JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Review

Efficacy and safety of drug therapies for treating tuberculous meningitis: a network meta-analysis

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Abstract

Introduction: The optimal treatment for tuberculous meningitis (TBM) remains inconclusive. This study intends to compare the efficacy and safety of available drug therapies for treating TBM from the perspective of mortality, neurological events, and adverse events.

Methods: PubMed (21/6/2025), Cochrane (21/6/2025), Embase (21/6/2025), and Web of Science (21/6/2025) were searched for randomized controlled trials (RCTs) of TBM. Risk of Bias 2.0 was used for the quality assessment of the included studies. R4.2.3 "gemtc" package was used for data analysis, and Stata 15.0 was utilized to assess publication bias. Odds ratios (ORs) with 95% credible intervals (95% CrIs) were calculated as effect sizes.

Results: Twenty-nine RCTs involving 4,640 TBM patients were included. The results showed that when combined with the standard treatment, prednisone might reduce TBM mortality [OR (95% CrI) = 0.26 (0.07, 0.78)]; both methylprednisolone [OR (95% CrI) = 0.13 (0, 0.98)] and prednisone [OR (95% CrI) = 0.18 (0.02, 0.76)] were likely to reduce the incidence of tuberculoma and other extracranial tuberculosis; prednisolone might increase the risk of neurological events [OR (95% CrI) = 5.98 (2.03, 20.7)], while standard-dose rifampicin was less likely to cause neurological events [OR (95% CrI) = 0.25 (0.06, 0.78)]; dexamethasone might increase the incidence of gastrointestinal events [OR (95% CrI) = 1.72 (1.04, 2.91)]; levofloxacin was more likely to cause hepatic events [OR (95% CrI) = 1.79 (1.05, 3.14)].

Conclusions: Prednisone, levofloxacin, and linezolid, rather than high-dose rifampicin, may reduce TBM mortality compared with standard-dose rifampicin. Prednisolone increases the risk of neurological events.

Key words: Central nervous system; meningitis; treatment outcome; adverse events; tuberculosis.

J Infect Dev Ctries 2026; 20(4):477-493. doi:10.3855/jidc.21300

(Received 10 January 2025 – Accepted 26 July 2025)

Introduction

According to the World Health Organization (WHO)'s Global Tuberculosis Report 2024, the number of new cases of tuberculosis worldwide reached 10.8 million in 2023, hitting the highest level since 1995, and the total deaths were approximately 1.25 million during the same period. The high-incidence areas for tuberculosis are mainly developing countries in Africa and Asia, imposing an inestimable health burden and health threat [1]. Tuberculous meningitis (TBM), a form of extrapulmonary tuberculosis caused by Mycobacterium tuberculosis infection in the central nervous system, is classified into different stages according to the UK MRC staging system. TBM symptoms range from cranial nerve damage and hemiplegia to consciousness disturbances, accompanied by obvious meningeal irritation signs. Moreover, TBM is one of the most severe types of tuberculosis and commonly occurs in children [2] and HIV-infected patients [3], and its mortality rate can still be up to 19.3% in children even after certain treatments, with a sequela-free survival rate of only 36.7% [4]. A meta-analysis [2] (2022) revealed that TBM accounts for approximately 13.91% of meningitis cases, with a mortality rate of 42.12% in hospitalized patients, and a high risk of neurological sequelae, posing a significant threat to public health, especially in developing countries.

Disappointingly and notably, as has been pointed out in multiple authoritative guidelines and review articles, TBM is recognized as one of the subtypes of tuberculosis with weak evidence and significant variation in treatment. The existing treatment regimens for TBM not only largely follow the treatment guidelines for pulmonary tuberculosis [5] but also lack evidence [6]. In order to achieve the WHO's goal of eradicating tuberculosis [7], relevant research is extremely necessary. Likewise, treatment of TBM has become a clinical priority.

Drug therapies, surgical interventions, and physical therapies are commonly used for treating TBM. Drug therapies, dominated by combined medication, include conventional first-line anti-tuberculosis drugs (e.g., isoniazid and rifampicin), quinolones (e.g., moxifloxacin and levofloxacin), high-dose rifampicin, steroids, and aspirin. However, these drugs have their own deficiencies. Steroids have been recognized as effective in reducing mortality of mild to moderate

TBM, but their efficacy in reducing the incidence of neurological adverse events and the mortality in HIV-positive patients remains to be clarified. Despite high cerebrospinal fluid exposure, the benefits of quinolones (including levofloxacin, rifapentine, ciprofloxacin, and gatifloxacin) in treating meningitis caused by non-drug-resistant Mycobacterium tuberculosis infection are uncertain. Similarly, the efficacy of high-dose rifampicin is yet to be defined. Although aspirin is considered potentially effective in reducing the risk of TBM-induced ischemic stroke and venous embolism, relevant evidence is lacking.

Currently, a direct comparison of treatments for TBM is lacking. Therefore, this study intends to compare the efficacy of different drug therapies by a network meta-analysis (NMA), providing better references and guidance for developing treatment regimens for TBM.

Methods

This NMA was carried out following PROSPERO [8] of the National Institute for Health Research (ID: CRD42024558783) and designed according to the PRISMA extension statement for NMA (PRISMA-NMA) (Supplementary Material 1).

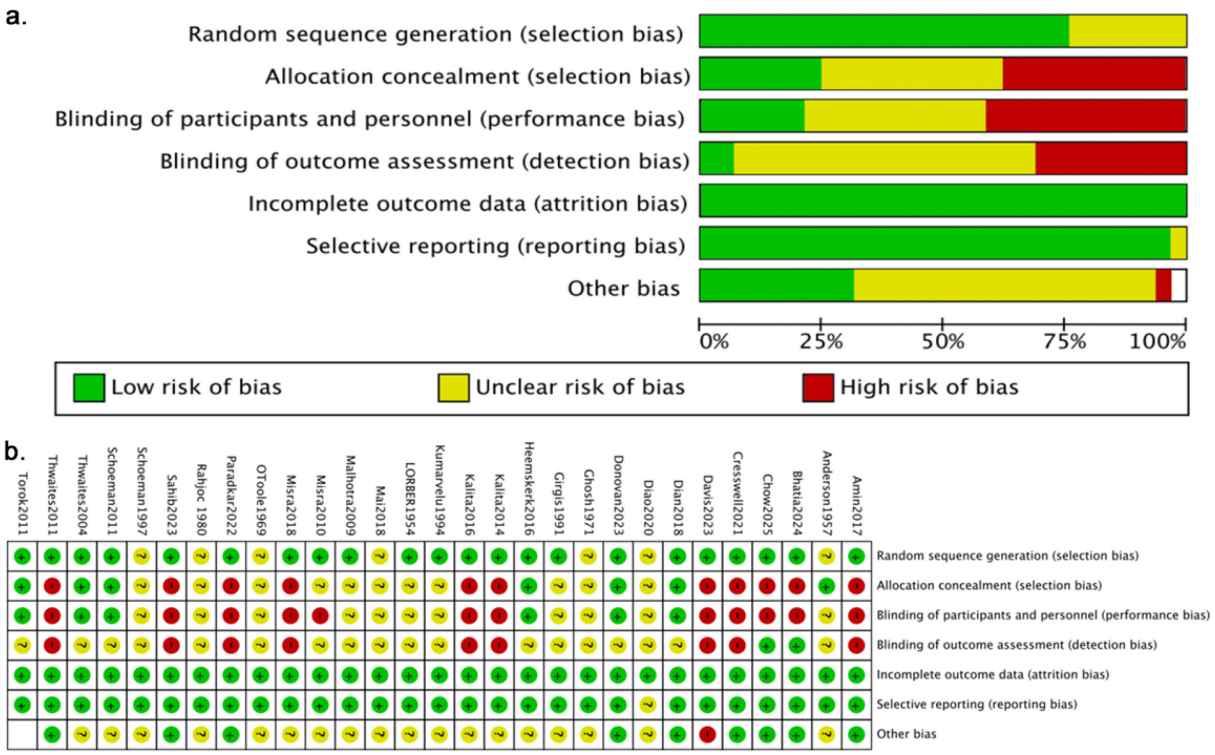
Literature retrieval

Cochrane, PubMed, Embase, and Web of Science were systematically searched from their inception to 21 June 2025 for randomized controlled trials (RCTs) on TBM, with language restricted to English and no restriction on the publication date. Disease terms including medical subject headings "tuberculosis, meningeal" combined with synonymous text words (e.g., "tuberculous meningitis", "tb meningitis") and lexical variations in titles/abstracts were utilized. The study design filter used was Publication type "randomized controlled trial" OR title/abstract text words "randomized", "randomised", "placebo", "clinical trial", or "rct". Disease terms and study design filter were combined with the Boolean operator AND. The complete search strategy is available in Supplementary Material 2.

Eligibility criteria

Inclusion criteria: The study subjects were patients with TBM, with the detection of Mycobacterium tuberculosis in cerebrospinal fluid (e.g., acid-fast bacteria were detected, and the Xpert test was positive) as the diagnostic criterion in the vast majority of studies. The intervention was limited to drug therapies, whereas the same treatment, except for the intervention drug, was adopted in the standard group. The primary outcome was mortality, and the secondary outcomes encompassed gastrointestinal events, neurological events, hepatic events, tuberculoma, and other

Figure 1. Risk of bias graph and summary.



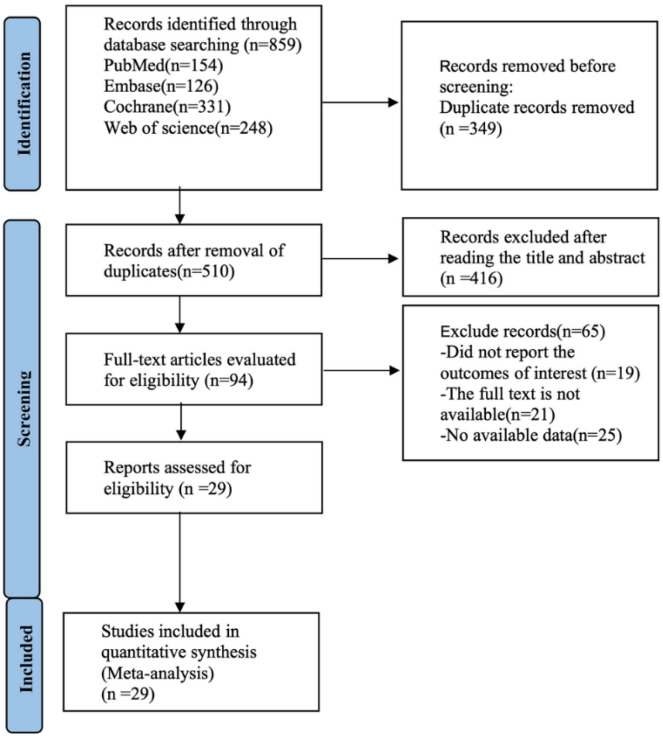
extracranial tuberculosis. Only RCTs were included. Standard treatment included different doses of some or all of the following drugs: isoniazid, rifampicin (both standard- and high-dose), streptomycin, aminosalicylic acid, dexamethasone, thiacetazone, isonicotinic acid, ethambutol, VitB6, acetazolamide, furosemide, prednisone, prednisolone, and ethionamide. Surgical treatment for patients with complications or antiretroviral therapy for HIV-infected patients could also be considered.

Exclusion criteria: Duplicate publications, animal studies, case reports, conference summaries, reviews, and studies with inaccessible full text, and regarding other organic diseases.

Data extraction

The two reviewers rigorously screened the studies based on the predefined eligibility criteria. In case of any disagreement, they could discuss with each other or consult a third party for a consensus. Then the following data were extracted: first author, year of publication, country, sample size, gender, age, intervention, and outcomes.

Figure 2. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic review and Meta-analysis.



Risk of bias (RoB) assessment

The RoB was assessed by the Cochrane Risk of Bias Assessment Tool [9] from five domains (bias arising from randomization; deviations from intended interventions; missing outcome data; outcome measurement; and selected reports). The included studies were rated as "Low risk", "Some concerns", or "High risk". The RoB assessment was carried out and cross-validated by two reviewers. The two reviewers should reach an agreement before study selection and data extraction, and exclude high-risk studies. The diagram of the overall RoB is shown in Figure 1.

Data analysis

Bayesian NMAs were conducted using R4.3.2 software. The pooled estimates and probability of each intervention being the most effective were calculated by the Markov chain Monte Carlo method [10]. Model convergence was assessed by trace plots, Brooks-Gelman-Rubin plots, and potential scale reduction factor (its value less than 1.05 indicates acceptable convergence). Dichotomous outcomes were described by odds ratio (OR) with 95% credible interval (CrI). The surface under the cumulative ranking curve (SUCRA) value was calculated to estimate the probability of being the optimal intervention. The closer the SUCRA value is to 1, the higher the likelihood that an intervention is in the top rank. Network diagrams were plotted using Stata 15.0 with a pass-through macro command loaded. Each circle indicated a drug, and the edges represented existing comparisons. The size of the circles was proportional to the number of patients included. Cumulative probability plots were created using the ggplot2 package.

The parameters of the Bayesian model involved in the study are provided in Supplementary Material 3. The R code used in this study is detailed in Supplementary Material 4.

Results

A total of 859 studies were initially retrieved, of which 29 RCTs [10-38] (4402 TBM patients) were included (Figure 2, Table 1). The included studies involved 16 interventions: isoniazid, dexamethasone, prednisolone, hydrocortisone, PAS, standard-dose and high-dose rifampicin (given no consensus on the definition of high-dose rifampicin across countries, the high dose was defined as ≥ 30 mg/kg orally or the same blood drug concentration intravenously, while the standard dose was defined as < 30 mg/kg), prednisone, methylprednisolone, aspirin, clopidogrel, ciprofloxacin, gatifloxacin, levofloxacin,

Table 1. Characteristics of studies included.

Study	Year	Country	Sample size	Gender (M/F)	Mean age(years)	Intervention	Outcome
Lorber	1954	UK	isoniazid: 12; standard: 10	not report	isoniazid: 6.25; standard: 6.5	isoniazid	F1
Anderson	1957	UK	standard: 30; isoniazid: 81	not report	not report	isoniazid	F1, F2, F3, F5
OToole	1969	U.S.A.	standard: 12; Dexamethasone: 11	12/11	not report	dexamethasone	F1, F2
Ghosh	1971	India	standard: 36; prednisolone: 42; hydrocortisone : 20	not report	not report	prednisolone/hydrocortisone	F1, F3
Rahjoc	1980	India	rifampicin: 22; PAS: 19	26/15	not report	rifampicin/PAS	F1, F3, F4
Girgis	1991	Egypt	standard: 135; dexamethasone: 145	158/122	not report	dexamethasone	F1, F3
Kumarvelu	1994	India	standard: 23; dexamethasone: 24	25/22	26.9 (for both group)	dexamethasone	F1
Schoeman	1997	South Africa	standard: 71; prednisone: 70	not report	not report	prednisone	F1, F3, F5
Thwaites	2004	Vietnam	standard: 271; dexamthasone: 274	331/214	standard: 35.0; dexamethasone: 36.0	dexamthasone	F1, F2, F3
Malhotra	2009	India	standard: 32; dexamethasone: 32; methylprednisolone: 33	43/48	standard: 32.87; dexamethasone: 31.97; methylprednisolone: 30.00	Dexamethasone / methylprednisolone	F1, F2, F4, F5
Misra	2010	India	standard: 59; Aspirin: 59	65/53	standard: 35.4; aspirin: 31.7	aspirin	F1
Schoeman	2011	South Africa	standard: 50; aspirin: 125	84/91	placebo: 27 months; low dose: 30; high dose: 19; pretreated: 37	aspirin	F1, F3
Thwaites	2011	Vietnam	standard: 15; Ciprofloxacin: 16; Gatifloxacin: 15; Levofloxacin: 15	36/25	standard: 15; Ciprofloxacin: 16; Gatifloxacin: 15; Levofloxacin: 15	Fluoroquinolone (ciprofloxcin / levofloxcin / gatifloxacin)	F1
Torok	2011	Vietnam	standard: 271; dexamethasone : 274	331/214	dexamethasone: 36.0; ST: 35.0	dexamthasone	F1
Kalita	2014	India	levofloxacin: 60; rifampicin: 60	(67/53)	Median: levofloxacin: 39.3; rifampicin: 38.0; for both group: 34.5	levofloxacin/Rifampicin	F1, F3, F5
Heemskerk	2016	Vietnam	standard: 409; levofloxacin: 408	560/357	standard treatment: 35; intensified treatmet: 35	levofloxacin	F1, F2, F3, F4
Kalita	2016	India	standard: 28; Levofloxacin: 29	30/27	HRZE: 37.36; HRZEL: 39.17	Levofloxacin 10 mg/kg*day 6 month	F1, F2, F3, F4, F5
Amin	2017	Pakistan	standard: 81; Aspirin: 81	79/83	standard: 1-5 19; 6-10 53; 11-15 9; aspirin: 1-5 18; 6-10 53; 11-15 10	aspirin: 60mg/kg per day	F1, F5
Dian	2018	Netherland	Standard: 20; high_does_Rifampicin: 20	32/28	standard: 28; high_does_Rifampicin: 33	Rifampicin (dose)	F1, F2
Mai	2018	Vietnam	standard: 41; aspirin: 79	79/41	standard: 43; 81mg aspirin: 39; 1000mg aspirin: 40	aspirin	F1, F2, F3, F4
Misra	2018	India	standard: 18; Fludrocortisone: 18	19/17	fludrocortisone: 27; standard: 31	fludrocortisone	F1, F3
Diao	2020	China	standard: 34; Methylprednisolone: 34	not report	not report	methylprednisolone	F2, F4
Cresswell	2021	U.K.	standard: 21; high dose Rifampicin: 40	34/27	standard: 34; high dose IV R: 33.5; high dose oral Rifampicin: 32.5	rifampicin	F1, F2, F3, F4
Paradkar	2022	India	standard: 14; high_dose_Rifampicin: 12; high_dose_Rifampicin_levofloxacin: 11	23/14	high_dose_Rifampicin: 56; high_dose_Rifampicin_levofloxacin: 57; standard: 72	Rifampicin / levofloxacin	F1
Davis	2023	South Africa	standard: 15; aspirin: 16	16/0	standard: 37; aspirin: 41.5	aspirin	F1, F3
Donovan	2023	Vietnam/Indonesia	standard: 257; dexamethasone: 263	396/124	standard: 36; dexamethasone: 36	dexamethasone	F1, F2, F3, F4
Sahib	2023	India	standard: 14; linezolid : 15	14/15	standard: 28.5; Linezolid: 24	linezolid	F1, F3, F4
Bhatia	2025	India	ST: 83; Aspirin: 77; Clopidogrel: 77	98/139	ST: 28.94; Aspirin: 29.93; Clopidogrel: 30.05	Aspirin; Clopidogrel	F1, F3
Chow	2025	U.S.A.	ST: 10; linezolid: 20; high dose rifampicin: 10	18/22	ST: 33; linezolid: 39; high dose rifampicin: 38	Linezolid; high dose rifampicin	F1, F2, F3

F1: death F2: Gastrointestinal events F3: Neurological events F4: Hepatic events F5: tuberculoma and other extra-cerebrospinal tuberculosis.

fludrocortisone, and linezolid. Studies involving thalidomide were excluded because of its serious adverse events [39]. All drugs and glucocorticoids were administered at standard doses, some of which were based on the local treatment guidelines. The detailed treatment regimens are displayed in Supplementary Material 5.

Due to the limited number of studies, dosage (except rifampicin) and route of administration of all drugs were not reported, the study groups were combined [13,34], and partial data were discarded in some studies [30,36]. The reason is that some early studies prolonged the treatment cycle for some patients [3], selected different routes of administration that had been proven to achieve the same drug concentration in the cerebrospinal fluid in subsequent studies [34], selected exploratory doses that did not conform to high-dose or standard-dose rifampicin in some subgroups [30], or employed cross-experimental designs [36]. To avoid the resulting errors, we reanalyzed the dataset after removing these data (Supplementary Material 6). The results showed that the data processing of these studies did not bring about significant changes to the analysis results. Data extraction and analysis were conducted on five 3-arm RCTs [16,21,35,37,38] and one 4-arm RCT [24] in the same way as other studies after verifying that they could be normally incorporated in the analysis. Although some studies were conducted in developed countries, they included subjects from less developed countries since TBM was more prevalent in these regions. The overall quality of the included studies was assessed as high, with some as "Some concerns" for bias arising from deviations from intended interventions. The studies with missing data were finally excluded due to no response to our requests for data from the authors.

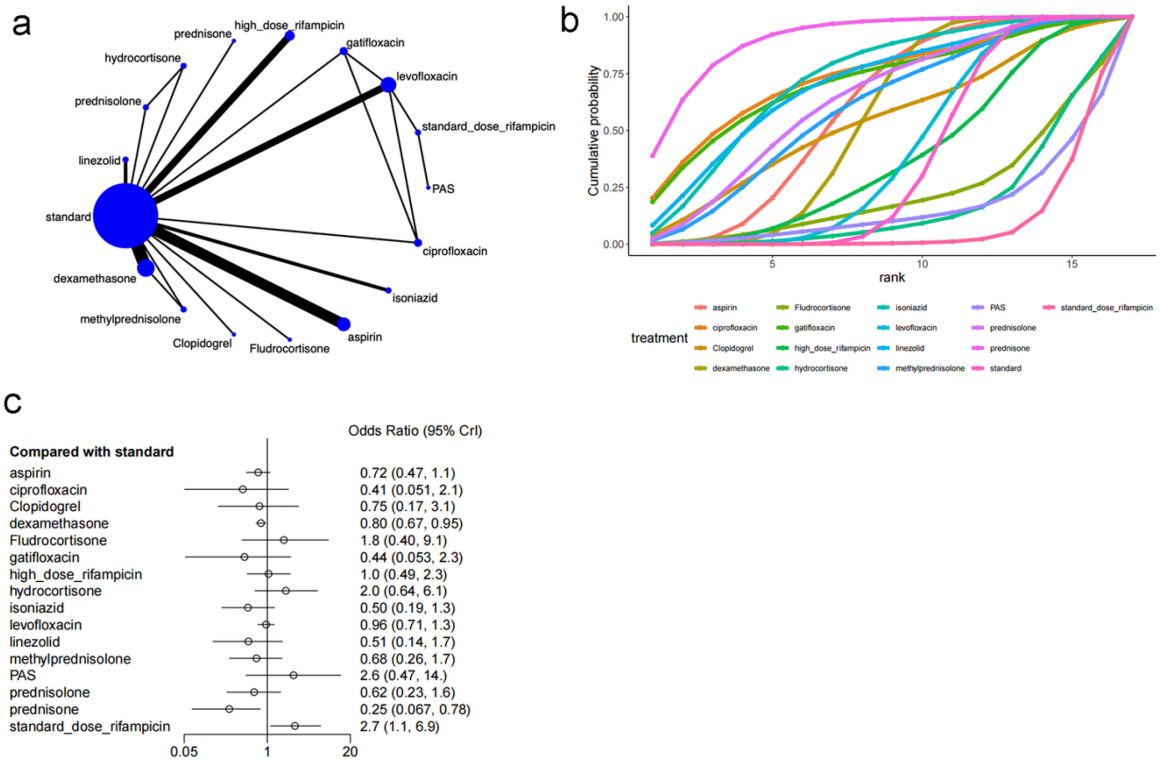
In addition, considering that only a few earlier studies on TBM treatment are available, and bias may be present in the drug combination and quality, studies published after the year 2000 were re-analyzed (Supplementary Material 7). Only two changes in the probability rankings were found (an exchange between levofloxacin and high-dose rifampicin in mortality and an exchange between standard and levofloxacin in gastrointestinal events), which were considered to have subtle impacts on the results.

Primary outcome

Mortality

The mortality was mentioned in 28 studies [11-32,34-40] (4572 TBM patients). No closed loop was formed in the network diagram (Figure 3a), so the

Figure 3. a: Network diagram for mortality; **b:** Cumulative probability ranking for mortality; graph **c:** Forest plot for mortality.



inconsistency test was not performed. Compared with the standard (Figure 3c), prednisone significantly decreased TBM mortality [OR (95% CrI) = 0.26 (0.07, 0.78)], whereas standard-dose rifampicin increased TBM mortality [OR (95% CrI) = 2.7 (1.1, 6.9)]. Levofloxacin was superior to standard-dose rifampicin in reducing TBM mortality [OR (95% CrI) = 0.35 (0.15, 0.81)], while no significant difference was detected between standard and high-dose rifampicin [OR (95% CrI) = 1.05 (0.49, 2.3)]. Meanwhile, TBM mortality was significantly increased by hydrocortisone [OR (95% CrI) = 7.8 (1.54, 44.7)] but decreased by isoniazid [OR (95% CrI) = 0.18 (0.05, 0.67)] compared with prednisone and standard-dose rifampicin (Table 2). In the league table, many drugs were inferior to prednisone in reducing TBM mortality, of which PAS [OR (95% CrI) = 10.25 (1.3, 85.91)], levofloxacin [OR (95% CrI) = 3.74 (1.17, 14.92)], hydrocortisone [OR

Table 2. League table for mortality.

OR 95% CrI																
aspirin																
1.75 (0.32, 14.59)	**ciprofloxacin**															
0.96 (0.22, 4.47)	0.54 (0.04, 5.14)	**Clopidogrel**														
0.9 (0.57, 1.43)	0.51 (0.06, 2.75)	0.94 (0.21, 3.88)	**dexamethasone**													
0.39 (0.08, 1.89)	0.22 (0.02, 2.16)	0.41 (0.05, 3.27)	0.44 (0.09, 1.99)	**Fludrocortisone**												
1.64 (0.29, 14.34)	0.93 (0.09, 10.02)	1.74 (0.18, 21.54)	1.81 (0.34, 15.48)	4.26 (0.43, 58.04)	**gatifloxacin**											
0.69 (0.28, 1.65)	0.39 (0.04, 2.45)	0.71 (0.13, 3.58)	0.76 (0.34, 1.68)	1.74 (0.32, 10.18)	0.42 (0.04, 2.64)	**high_dose_rifampicin**										
0.37 (0.11, 1.22)	0.21 (0.02, 1.57)	0.38 (0.06, 2.31)	0.4 (0.13, 1.27)	0.93 (0.14, 6.49)	0.22 (0.02, 1.69)	0.53 (0.13, 2.1)	**hydrocortisone**									
1.44 (0.5, 4.05)	0.81 (0.08, 5.59)	1.5 (0.26, 8.2)	1.6 (0.6, 4.15)	3.67 (0.61, 22.98)	0.87 (0.09, 6.01)	2.1 (0.61, 7.21)	3.94 (0.9, 17.35)	**isoniazid**								
0.75 (0.45, 1.26)	0.43 (0.05, 2.25)	0.78 (0.17, 3.3)	0.83 (0.59, 1.17)	1.91 (0.41, 9.58)	0.46 (0.05, 2.43)	1.09 (0.48, 2.53)	2.05 (0.64, 6.69)	0.52 (0.19, 1.42)	**levofloxacin**							
1.44 (0.39, 5.47)	0.81 (0.07, 6.75)	1.5 (0.22, 9.97)	1.59 (0.46, 5.74)	3.66 (0.52, 27.95)	0.87 (0.08, 7.19)	2.09 (0.49, 9.28)	3.94 (0.74, 21.74)	1 (0.21, 4.86)	1.91 (0.54, 7.07)	**linezolid**						
1.07 (0.39, 3.06)	0.6 (0.06, 4.2)	1.11 (0.2, 6.14)	1.18 (0.47, 3.12)	2.72 (0.46, 17.31)	0.65 (0.06, 4.51)	1.56 (0.46, 5.39)	2.93 (0.67, 13.07)	0.74 (0.2, 2.88)	1.42 (0.54, 3.92)	0.74 (0.15, 3.54)	**methylprednisolone**					
0.28 (0.05, 1.6)	0.16 (0.01, 1.7)	0.29 (0.03, 2.63)	0.31 (0.06, 1.7)	0.71 (0.07, 7.13)	0.17 (0.01, 1.83)	0.41 (0.06, 2.62)	0.77 (0.1, 5.93)	0.19 (0.03, 1.36)	0.37 (0.07, 1.98)	0.19 (0.02, 1.56)	0.26 (0.04, 1.81)	**PAS**				
1.16 (0.4, 3.36)	0.65 (0.07, 4.55)	1.2 (0.2, 6.71)	1.28 (0.48, 3.47)	2.94 (0.49, 18.8)	0.7 (0.07, 4.95)	1.69 (0.49, 5.88)	3.15 (1.03, 10.03)*	0.8 (0.21, 3.14)	1.54 (0.56, 4.29)	0.8 (0.16, 3.87)	1.08 (0.28, 4.18)	4.13 (0.59, 29.4)	**prednisolone**			
2.82 (0.84, 11.54)	1.61 (0.15, 13.31)	2.97 (0.45, 20.45)	3.15 (1.01, 12.23)*	7.26 (1.08, 56.59)*	1.72 (0.16, 14.78)	4.12 (1.04, 19.55)*	7.8 (1.54, 44.7)*	1.96 (0.45, 10.18)	3.74 (1.17, 14.92)*	1.98 (0.35, 11.98)	2.65 (0.6, 13.5)	10.25 (1.3, 85.91)*	2.46 (0.54, 12.66)	**prednisone**		
0.72 (0.47, 1.1)	0.41 (0.05, 2.15)	0.75 (0.17, 3.06)	0.8 (0.67, 0.95)*	1.83 (0.4, 8.94)	0.44 (0.05, 2.34)	1.05 (0.49, 2.3)	1.97 (0.64, 6.22)	0.5 (0.2, 1.31)	0.96 (0.71, 1.29)	0.5 (0.14, 1.71)	0.68 (0.26, 1.7)	2.57 (0.47, 14)	0.62 (0.23, 1.63)	0.26 (0.07, 0.78)*	**standard**	
0.27 (0.1, 0.7)*	0.15 (0.02, 0.98)*	0.28 (0.05, 1.46)	0.29 (0.11, 0.72)*	0.67 (0.11, 4.12)	0.16 (0.02, 1.05)	0.39 (0.12, 1.26)	0.72 (0.17, 3.08)	0.18 (0.05, 0.67*)	0.35 (0.15, 0.81)*	0.18 (0.04, 0.84)*	0.25 (0.06, 0.89)*	0.95 (0.22, 3.92)	0.23 (0.06, 0.85)*	0.09 (0.02, 0.4)*	0.37 (0.15, 0.89)*	**Standard dose rifampicin**

*means $p < 0.05$; OR < 1 indicates benefit.

(95% CrI) = 7.8 (1.54, 44.7)], high-dose rifampicin [OR (95% CrI) =], fludrocortisone [OR (95% CrI) = 7.26 (1.08, 56.59], and dexamethasone [OR (95% CrI) = 4.12 (1.04, 19.55)] had statistical significance. Compared with the standard, prednisone [OR (95% CrI) = 0.26 (0.07, 0.78)] and dexamethasone [OR (95% CrI) = 0.8 (0.67, 0.95)] could significantly reduce TBM mortality. Furthermore, the vast majority of drugs had statistically significant differences from standard-dose rifampicin in reducing mortality. Additionally, the SUCRA value was the highest for prednisone (90.3%), followed by linezolid (70.5%), ciprofloxacin (73.9%), gatifloxacin (71.9%), isoniazid (72.9%), prednisolone (63.8%), methylprednisolone (60.1%), aspirin (59.5%), dexamethasone (54.3%), clopidogrel (54.3%), levofloxacin (40.5%), high-dose rifampicin (37.9%), standard (36.2%), fludrocortisone (22.7%), hydrocortisone (17.2%), PAS (15.3%), and standard-dose rifampicin (8.6%) (Table 3). The cumulative probability curve of the outcome is provided in Figure 3b.

Secondary outcomes

Tuberculoma and other extracranial tuberculosis

Six studies [13,19,21,26,28,29] (688 TBM patients) reported tuberculoma and other extracranial tuberculosis. No closed loop was formed in the network diagram (Figure 4a), so the local inconsistency test was not performed. Compared with the standard (Figure 4c), methylprednisolone reduced the incidence of tuberculoma and other extracranial tuberculosis [OR (95% CrI) = 0.13 (0, 0.98)], similar to prednisone [OR (95% CrI) = 0.18 (0.02, 0.76)] (Table 4). Due to the small sample size, no heterogeneity test was performed. The SUCRA value was the highest for methylprednisolone (88.6%), followed by prednisone (85.6%), dexamethasone (72.3%), standard-dose rifampicin (43.2%), standard (40.9%), levofloxacin (35.9%), aspirin (30.0%), and isoniazid (3.5%) (Table 3). The cumulative probability curve of the outcome is provided in Figure 4b.

Neurological events

Neurological events were described in 18 studies [10,12,14-16,18,19,21,22,25-27,30,33,35-38] (3502 TBM patients). No closed loop was formed in the network diagram (Figure 5a), so the inconsistency test was not performed. Compared with the standard (Figure 5c), standard-dose rifampicin reduced the risk of neurological events [OR (95% CrI) = 0.25 (0.06, 0.78)], while prednisolone was likely to increase the risk of neurological events [OR (95% CrI) = 5.98 (2.03, 20.7)]. The results of heterogeneity tests revealed a significant difference between prednisolone and standard [OR

Figure 4. a: Network diagram for tuberculoma and other extracranial tuberculosis; **b:** Cumulative probability ranking for tuberculoma and other extracranial tuberculosis.

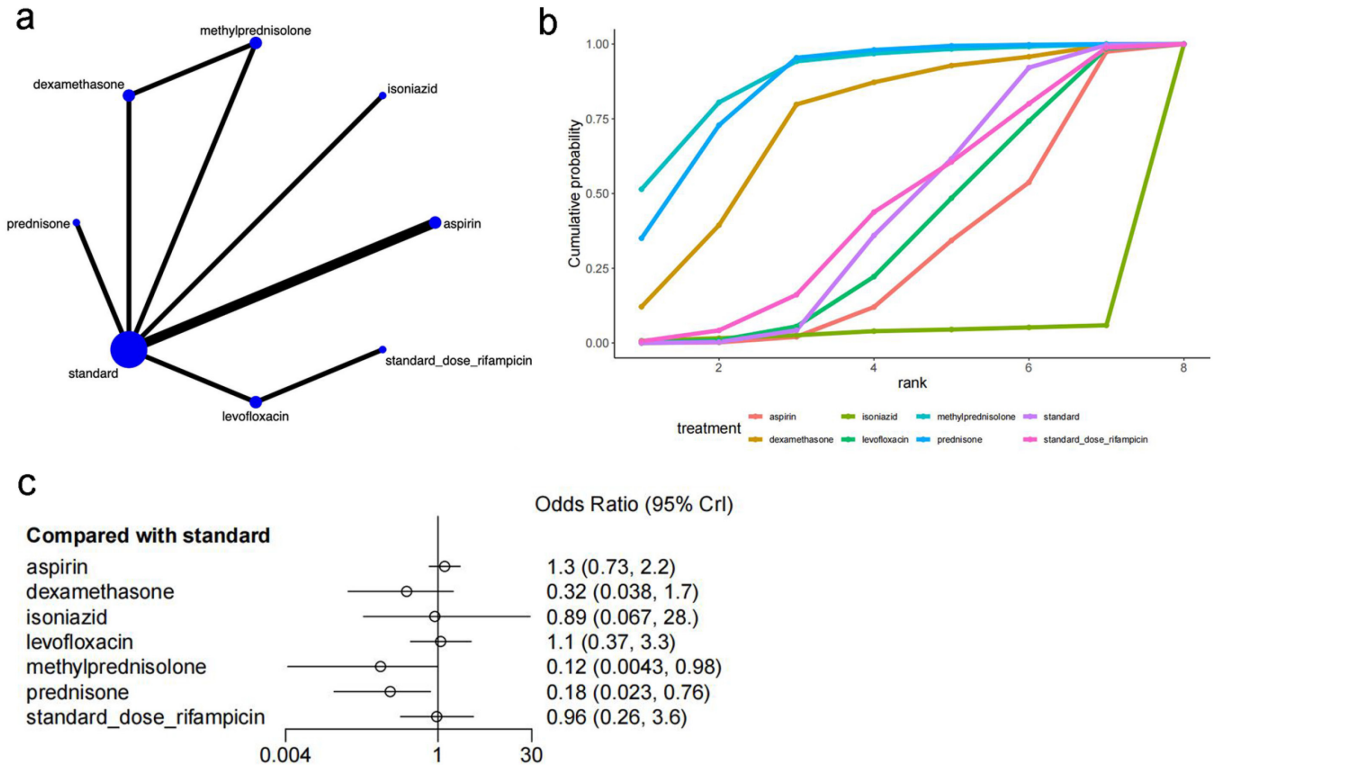


Table 3. Cumulative probability ranking.

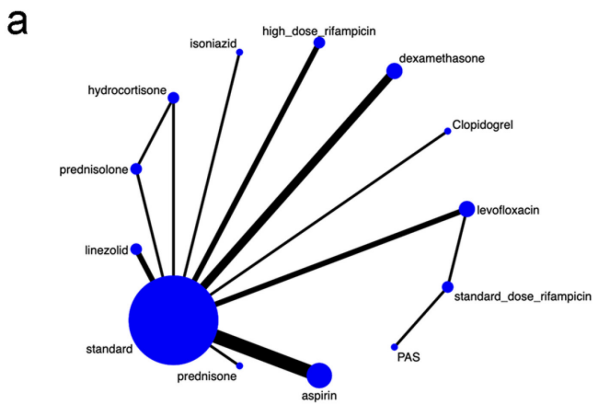
Treatment	Mortality(%)	Gastrointestinal events (%)	Neurological events (%)	Hepatic events (%)	Tuberculoma and other extra-cerebrospinal tuberculosis (%)
Aspirin	59.5	79.1	54.8	64.6	30.0
Ciprofloxacin	73.9				
Clopidogrel	54.3		65.4		
Dexamethasone	54.3	30.6	58.3	39.4	72.3
Fludrocortisone	22.7				
Gatifloxacin	71.9				
High_Dose_Rifampicin	37.9	46.2	53.1	58.3	
Hydrocortisone	17.2		44.9		
Isoniazid	72.9	48.8	43.2		3.5
Levofloxacin	40.5	57.0	28.3	11.1	35.9
Linezolid	70.5	1.8	60.3	67.6	
Methylprednisolone	60.1	70.6		57.0	88.6
PAS	15.3		56.7		
Prednisolone	63.8		8.7		
Prednisone	90.3		44.2		85.6
Standard	36.2	65.9	44.7	51.9	40.9
standard_dose_rifampicin	8.6		95.2		43.2

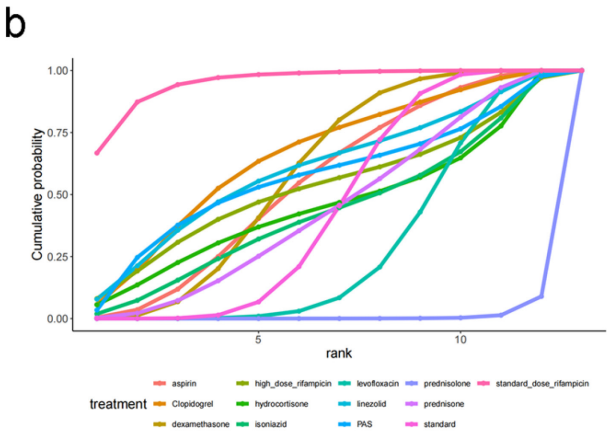
Table 4. League table for tuberculoma and other extra-cerebrospinal tuberculosis.

OR 95% CrI								
aspirin								
3.97 (0.66, 35.83)	**dexamethasone**							
1.43 (0.04, 20.07)	0.34 (0.01, 7.82)	**isoniazid**						
1.16 (0.34, 4)	0.29 (0.03, 2.24)	0.82 (0.05, 29.99)	**levofloxacin**					
10.26 (1.21, 312.7)	2.58 (0.19, 85.2)	8.15 (0.26, 841.69)	9.04 (0.83, 302.96)	**methylprednisolone**				
7.41 (1.51, 63.08)	1.89 (0.14, 26.17)	5.56 (0.26, 279.84)	6.48 (1, 65.4)*	0.72 (0.02, 13.04)	**prednisone**			
1.28 (0.73, 2.24)	0.32 (0.04, 1.74)	0.89 (0.07, 28.18)	1.1 (0.37, 3.34)	0.13 (0, 0.98)*	0.18 (0.02, 0.76)*	**standard**		
1.33 (0.32, 5.62)	0.33 (0.03, 2.91)	0.94 (0.05, 36.71)	1.15 (0.56, 2.38)	0.13 (0, 1.55)	0.18 (0.02, 1.33)	1.04 (0.28, 3.92)	**standard_dose_rifampicin**	

*means $p < 0.05$; OR < 1 indicates benefit.

Figure 5. a: Network diagram for neurological events; **b:** Cumulative probability ranking for neurological events; **c:** Forest plot for neurological events.





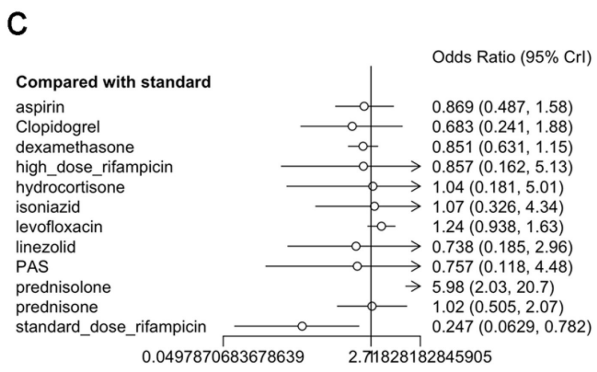


Table 5. League table for neurological events.

OR 95% CrI											
aspirin											
1.28 (0.4, 4.27)	**Clopidogrel**										
1.02 (0.53, 1.99)	0.8 (0.27, 2.31)	**dexamethasone**									
1.01 (0.16, 5.83)	0.79 (0.1, 5.46)	0.99 (0.17, 5.29)	**high_dose_rifampicin**								
0.83 (0.15, 5.15)	0.65 (0.1, 4.76)	0.81 (0.16, 4.67)	0.83 (0.08, 9.47)	**hydrocortisone**							
0.81 (0.18, 3.14)	0.63 (0.11, 3.07)	0.8 (0.19, 2.75)	0.8 (0.09, 6.82)	0.96 (0.11, 7.24)	**isoniazid**						
0.7 (0.37, 1.36)	0.55 (0.19, 1.57)	0.69 (0.46, 1.03)	0.69 (0.13, 4.17)	0.85 (0.15, 4.26)	0.87 (0.25, 3.59)	**levofloxacin**					
1.18 (0.26, 5.26)	0.92 (0.16, 5.11)	1.16 (0.28, 4.7)	1.17 (0.13, 10.8)	1.41 (0.16, 11.86)	1.47 (0.23, 10.19)	1.68 (0.41, 6.84)	**linezolid**				
1.15 (0.17, 8.21)	0.9 (0.11, 7.4)	1.13 (0.18, 7.41)	1.15 (0.1, 14.61)	1.39 (0.12, 16.11)	1.45 (0.16, 14.36)	1.64 (0.28, 10.29)	0.98 (0.1, 9.84)	**PAS**			
0.14 (0.04, 0.5)*	0.11 (0.02, 0.5)*	0.14 (0.04, 0.44)*	0.14 (0.02, 1.13)	0.17 (0.04, 0.65)*	0.18 (0.03, 1.03)	0.2 (0.06, 0.63)*	0.12 (0.02, 0.72)*	0.12 (0.01, 1.02)	**prednisolone**		
0.85 (0.34, 2.14)	0.66 (0.19, 2.31)	0.83 (0.39, 1.78)	0.84 (0.14, 5.59)	1.03 (0.16, 5.82)	1.05 (0.26, 4.96)	1.21 (0.57, 2.57)	0.72 (0.15, 3.44)	0.74 (0.1, 5.07)	5.94 (1.62, 24.37)*	**prednisone**	
0.87 (0.49, 1.58)	0.68 (0.24, 1.88)	0.85 (0.63, 1.15)	0.86 (0.16, 5.13)	1.04 (0.18, 5.01)	1.07 (0.33, 4.34)	1.24 (0.94, 1.63)	0.74 (0.19, 2.96)	0.76 (0.12, 4.48)	5.98 (2.03, 20.7)*	1.02 (0.51, 2.07)	**standard**
3.53 (0.96, 15.7)	2.77 (0.58, 14.9)	3.45 (1.05, 14.01)*	3.55 (0.46, 32.04)	4.31 (0.53, 34.5)	4.42 (0.81, 30.14)	4.99 (1.63, 19.15)*	3.03 (0.49, 20.74)	3.07 (0.85, 11.97)	24.92 (4.91, 153.37)*	4.16 (1.07, 19.07)*	4.05 (1.28, 15.9)*

*means $p < 0.05$; OR < 1 indicates benefit.

(95% CrI) = 5.98 (2.03, 20.7)], hydrocortisone and prednisolone [OR (95% CrI) = 0.17 (0.04, 0.65)], and levofloxacin and standard-dose rifampicin [OR (95% CrI) = 0.35 (0.15, 0.81)]. The results suggested that both prednisolone and levofloxacin may increase the incidence of neurological events when combined with the standard treatment, and standard-dose rifampicin may have better neurosafety than levofloxacin. As shown in the league table (Table 5), the vast majority of drugs showed higher neuro-safety than prednisolone, while the neuro-safety of standard-dose rifampicin was higher than most drugs (including aspirin, dexamethasone, levofloxacin, prednisolone, and prednisone). The SUCRA value was the highest for standard-dose rifampicin (95.2%), followed by clopidogrel (65.4%), linezolid (60.3%), dexamethasone (58.3%), PAS (56.7%), aspirin (54.8%), high-dose rifampicin (53.1%), hydrocortisone (44.9%), standard (44.7%), prednisone (44.2%), isoniazid (43.2%),

Figure 6. a: Network diagram for gastrointestinal events; **b:** Cumulative probability ranking for gastrointestinal events; **c:** Forest plot for gastrointestinal events.

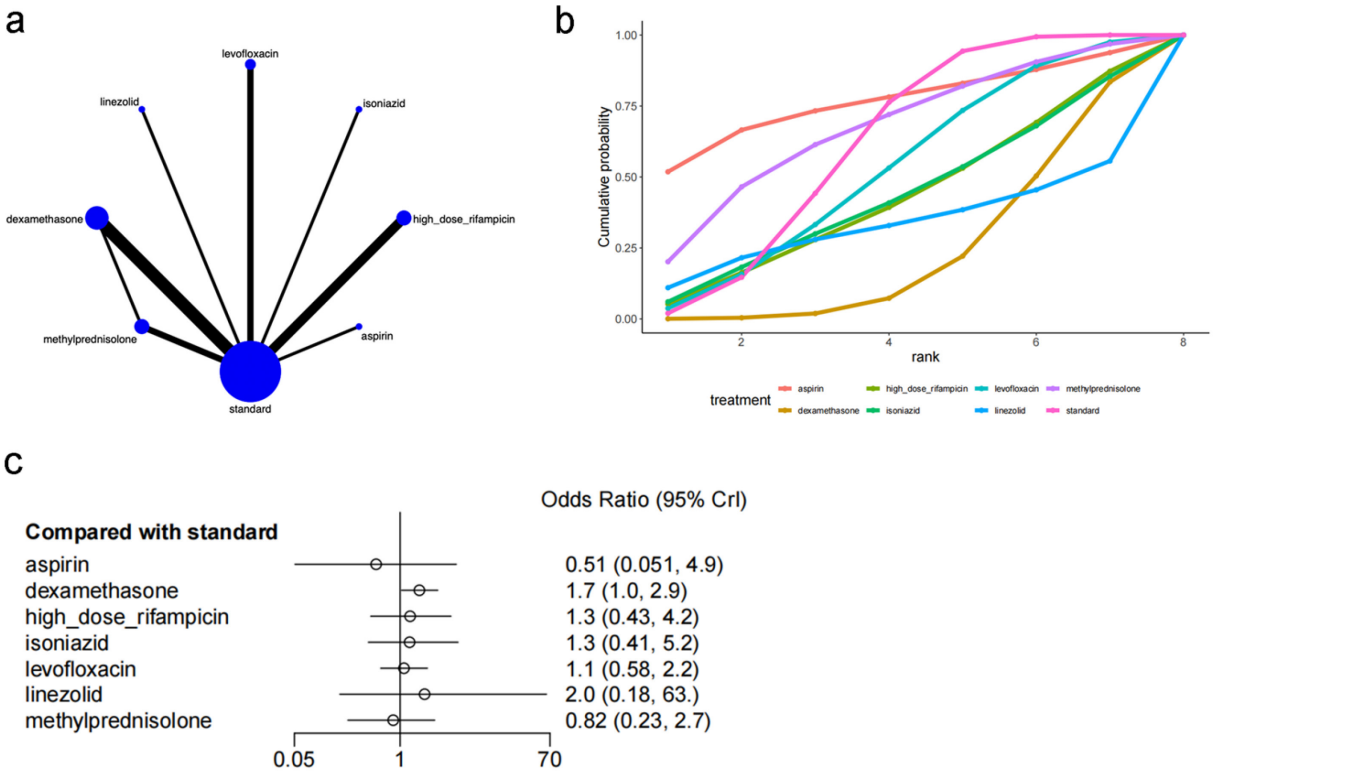


Figure 7. Local inconsistency test of gastrointestinal events.

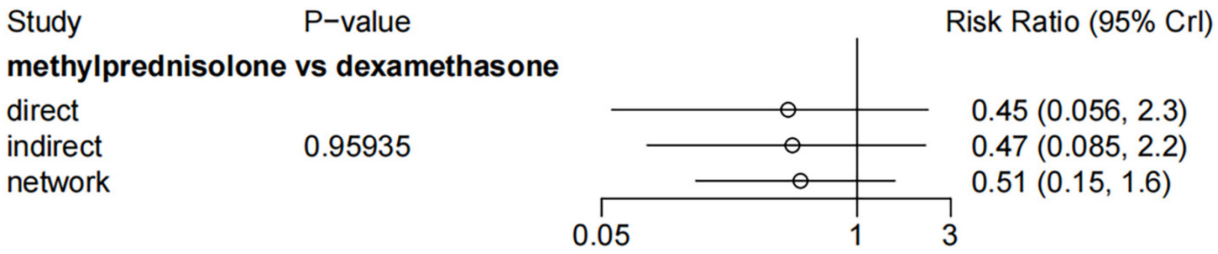


Figure 8. a: Network diagram for hepatic events; **b:** Cumulative probability ranking for hepatic events; **c:** Forest plot for hepatic events.

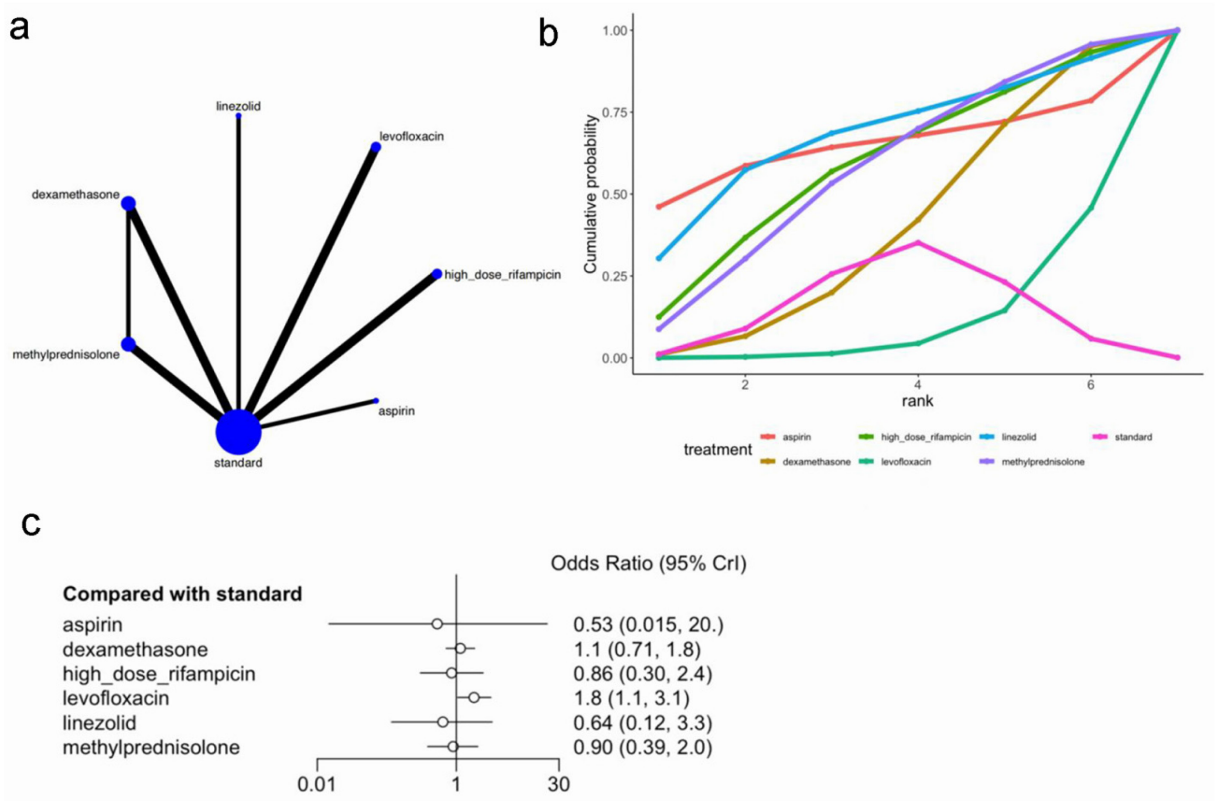


Figure 9. Local inconsistency test of hepatic events.

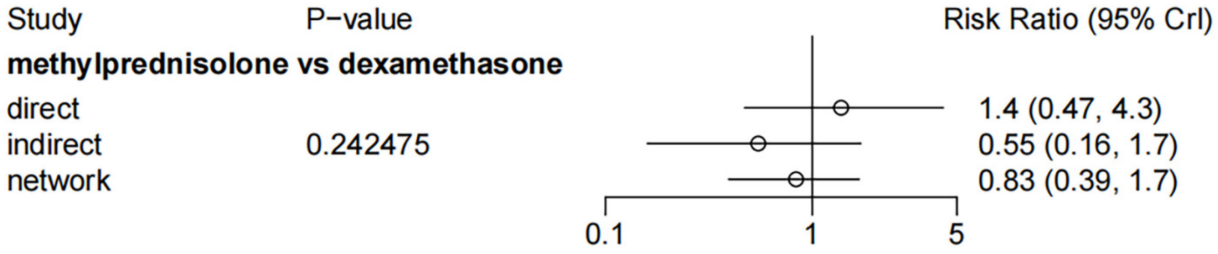


Table 6. League table for gastrointestinal events.

OR 95% CrI							
aspirin							
0.29 (0.03, 3)	**dexamethasone**						
0.38 (0.03, 4.71)	1.29 (0.37, 4.49)	**high_dose_rifampicin**					
0.38 (0.03, 4.92)	1.31 (0.3, 4.74)	1.01 (0.17, 5.28)	**isoniazid**				
0.45 (0.04, 4.8)	1.54 (0.67, 3.58)	1.2 (0.32, 4.52)	1.18 (0.31, 5.41)	**levofloxacin**			
0.24 (0, 6.79)	0.86 (0.03, 10)	0.66 (0.02, 9.55)	0.65 (0.02, 10.42)	0.56 (0.02, 6.65)	**linezolid**		
0.61 (0.05, 8.18)	2.09 (0.61, 7.87)	1.62 (0.31, 8.96)	1.62 (0.3, 10.23)	1.35 (0.35, 5.72)	2.49 (0.17, 96.64)	**methylprednisolone**	
0.5 (0.05, 4.93)	1.72 (1.04, 2.91)*	1.33 (0.43, 4.21)	1.31 (0.41, 5.2)	1.12 (0.58, 2.18)	2 (0.18, 63.19)	0.82 (0.23, 2.67)	**standard**

*means $p < 0.05$; OR < 1 indicates benefit.

levofloxacin (28.3%), and prednisolone (8.7%) (Table 3). The cumulative probability curve of the outcome is provided in Figure 5b.

Gastrointestinal events

Gastrointestinal events were described in 12 studies [11,13,14,20,21,27,28,30-33,38] (2499 TBM patients). A closed loop was formed in the network diagram (Figure 6a), so inconsistency tests were performed. The results indicated no significant inconsistency among direct comparison, indirect comparison, and network comparison (all $p > 0.05$, Figure 7). In addition, as shown in the league table (Table 6) and the tree diagram (Figure 6c), dexamethasone significantly increased the incidence of gastrointestinal events [OR (95% CrI) = 1.72 (1.04, 2.91)] compared with standard. The SUCRA value was the highest for aspirin (79.1%), followed by methylprednisolone (70.6%), standard (65.9%), levofloxacin (57.0%), isoniazid (48.8%), high-dose rifampicin (46.2%), dexamethasone (30.6%), and linezolid (1.8%) (Table 3). The cumulative probability curve of the outcome is provided in Figure 6b.

Hepatic events

Hepatic events were mentioned in 10 studies [11,16,21,27,28,30,31,33,34,40] (1850 TBM patients). A closed loop was formed in the network diagram (Figure 8a), so inconsistency tests were carried out. The results indicated no significant inconsistency among direct comparison, indirect comparison, and network comparison (Figure 9). Compared with the standard (Figure 8c), levofloxacin was associated with a higher incidence of hepatic events [OR (95% CrI) = 1.79 (1.05, 3.14)], while other drugs displayed no statistically significant difference. Meanwhile, other drugs displayed no statistically significant difference in the league table (Table 7). Similarly, the results of heterogeneity tests revealed no significant heterogeneity among studies. The SUCRA value was the highest for linezolid (67.6%), followed by aspirin (64.6%), high-dose rifampicin (58.3%), methylprednisolone (57.0%), standard (51.9%), dexamethasone (39.4%), and levofloxacin (11.1%) (Table 3). The cumulative probability curve of the outcome is provided in Figure 8b.

Publication bias

The publication bias was assessed for the primary and secondary outcomes using funnel plots. The results indicated less publication bias in studies on tuberculoma and other extracranial tuberculosis, and hepatic events (Figure 10). The DIC values of the model are provided in Supplementary Material 3.

Discussion

This NMA included 29 RCTs to assess the efficacy of different drug therapies for reducing TBM mortality and incidence of gastrointestinal, neurological, and hepatic events, tuberculoma, and other extracranial tuberculosis.

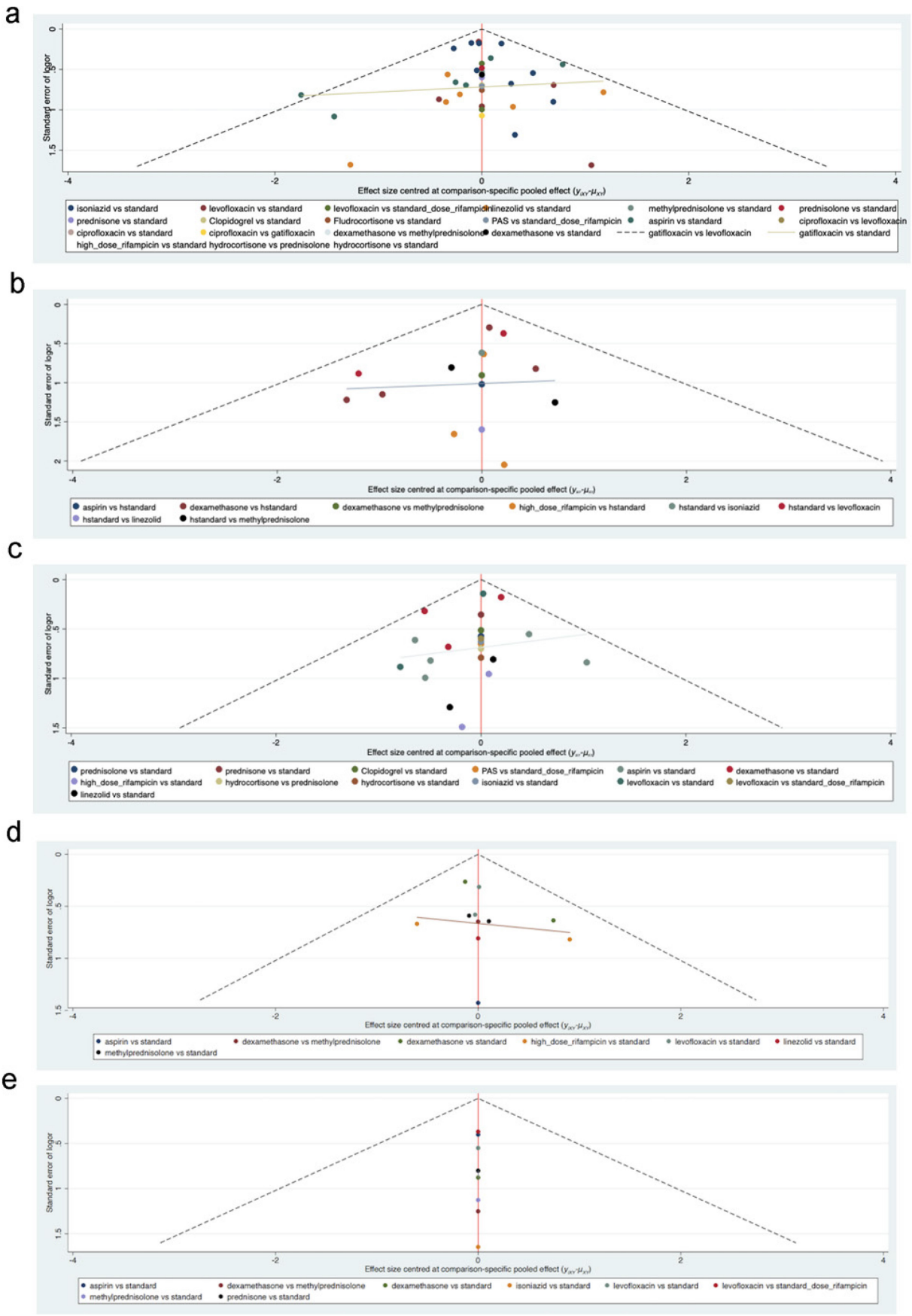
Although the SUCRA ranking is a measure of the relative probability of each intervention being the best option, it alone cannot imply clinical superiority but can only serve as a reference, particularly when CrIs overlap. The SUCRA ranking indicated that prednisone (90.3%) had the highest relative probability of being the most effective intervention for reducing TBM mortality. This finding aligns with the direct evidence from pairwise comparisons that prednisone significantly reduced TBM mortality compared with the standard [OR (95% CrI) = 0.26 (0.07, 0.78)]. Consistently, a previous single-center study in China

Table 7. League table for hepatic events.

OR 95%CrI						
aspirin						
0.47 (0.01, 17.34)	**dexamethasone**					
0.62 (0.02, 26.01)	1.34 (0.42, 4.15)	**high_dose_rifampicin**				
0.3 (0.01, 11.14)	0.64 (0.31, 1.3)	0.48 (0.15, 1.56)	**levofloxacin**			
0.84 (0.02, 44.19)	1.79 (0.33, 10.35)	1.35 (0.2, 9.79)	2.82 (0.5, 16.77)	**linezolid**		
0.59 (0.02, 23.16)	1.26 (0.53, 3.11)	0.95 (0.25, 3.66)	1.99 (0.74, 5.45)	0.71 (0.11, 4.45)	**methylprednisolone**	
0.53 (0.02, 20.41)	1.14 (0.71, 1.83)	0.86 (0.3, 2.44)	1.79 (1.05, 3.14)*	0.64 (0.12, 3.28)	0.90 (0.39, 2.06)	**standard**

*means $p < 0.05$; OR < 1 indicates benefit.

Figure 10. a: Funnel plot for mortality; **b:** Funnel plot for gastrointestinal events; **c:** Funnel plot for neurological events; **d:** Funnel plot for hepatic events; **e:** Funnel plot for tuberculoma and other extracranial tuberculosis.



[41] indicated that prednisone at 30-90 mg/d can improve the prognosis of TBM, but its efficacy is limited when its dose exceeds 120 mg/d. The WHO recommends prednisone and dexamethasone [6] as therapeutic drugs for TBM. Although the effect of glucocorticoids on the short-term mortality of TBM has been explained in previous literature [42], there is a lack of reliable cross-sectional comparative studies on glucocorticoid preparations. Dexamethasone is usually the preferred drug for TBM in the current treatment guidelines [6,43] due to its intravenous route of administration, which can prevent the reduction of absorption caused by vomiting, and maintain long-term blood drug concentration. Although dexamethasone has stronger biological activity than prednisone [44], its therapeutic effect is not superior to prednisone, as revealed by some previous studies on immune diseases (such as asthma) [45]. Prednisone remains the most frequently prescribed oral glucocorticoid worldwide, particularly in resource-limited settings. As an inactive prodrug requiring hepatic conversion to active prednisolone [46], the delayed pharmacokinetic profile of prednisone results in a more gradual plasma concentration-time curve compared with intravenous formulations. This characteristic, combined with its oral accessibility and low cost, significantly enhances patient compliance in developing countries. Importantly, prednisolone possesses moderate blood-brain barrier penetration, achieving required drug concentrations in the cerebrospinal fluid for neuroinflammatory conditions like TBM. If confirmed, transitioning to oral prednisone in resource-limited settings can improve accessibility while reducing costs by 80%-90% compared with intravenous formulations, which is a critical advantage in TB-endemic regions accounting for 85% of TBM deaths [6]. In addition, hyponatremia and cerebral salt wasting are common complications of TBM, and they are treated with appropriate mineralocorticoid [47] that can antagonize sodium loss by inhibiting the renin angiotensin-aldosterone system. Considering certain mineralocorticoid receptor [46] activity in prednisone, its value in preventing or treating complications deserves further research and evaluation. In addition, linezolid ranked highly (SUCRA 74.6%) for potentially reducing mortality. However, the primary results did not highlight direct comparative evidence from league tables or forest plots that linezolid achieved a significant mortality reduction compared with the standard, necessitating caution. The excellent blood-brain barrier permeability of linezolid has been confirmed in some recent pharmacokinetic studies [48,49], suggesting that it holds great potential as a treatment for TBM. Similarly, a previous retrospective study conducted in Shenzhen, China, showed that linezolid can reduce TBM mortality caused by drug-resistant Mycobacterium tuberculosis infection [50]. Moreover, ciprofloxacin (SUCRA 73.9%) and gatifloxacin (SUCRA 71.0%) also ranked highly for reducing mortality. The clinical significance of these rankings requires careful consideration along with the primary effect estimates and CrIs, particularly where direct comparisons may show overlapping CrIs. A meta-analysis (2018) found no significant evidence that quinolones added decreased mortality, but a study (2015) showed that patients with moderate or high cerebrospinal fluid exposure to quinolone have a decreased incidence of adverse outcomes compared with those with low exposure [24]. Similarly, in a clinical study conducted in China (2015), after fluoroquinolone (moxifloxacin) was used for treating refractory TBM, the cerebrospinal fluid biochemical improvement and HAMA scores of the experimental group were significantly superior to those of the control group [51]. Fluoroquinolones exhibit a unique antibacterial mechanism by specifically targeting bacterial type II topoisomerases, primarily DNA gyrase and topoisomerase IV. By binding to enzyme-DNA complexes, they stabilize DNA break intermediates, prevent break-end reconnection, and induce double-strand DNA breaks. These fragmented DNA segments disseminate throughout chromosomes, halting DNA replication and ultimately exerting potent bactericidal effects [52]. Given the significant burden of drug-resistant TB in endemic regions [53], optimized regimens are crucial. Consequently, clinical guidelines such as Spain's 2020 TB Treatment Guidelines recommend fluoroquinolones for drug-resistant TB [54]. A 2016 meta-analysis demonstrated that fluoroquinolone supplementation increases sputum culture conversion rates despite an elevated incidence of adverse events. Critically, most fluoroquinolones exhibit excellent blood-brain barrier permeability [55]. Our data also prioritized the use of these blood-brain barrier-penetrating agents, consistent with India's 2021 TB guidelines [56]. Finally, high-dose rifampicin (41.9%) did not significantly reduce mortality compared with the standard (36.2%), consistent with the findings of a meta-analysis (2021) that exposure to high-dose rifampicin is not associated with decreased mortality [57].

According to the SUCRA rankings, methylprednisolone (88.6%), prednisone (85.6%), and dexamethasone (72.3%) were the top three

interventions for reducing the incidence of tuberculoma/extracranial TBM. This aligns with the direct evidence that methylprednisolone and prednisone significantly reduced TBM incidence compared with the standard. However, interpreting these SUCRA values requires caution due to a very small sample size (n = 688) for this outcome, resulting in an extreme value (e.g., CrI [0, 0.98] for methylprednisolone) and considerable uncertainty. An early study [58] suggested that corticosteroids may ameliorate the outcome of tuberculoma by modulating inflammation and reducing intracranial pressure. As shown in the league table, levofloxacin might increase the incidence of tuberculoma and other extracranial tuberculosis compared with prednisone [OR (95% CrI) = 6.48 (1, 65.4)], while methylprednisolone [OR (95% CrI) = 0.13 (0, 0.98)] or prednisone [OR (95% CrI) = 0.18 (0.02, 0.76)] might reduce such incidence when combined with the standard treatment. However, the small sample size rendered these estimates imprecise. Glucocorticoids can inhibit the proliferation of capillaries and reduce the deposition of collagen, thereby suppressing the formation of granulomas. Despite immunosuppressive functions, the effect of glucocorticoids still requires further clinical evidence. Given that tuberculoma is a major cause of TBM-related epilepsy in endemic regions [59], our data support the immediate administration of corticosteroids when neuroimaging indicates a risk of granuloma formation, particularly in TB-endemic countries (> 300 per 100,000) where diagnostic delays are often significant. However, due to the limited number of included studies, we did not find a statistically significant difference in the comparison.

Although previous studies have found that linezolid may cause a range of neurological events [60], including serotonin syndrome, this NMA suggested a potentially favorable neuro-safety profile for linezolid for treating TBM, reflected in its third place in SUCRA ranking (60.3%). This aligns with the findings from the league table that linezolid caused no significant increase in neurological events compared with other drugs, and it significantly reduced TBM incidence compared with prednisolone [OR (95% CrI) = 0.12 (0.02, 0.72)]. In the included studies, linezolid was administered at 600 mg once daily (QD) for a short duration (typically 28 days). Some of the latest clinical articles have pointed out that the prolonged treatment cycle is a major risk factor for neurological events triggered by linezolid [61]. The main target of linezolid is the 23S rRNA of bacterial ribosomes. However, the human mitochondrial ribosome (16S rRNA) is highly homologous to the bacterial 23S rRNA. Therefore, the dose accumulation caused by long-term drug use will simultaneously inhibit mitochondrial protein synthesis [47], and short-term use is safe, as further validated by this study. Standard-dose rifampicin demonstrated better neuro-safety than many other drugs, as shown in the league table (Table 5), but some studies [62] have shown that a conventional dose of 10 mg/kg produces minimal cerebrospinal fluid exposure, and a dose of 40 mg/kg will achieve 65% maximum effective exposure. This mechanism may underlie the finding that standard-dose rifampicin was associated with the lowest risk of neurological events in the direct comparisons [e.g., OR (95% CrI) = 0.25 (0.06, 0.78) vs. standard], reflected in its highest SUCRA value (95.2%). In addition, dexamethasone (64.0%) also appeared to trigger fewer neurological events (especially compared with other glucocorticoid preparations). Given that standard-dose rifampicin performed poorly in reducing TBM mortality, it seems that excessive expectations should not be placed on it for treating TBM.

Additionally, aspirin was associated with fewer gastrointestinal events (SUCRA 73.0%). The possible reason is that aspirin is typically used for treating TBM for a short time, and the resulting gastrointestinal ulcers are more common due to its long-term use, making adverse events less significant in the combination therapy. Methylprednisolone (61.0%) and levofloxacin (57.8%) also performed well in this respect.

For hepatic safety, linezolid had the highest SUCRA value (67.6%), consistent with previous large-scale studies. According to a worldwide study of drug safety (2003), "there was no evidence to suggest any clinically significant untoward effects of linezolid on the liver" [63]. The analysis results on aspirin were also consistent with the current consensus [64], suggesting that aspirin is friendly to liver function. Besides, high-dose rifampicin exhibited higher hepatic safety. Consistent with this NMA, a meta-analysis (2021) [65] indicated that the incidence of grade 3 and 4 hepatotoxicity has no statistically significant difference for high-dose rifampicin. The analysis results must be validated through larger-scale clinical trials.

This study still had limitations as follows: First, an incomplete blinding method was adopted among the studies, and many of the studies were open-ended. Second, the interventions could not be classified according to the specific dosage and usage in some studies. Although the vast majority of studies claimed to use standard doses of corresponding drugs or under certain definitions, the definitions of standard doses had slight differences across regions. Therefore, except for

rifampicin (standard-dose and high-dose), the drug doses were heterogeneous, making it impossible to explore the most applicable dose. Third, the synergistic and antagonistic effects of the drug combination were not investigated. Fourth, the most appropriate time and duration of medication could not be determined. Fifth, few studies are available on TBM worldwide compared with other types of tuberculosis, which led to smaller sample sizes for some drugs and might result in variations in statistical results. Finally, like most similar studies, the certainty of evidence was not evaluated using the GRADE system. Furthermore, these limitations (particularly dose heterogeneity and small sample sizes for specific interventions and outcomes) directly impacted the precision of effect estimates and the reliability of SUCRA rankings. Therefore, rankings should not be equated with proven clinical superiority, especially where CrIs overlap substantially.

Conclusions

This NMA revealed the efficacy and safety of drug therapies for treating TBM: Prednisone reduced TBM mortality (OR = 0.26), while high-dose rifampicin showed no benefits (OR = 1.05), and levofloxacin outperformed standard-dose rifampicin (OR = 0.35); the risk of neurological events was decreased by standard-dose rifampicin (OR = 0.25) but increased by prednisolone (OR = 5.98); dexamethasone raised the incidence of gastrointestinal events (OR = 1.72), and levofloxacin was more likely to cause hepatic events (OR = 1.79); methylprednisolone (OR = 0.13) and prednisone (OR = 0.18) protected against tuberculoma/extracranial TBM. Limitations included the limited number of included studies and baseline heterogeneity. Future validation may enable global consensus on TBM treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Authors contributions

All authors contributed to the study conception and design. Writing - original draft preparation: Mengyu Luan; Writing - review and editing: Mengyu Luan, Xiaoyou Chen; Conceptualization: Mengyu Luan, Xiaoyou Chen; Methodology: Mengyu Luan; Formal analysis and investigation: Mengyu Luan; Supervision: Xiaoyou Chen, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript**.**

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Conflict of interest

No conflict of interest is declared.

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