95% CI: 0.67–1.00, subgroup difference: p = 0.04; Fig. 4).[15]

Effectiveness of different TPT regimens in patients with RD

32 studies used INH monotherapy and only 4 studies had RIF-based regimen. In comparison to TPT including RIF, which did not show a significant preventative effect comparing to the TB prevention strategies including the usage of RIF without significant prevention performance (RR: 0.52, 95% CI: 0.13–2.05; Fig. 5A), patients with RD seemed to potentially benefit more from using INH monotherapy with a significant decreased risk of developing TBD by 32% (RR: 0.68, 95% CI: 0.50–0.92; subgroup difference: p = 0.70;

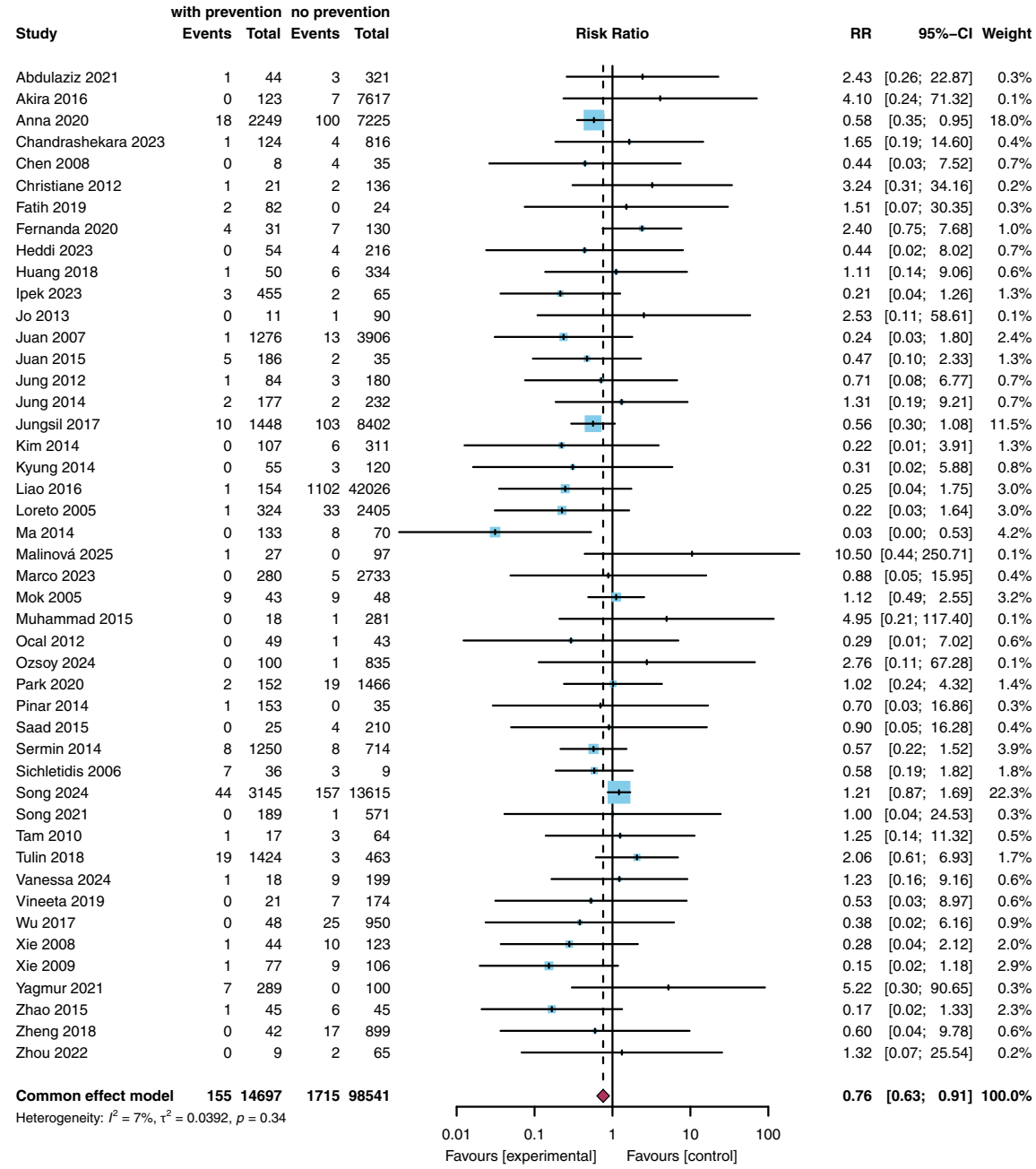


***Fig. 3:* Overall effectiveness of TPT in all patients with RD.** TB, tuberculosis; RD, rheumatic disease.

Fig. 5A). And then we took a close look at detailed usage of INH in TB prevention: 5 studies didn't provide detailed usage of INH (RR: 0.71, 95% CI: 0.38–1.33; Fig. 5B); 9 studies used INH shorter than 9 months seemed to be not very effective in preventing TBD (RR: 1.01, 95% CI: 0.55–1.86; Fig. 5B); but 16 studies used INH 9–12 months effectively decreased risk of developing TBD by 46% (RR: 0.54, 95% CI: 0.35–0.85; Fig. 5B). Although the difference between subgroups was not statistically significant (p = 0.27), extending the duration of INH treatment appeared to improve the effectiveness of TPT.

Effectiveness of TPT with different TBI screening strategies in patients with RD

Most patients with RD will undergo TBI screening before receiving TPT. TST and IGRA are the two most used TBI screening methods. We divided these studies

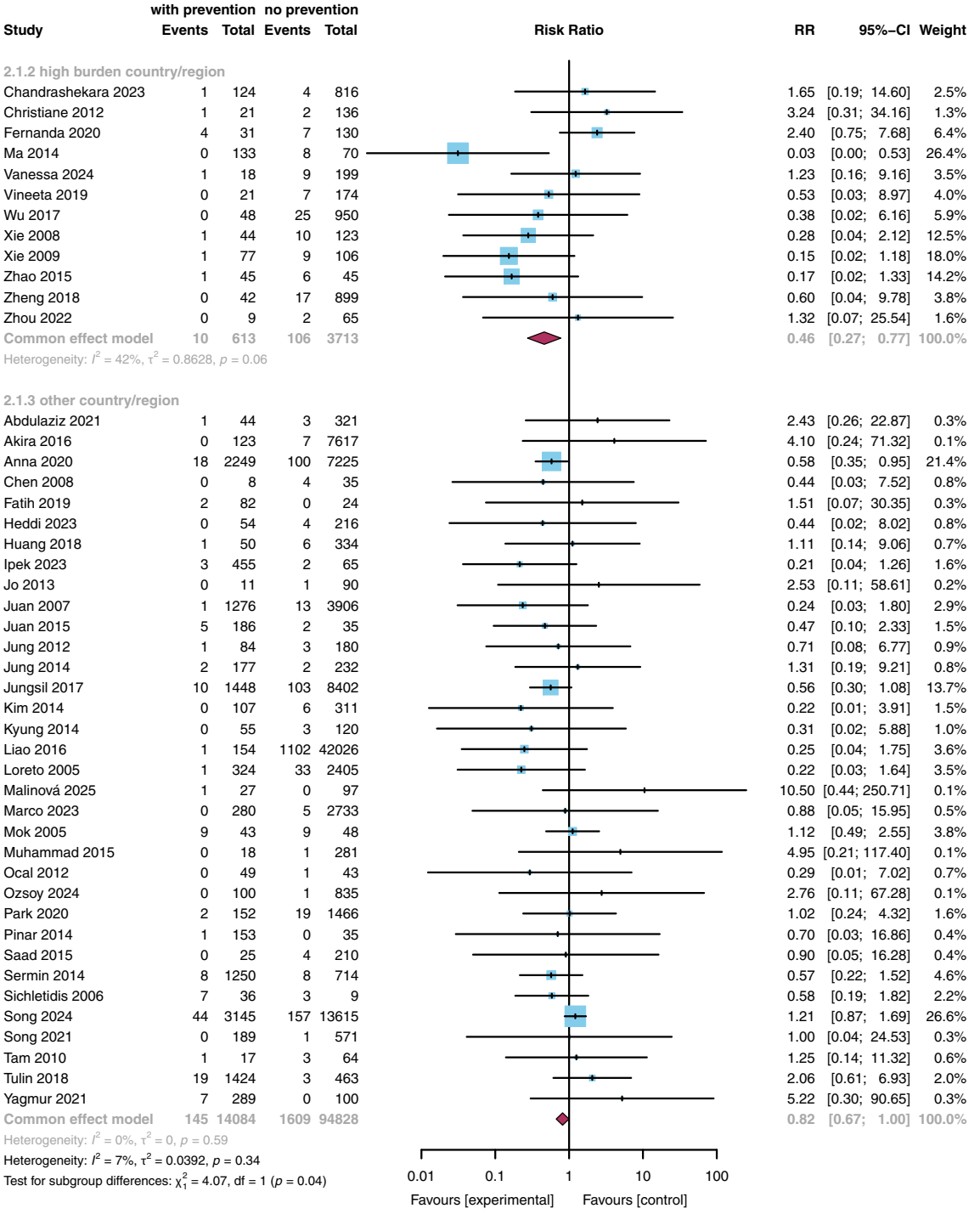


Fig. 4: **Effectiveness of TPT in high TB burden and other countries/regions**. TB, tuberculosis.

into three different subgroups according to their TBI screening methods. Patients with RD who received TST (17 studies, RR: 0.69, 95% CI: 0.52–1.26; Fig. 6A) or IGRA screening (6 studies, RR: 0.89, 95% CI: 0.32–2.50; Fig. 6A) alone did not reduce their risk of developing TBD significantly during the follow up. However, although there was no significant subgroup difference, 12 studies with TST and IGRA combined screening

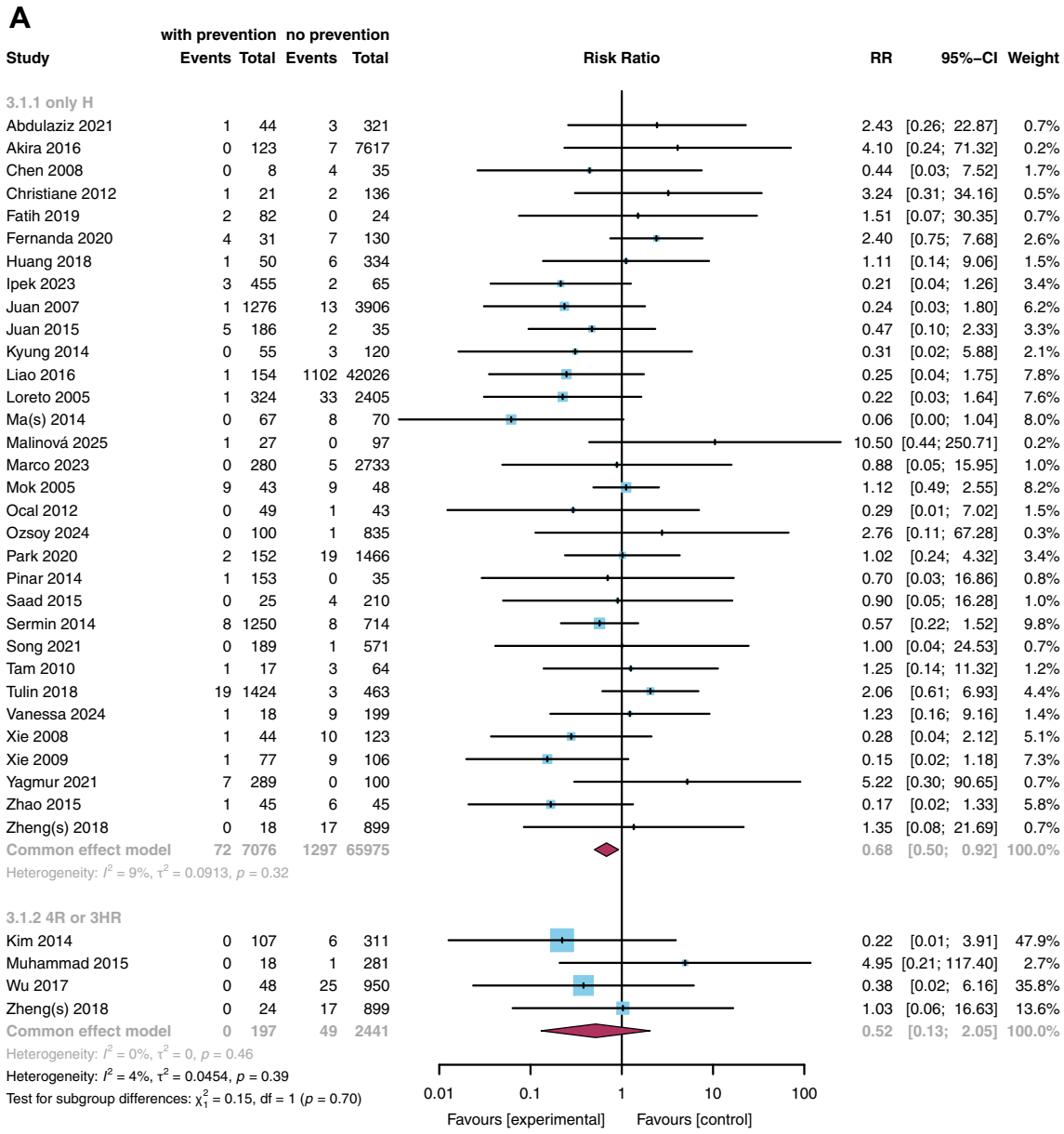


Fig. 5: **Effectiveness of different TPT regimens in patients with RD**. **A**: Effectiveness of TPT of INH and RIF based regimens. **B**: Effectiveness of INH monotherapy with different prophylactic durations. H, isoniazid; R, rifampin; TB, tuberculosis; RD, rheumatic disease; s, subset.

method significantly decreased the risk of TBD by 42% (RR: 0.58, 95% CI: 0.39–0.88; subgroup difference: p = 0.71; Fig. 6A). Additionally, using T-SPOT.TB assay as a screening method showed the trend to be superior to QuantiFERON-TB Gold In-Tube (QFT-GIT) assay. However, due to the limited sample size of studies for each method and overly wide CI, the difference between two methods was not significant. (T-SPOT.TB assay RR: 0.47, 95% CI: 0.06–3.34; QFT-GIT assay RR: 1.33, 95% CI: 0.39–4.53, subgroup difference: p = 0.38, Fig. 6B).

Effectiveness of TPT in patients with RD with different TBI status in the control group

In all studies most patients with TBI received TPT but the TBI status of control groups varied. As TBI would increase the risk of TBD, we tried to control this variable. We stratified studies into three subgroups according to the TBI status of the control group. The effectiveness of TPT showed a significant increasing trend in three subgroups: TBI negative control subgroup (32 studies) showed the trend of decreasing risk

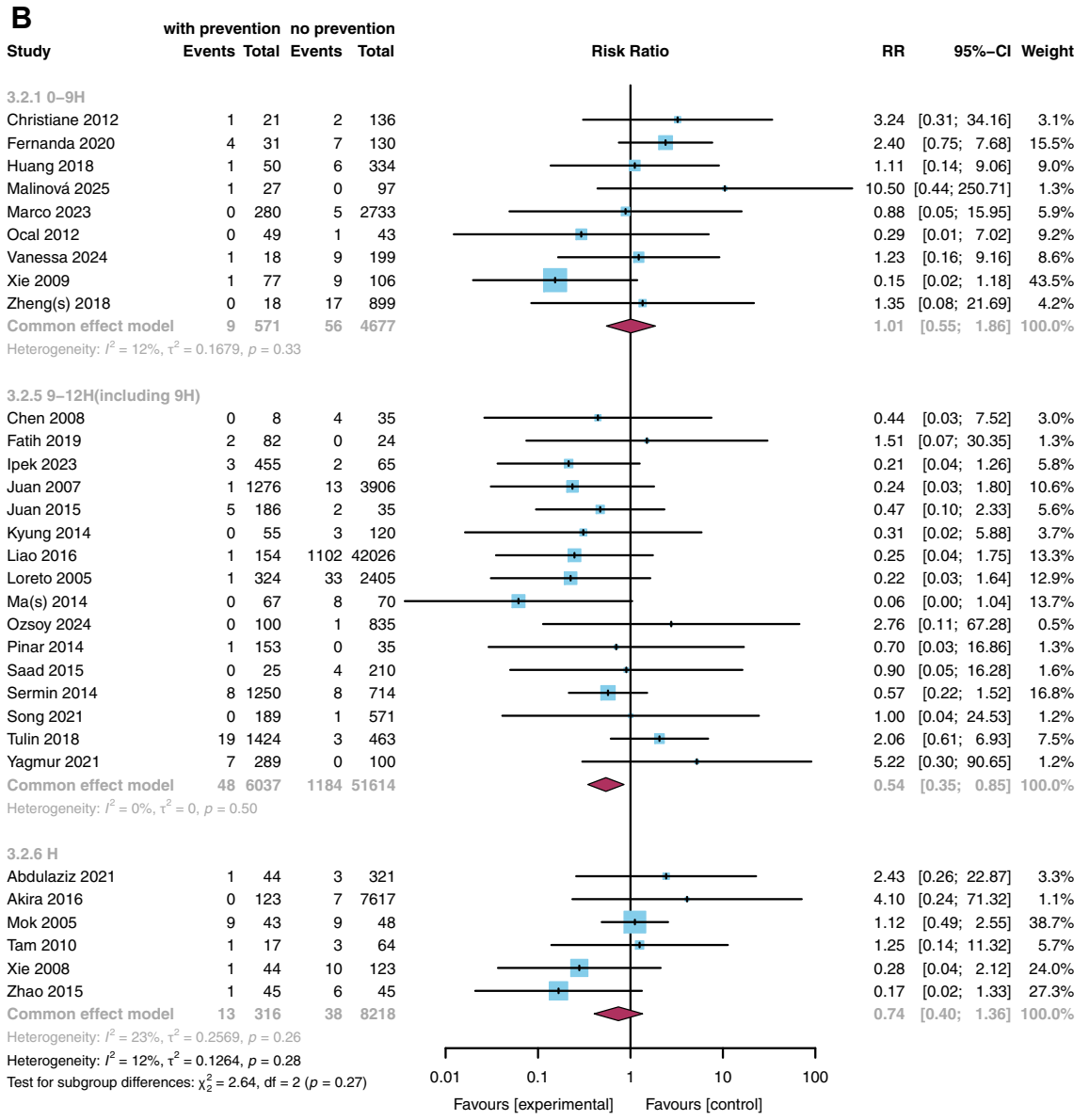
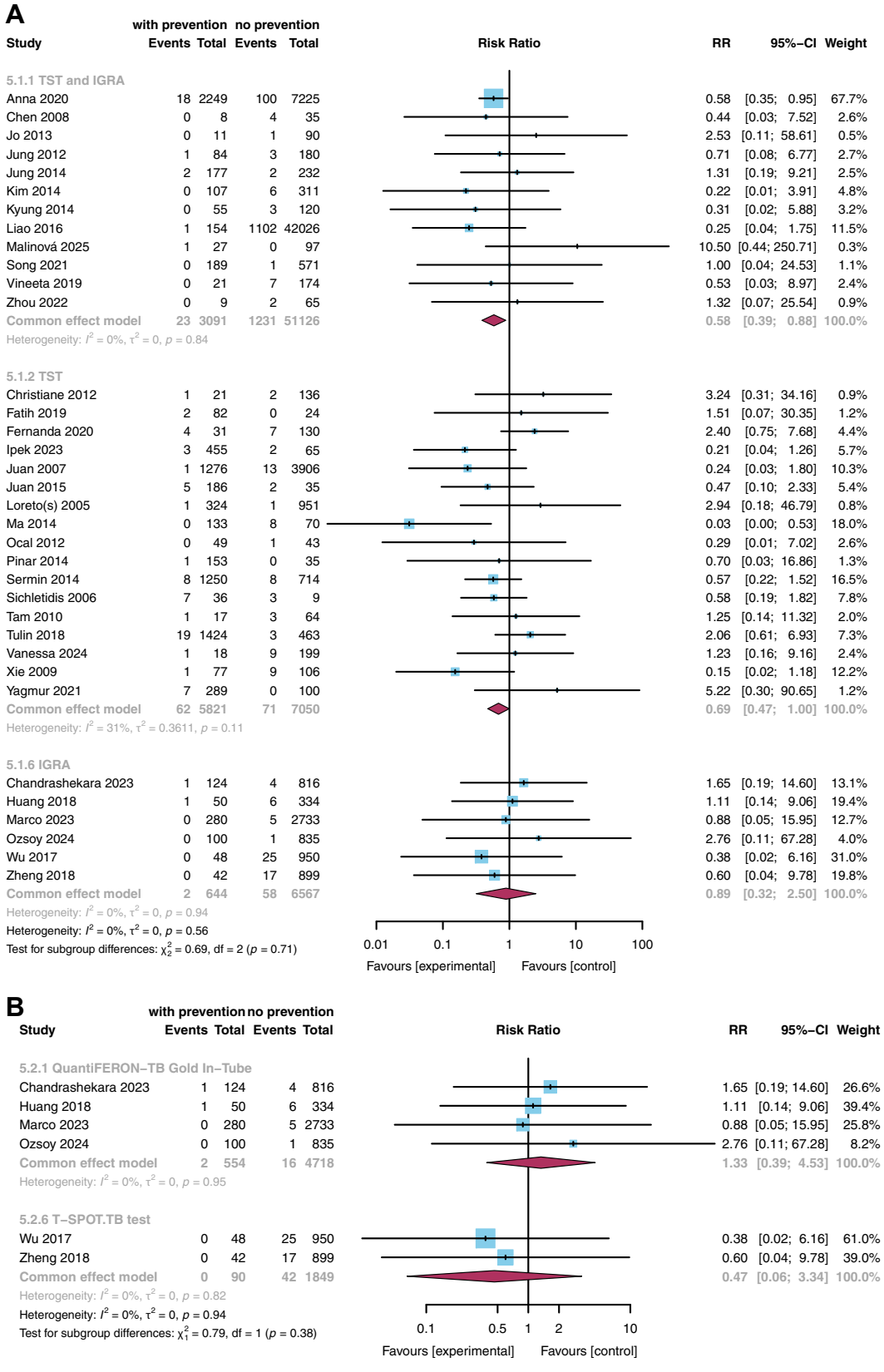


Fig. 5: Continued.

of TBD by 7% (RR: 0.93, 95% CI: 0.75–1.15; Fig. 7), TBI mixed status subgroup (11 studies) decreased the risk of TBD by 45% (RR: 0.55, 95% CI: 0.36–0.84; Fig. 7) and TBI positive subgroup (4 studies) decreased the risk of TBD by 89% (RR: 0.11, 95% CI: 0.04–0.32; subgroup difference: p < 0.01; Fig. 7). This meant that the effect of TPT in TBI-positive RD population might be more significant than previously anticipated.

Effectiveness of TPT in patients with RD receving different rheumatic medications

Patients with RD commonly have various therapeutic backgrounds. We stratified the studies into different subgroups based on the usage of RD medications. We found that patients with RD with only traditional treatments showed a 56% decrease in the risk of TBD after TPT (RR: 0.44, 95% CI: 0.27–0.73; Fig. 8), which was better than patients with RD receiving biologic agents (RR: 0.83, 95% CI: 0.68–1.02; Fig. 8). Of the 37 studies with biologic agent usage, 32 predominantly involved the use of TNF-α inhibitors, and TPT helped decrease the risk of TBD by 33% (RR: 0.67, 95% CI: 0.52–0.88; Fig. 8). Of the 10 studies with traditional treatments, five studies involved patients who received only glucocorticoids (RR: 0.26, 95% CI: 0.12–0.58; Fig. 8), two studies involved patients who received only DMARDs (RR: 0.26,


A
with prevention
no prevention
Study
Events Total Events Total
Risk Ratio
RR 95%−CI Weight
5.1.1 TST and IGRA
Anna 2020 18 2249 100 7225 0.58 [0.35; 0.95] 67.7%
Chen 2008 0 8 4 35 0.44 [0.03; 7.52] 2.6%
Jo 2013 0 11 1 90 2.53 [0.11; 58.61] 0.5%
Jung 2012 1 84 3 180 0.71 [0.08; 6.77] 2.7%
Jung 2014 2 177 2 232 1.31 [0.19; 9.21] 2.5%
Kim 2014 0 107 6 311 0.22 [0.01; 3.91] 4.8%
Kyung 2014 0 55 3 120 0.31 [0.02; 5.88] 3.2%
Liao 2016 1 154 1102 42026 0.25 [0.04; 1.75] 11.5%
Malinová 2025 1 27 0 97 10.50 [0.44; 250.71] 0.3%
Song 2021 0 189 1 571 1.00 [0.04; 24.53] 1.1%
Vineeta 2019 0 21 7 174 0.53 [0.03; 8.97] 2.4%
Zhou 2022 0 9 2 65 1.32 [0.07; 25.54] 0.9%
Common effect model 23 3091 1231 51126 0.58 [0.39; 0.88] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.84
5.1.2 TST
Christiane 2012 1 21 2 136 3.24 [0.31; 34.16] 0.9%
Fatih 2019 2 82 0 24 1.51 [0.07; 30.35] 1.2%
Fernanda 2020 4 31 7 130 2.40 [0.75; 7.68] 4.4%
Ipek 2023 3 455 2 65 0.21 [0.04; 1.26] 5.7%
Juan 2007 1 1276 13 3906 0.24 [0.03; 1.80] 10.3%
Juan 2015 5 186 2 35 0.47 [0.10; 2.33] 5.4%
Loreto(s) 2005 1 324 1 951 2.94 [0.18; 46.79] 0.8%
Ma 2014 0 133 8 70 0.03 [0.00; 0.53] 18.0%
Ocal 2012 0 49 1 43 0.29 [0.01; 7.02] 2.6%
Pinar 2014 1 153 0 35 0.70 [0.03; 16.86] 1.3%
Sermin 2014 8 1250 8 714 0.57 [0.22; 1.52] 16.5%
Sichletidis 2006 7 36 3 9 0.58 [0.19; 1.82] 7.8%
Tam 2010 1 17 3 64 1.25 [0.14; 11.32] 2.0%
Tulin 2018 19 1424 3 463 2.06 [0.61; 6.93] 7.3%
Vanessa 2024 1 18 9 199 1.23 [0.16; 9.16] 2.4%
Xie 2009 1 77 9 106 0.15 [0.02; 1.18] 12.2%
Yagmur 2021 7 289 0 100 5.22 [0.30; 90.65] 1.2%
Common effect model 62 5821 71 7050 0.69 [0.47; 1.00] 100.0%
Heterogeneity: I^2 = 31%, τ^2 = 0.3611, p = 0.11
5.1.6 IGRA
Chandrashekara 2023 1 124 4 816 1.65 [0.19; 14.60] 13.1%
Huang 2018 1 50 6 334 1.11 [0.14; 9.06] 19.4%
Marco 2023 0 280 5 2733 0.88 [0.05; 15.95] 12.7%
Ozsoy 2024 0 100 1 835 2.76 [0.11; 67.28] 4.0%
Wu 2017 0 48 25 950 0.38 [0.02; 6.16] 31.0%
Zheng 2018 0 42 17 899 0.60 [0.04; 9.78] 19.8%
Common effect model 2 644 58 6567 0.89 [0.32; 2.50] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56
Test for subgroup differences: χ^2_2 = 0.69, df = 2 (p = 0.71)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
B
with prevention
no prevention
Study
Events Total Events Total
Risk Ratio
RR 95%−CI Weight
5.2.1 QuantiFERON−TB Gold In−Tube
Chandrashekara 2023 1 124 4 816 1.65 [0.19; 14.60] 26.6%
Huang 2018 1 50 6 334 1.11 [0.14; 9.06] 39.4%
Marco 2023 0 280 5 2733 0.88 [0.05; 15.95] 25.8%
Ozsoy 2024 0 100 1 835 2.76 [0.11; 67.28] 8.2%
Common effect model 2 554 16 4718 1.33 [0.39; 4.53] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95
5.2.6 T−SPOT.TB test
Wu 2017 0 48 25 950 0.38 [0.02; 6.16] 61.0%
Zheng 2018 0 42 17 899 0.60 [0.04; 9.78] 39.0%
Common effect model 0 90 42 1849 0.47 [0.06; 3.34] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.82
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94
Test for subgroup differences: χ^2_1 = 0.79, df = 1 (p = 0.38)
0.1 0.5 1 2 10
Favours [experimental] Favours [control]

95% CI: 0.05–1.23; Fig. 8), three studies involved patients who received both DMARDs and glucocorticoids (RR: 1.05, 95% CI: 0.49–2.27; Fig. 8). Patients using only glucocorticoids or DMARDs seemed to benefit from TPT with a 74% reduction in the risk of TBD.

Effectiveness of TPT in patients with different types of RD

Different types of RD carry different risks of developing TBD, so we evaluated the effectiveness of TPT respectively in patients with various types of RD. We divided all diseases information extractable studies into two groups: 5 studies with SLE and 31 studies of major arthritis. TPT tended to perform greater protective effect in SLE subgroup with 58% significant reduction of TBD risk (RR: 0.42, 95% CI: 0.23–0.76; Fig. 9) than arthritis with only a trend of 18% protective effect (RR: 0.82, 95% CI: 0.67–1.01; Fig. 9). RA was the main component of arthritis, TPT tended to be effective in 12 studies of patients with RA with 14% protective effect (RR: 0.86, 95% CI: 0.67–1.10, Fig. 9) but not in PsA subgroup (RR: 1.14, 95% CI: 0.16–8.44, Fig. 9).

Although we chose to adopt fixed-effect model in meta-analysis of TPT in different types of RD for the overall minority heterogeneity, SLE subgroup showed nonnegligible heterogeneity with I^2 = 60%, we performed sensitivity analysis and found two studies: Mok 2005 and Ma 2014 may be the source of heterogeneity since excluding of each study would cause their omitting result inconsistent with pooled result in fixed-effect model or random-effects model (Supplementary Figure S12). But the exclusion of Mok 2005 reduced the heterogeneity to a minimum (I^2 = 15%, Supplementary Figure S12A). The major difference of Mok 2005 compared to the others was that it was conducted in Hong Kong, China and the rest were in Chinese mainland. Hong Kong was a highly developed area of China with low TB incidence, so it was reasonable that TPT performed less effectively there compared to Chinese mainland. So, TPT emerged a remarkable effectiveness in China patients with SLE (RR: 0.16, 95% CI: 0.06–0.46, Supplementary Figure S12A).

Discussion

Previous studies have already demonstrated that patients with RD are at higher risk of developing TBD than general population with various risk factors including TB exposure history, the use of biologics or traditional RD drug and types of disease.[11–13] WHO's "consolidated guidelines on tuberculosis" also have listed people who are initiating anti-TNF treatment as a high-risk population who should receive TPT, but it also acknowledges there is gaps in the research of evaluating the effectiveness of TPT in patients with RD.[84]

Here we systematically evaluated the effectiveness of TPT in patients with RD and our main result was that TPT did decrease the risk of developing TBD in overall patients with RD. IR of TBD decreased by approximately 25% when patients with RD received TPT. Such results had not been reported before.

What's more, applying TPT in high TB burden countries/regions results in a better effect. This could be explained by results from a single meta-analysis that although IR of TBD in high TB burden countries/regions was about three times higher than that in other countries/regions, it declined to the same level after TPT.

As for the drug usage strategy of TPT, it was another important aspect of our study. According to WHO, patients with RD can receive chemoprophylaxis just like general population, including mainly five TPT regimens: (1) 6 or 9-month of daily isoniazid; (2) 3-month regimen of weekly rifapentine (RPT) plus isoniazid; (3) 3-month regimen of daily isoniazid plus RIF; (4) 1-month regimen of daily RPT plus isoniazid; (5) 4-month of daily RIF alone may also be offered as alternatives; levofloxacin was also an alternative option but no studies mentioned about.[84] Here we divided studies into two group according to whether RIF or rifapentine (RPT) was used. Interestingly, we found that INH preventive therapy had better TB prevention effectiveness with a RR of 0.68. Although this result contradicts some previous trials suggesting that TPT with RIF or RPT should have equivalent effectiveness to INH monotherapy,[85,86] this discrepancy may be attributed to the limited number of articles evaluating the effectiveness of TPT with rifamycins-based regimens. Specifically, our search yielded only 4 studies on TPT regimens with rifamycins, all of which used RIF rather than RPT. However, with sufficient statistical power, TPT including RIF or RPT may possibly show better results than INH monotherapy, as it has already shown a RR of 0.52 and only needs to reach a statistical significant. Furthermore, we carefully examined the effectiveness of INH with different treatment durations and found that courses lasting 9–12 months yielded the best effectiveness with a RR of 0.54, demonstrating that both the treatment duration and the number of doses contribute to improving the effectiveness of TPT.[10]

Regarding the results of TBI screening method applied to patients with RD, our study indicated that TST combined with IGRAs trended to be more effective

Fig. 6: **Effectiveness of TPT with different TBI screening strategies in patients with RD. A**: Effectiveness of TPT using TST, IGRA, and TST combined with IGRA for TBI screening. **B:** Effectiveness of TPT using QFT-GIT and T-SPOT.TB for TBI screening. TST, tuberculin skin test; IGRA, interferon gamma release assay; QFT-GIT, QuantiFERON-TB Gold In-Tube; T-SPOT.TB, T-cell spot of tuberculosis; TBI, tuberculosis infection; RD, rheumatic disease; s, subset.

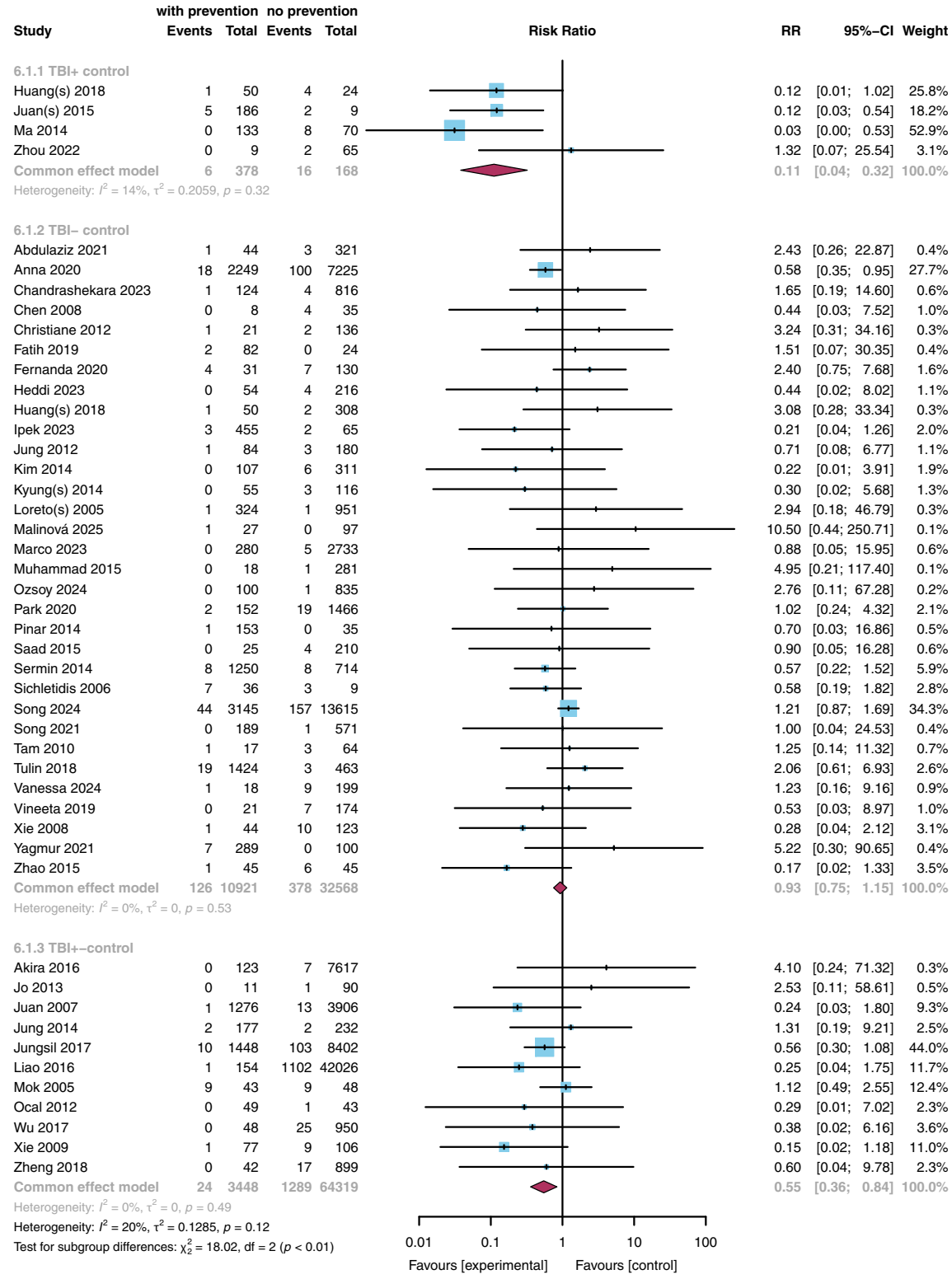


Fig. 7: **Effectiveness of TPT in Patients with RD with different TBI status in the control group**. TBI, tuberculosis infection; TBI+, TBI positive status; TBI + -, TBI mixed status; TBI-, TBI negative status; s, subset.

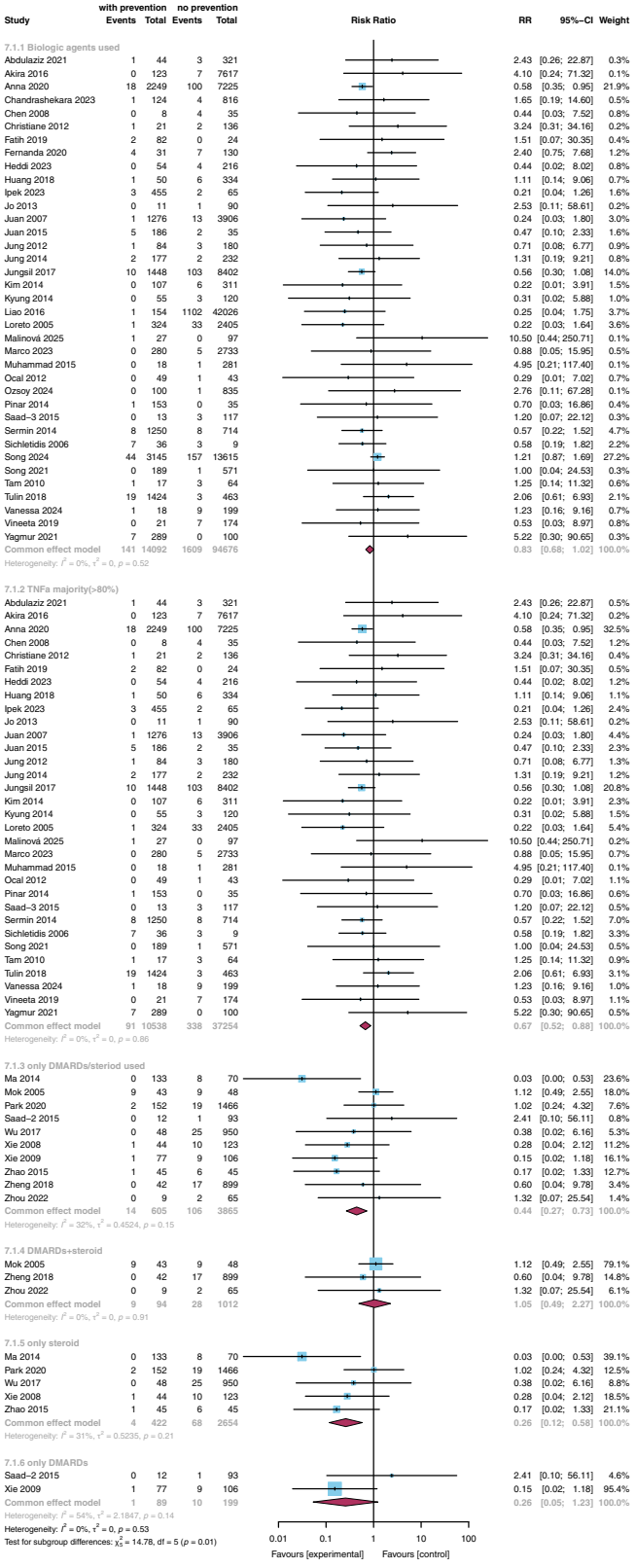


Fig. 8: **Effectiveness of TPT in Patients with RD receving different rheumatic medications**. DMARD, disease modifying antirheumatic drug; RD, rheumatic disease; TNFα, tumor necrosis factor-alpha; s, subset.

than using TST or IGRAs alone.[87,88] Since the screening results between TST and IGRA were not consistent, various factors may influence their TBI screening efficacy, such as medication, disease type, and even the interpretation criteria of TST.[89] A systematic review including 17 studies with 3197 patients suffering from autoimmune diseases showed that immunosuppressive therapy, including glucocorticoids, oral immunosuppressants, and TNF-α inhibitors, can affect the positive rates of IGRA (OR = 0.66, 95% CI 0.53–0.83) and TST (OR = 0.51, 95% CI 0.42–0.61). Some studies found that the use of immunomodulators would decrease the sensitivity of TST, while there was a study indicating a good concordance between TST and IGRA in patients with autoimmune diseases.[51,88,90] Also, the immune status of patients could influence the screening results of IGRA. Our previous study on patients with SLE also found that the positive rate of IGRA was affected by the dose of glucocorticoids and the disease activity, indicating that severe SLE activity and an immunocompromised status would increase the false negative results of IGRA.[91] It's rational that the combination of TST and IGRAs would effectively reduce the false negative results by maximizing the detection rate of TBI.[48] Also, there were two main subtypes of IGRAs including QFT-GIT and T-SPOT.TB, as they detect the IFN-γ produced by T cell in response to *M. tuberculosis* antigens in different ways. A meta-analysis showed that compared with QFT, immunosuppressive therapy may have a less impact on the positive rate of T-SPOT.TB (QFT OR = 0.65, 95% CI 0.50–0.84, T-SPOT.TB OR = 0.81, 95% CI 0.59–1.10). Our study similarly found that using T-SPOT.TB as a TBI screening method may lead to better outcomes for TPT. However, due to the limited number of studies (only four), no significant difference was found between QFT-GIT and T-SPOT.TB.[90,92]

One of the risk factors for patients with RD developing TBD is their use of RD-related medication. Both traditional treatments and newly developed biologic agents increase the risk of TBD in patients with RD, especially anti-TNF-α treatment is considered the highest risk factor for TBD, which can be up to 18 times higher than that in the general population. This may be because TNF-α plays a central role both in the host immune response to TB infection and in the immunopathology of TB.[2,8,13] Our study demonstrated that TPT was effective in patients with RD receiving TNF-α inhibitors, although the effectiveness may not be superior to that in patients with RD who received only traditional treatments. As for why TPT showed no effect in patients

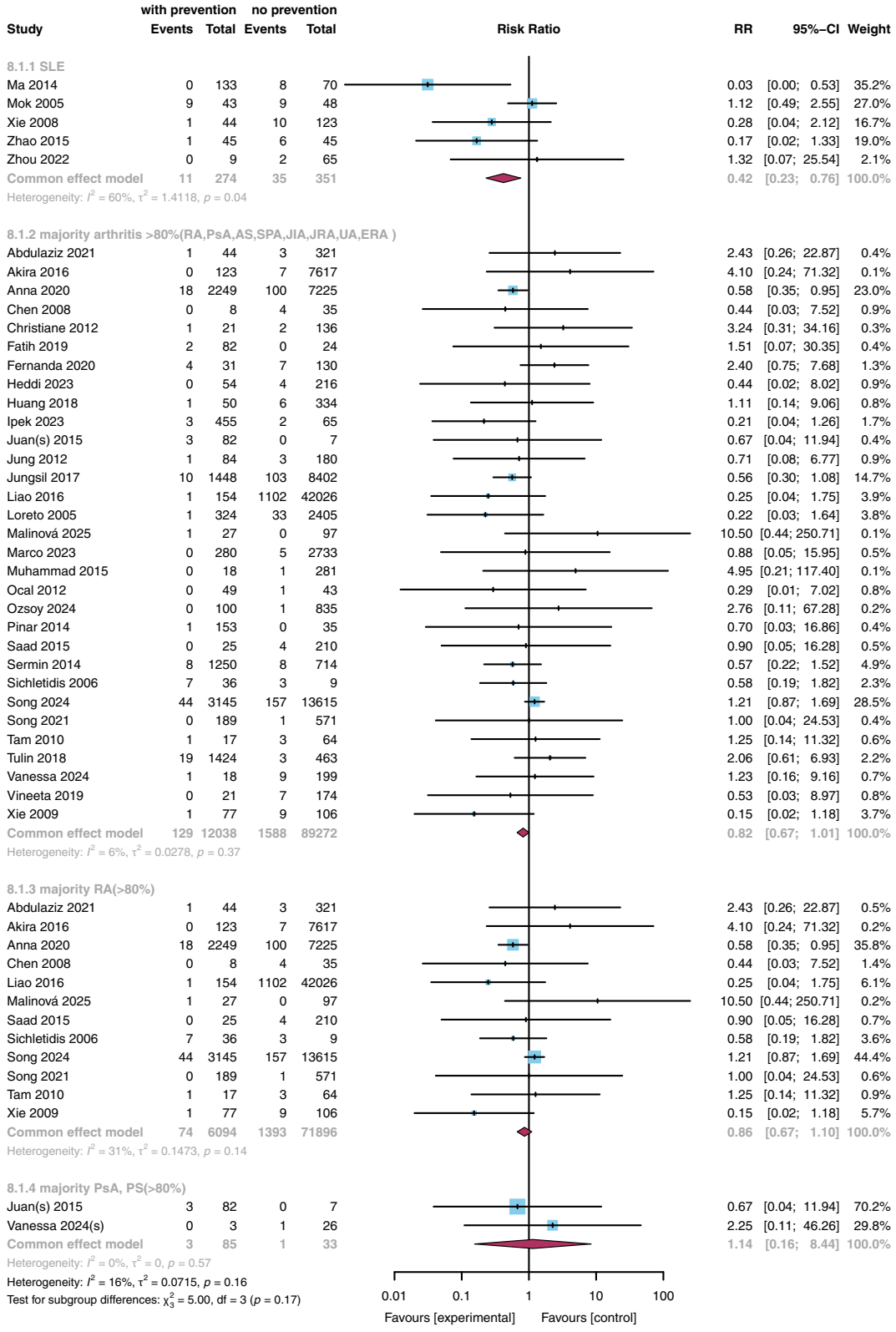


Fig. 9: **Effectiveness of TPT in patients with different types of RD**. RD, rheumatic disease; TPT, tuberculosis preventive treatment; SLE, Systematic Lupus Erythematosus; RA, Rheumatoid Arthritis; PsA, Psoriatic Arthritis; AS, Ankylosing Spondylitis; SPA, Spondyloarthritis; JIA, Juvenile Idiopathic Arthritis; JRA, Juvenile Rheumatoid Arthritis; ERA, Enthesitis Related Arthritis; UA, Undifferentiated Arthritis; s, subset.

using both DMARD and glucocorticoids, two possible explanations may apply: (1) there is a lack of sufficient studies to support this result; (2) patients may have severe RD when taking both drugs, resulting in higher disease activity and more severe immune compromise, which in turn increases the risk of TBD.[93]

Disease type is another risk factor that affects the IRof TBD in patients with RD. We divided RD into two subgroups: SLE and arthritis. Studies on SLE demonstrated a significantly protective effect of TPT, reducing the risk of TBD by 58%. As for patients with arthritis, TPT also showed the trend to decrease the risk of TBD by 18%. And RA as the representative disease of arthritis obtained a RR of 0.86 with TPT. The lack of a protective trend in PsA may be caused by only two relevant studies being available. Although the IR of TBD in patients with SLE were over three times higher than that in patients with RA, there were three aspects to help us understand why TPT performed better in SLE than in arthritis: (1) TPT performed better in high TB burden countries/regions, such as China; (2) biologic agents especially TNF-α inhibitors were widely used in patients with arthritis, which may encumber the therapeutic effect of TPT; (3) our single-rate meta-analysis demonstrated that the IR of TBD in patients with SLE was much higher than that in patients with arthritis. However, with the application of TPT, their IRs of TBD could be controlled to the same level.[11]

Last but not least, we also made a correction to our study. As in most studies, only TBI positive patients are treated with TPT, which made a nonnegligible difference between the control group and the TPT receiving group, since patients with TBI had a higher possibility of developing TBD.[12] So, we categorized all studies into three groups according to the TBI status of the control group and found that the risk of TBD significantly decreased when control and TPT receiving patients were all TBI positive with a RR of 0.11. This was followed by intermediate control group with a RR of 0.55 and TBI negative control group which held a RR of 0.93. This corrected analysis suggested that TPT may be more effective than initially expected in TBI positive patients with RD.

However, several limitations still exist: (1) We conducted our meta-analysis based on crude RR extracted from original research data, and all the research also didn't provide adjusted estimates. Although according to Greenland's method it could be adjusted by external estimates of confounding with formula RRa = RRu/U, no such proper external estimates were found. So, we hypothesized that the TBI status in control group could be a great confounding bias and our result proved the difference was significant, which we thought could be used as external estimates for subsequent articles.[94] (2) Many studies included in our meta-analysis contained only several or no TBD cases, which could be an important bias and limitation to evaluate RR or IR according to previous research.[95] (3) Another limitation of our study was that the we didn't apply inverse probability weighting using population weights, which might cause potential biases arising from non-representative samples or imbalances in study populations. (4) Insufficient statistic power and inaccurate estimation of between-study heterogeneity were brought by the limited study numbers in some subgroups such as TBI positive control subgroup and short-course regimens containing rifamycins subgroups, resulting in an overly wide confidence interval for the combined results, which is not sufficient to draw valid conclusions. (5) Only SLE and arthritis related rheumatic diseases were included in this meta-analysis, this could be due to the rare incidence and lack of enough attention, immune mediated diseases could be a future research direction. (6) The inconsistent conditions between TPT receiving and control group like TBI status may affect the reliability of our results, but according to our correction analysis TPT could have better performance than we expected. (7) High-quality RCT studies are extremely scarce, and this should be the direction of future research.

In conclusion, this meta-analysis systematically evaluated the effectiveness of TPT in patients with RD and revealed that TPT is effective for overall patients with RD. TPT performs better in high TB burden countries/regions, when using INH for more than 9 months and receiving a combined TST and IGRA screening strategy for TBI. Factors such as drug use, disease type and TBI status of the control group were also critical in affecting TPT effectiveness and should be carefully considered. Based on these results, we propose additional evidence and recommendations for TB prevention in future patients with RD. More types of RDs, short-course TPT regimens containing rifamycins and high-quality RCT should be the focus of future research.

Contributors

Beiming Wang, Shi Chen and Lifan Zhang designed the study. Beiming Wang and Shi Chen did the literature search and data extraction. Beiming Wang and Lifan Zhang analysed the data, wrote the report and designed figures. Beiming Wang, Shi Chen and Lifan Zhang accessed and verified the data. Lifan Zhang and Xiaoqing Liu helped revise the report.

Data sharing statement

All data will be available through email with publication after getting permission from corresponding author.

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103177.

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