

Clinical Efficacy of a Combination of Thymopentin and Antituberculosis Drugs in Treating Drug-Resistant Pulmonary Tuberculosis: Meta Analysis

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Objective: To make a systematic evaluation of the clinical efficacy of thymopentin combined with antituberculous drugs in treating drug-resistant pulmonary TB (PTB).

Methods: Relevant studies were retrieved from PubMed, Embase, Cochrane Library, Chinese Biomedical Literature Database, CNKI, and Wanfang Database. STATA software was used to evaluate the differences in focal absorption rate, the time to cough symptom remission, sputum culture-negative rate, CD3⁺ T, CD4⁺ T, and CD8⁺ T cell levels after treatment.

Results: A total of 23 randomized controlled trials literature involving 2031 cases were included. Meta-analysis revealed that compared with conventional therapy, the sputum culture-negative rate was significantly increased after 2–3 months and 6–9 months of treatment and the whole course of combined thymopentin treatment. The risk ratio (RR, 95% CI) was 1.44 (1.26–1.64), 1.47 (1.21–1.78), and 1.27 (1.18–1.36), respectively. In the combined thymopentin treatment group, the focal absorption rate was higher, with RR (95% CI) = 1.36 (1.25–1.47), the time of cough remission was shortened, with WMD (95% CI) = -9.46d (-10.36, -8.57) and the differences were all statistically significant. Combined thymopentin therapy could effectively improve the levels of CD3⁺ T and CD4⁺ T lymphocytes in patients with drug-resistant PTB after 2–3 months, 6–9 months of treatment. The WMD (95% CI) were 9.96% (7.84, 12.08), 4.68% (2.90, 6.47) and 10.26% (7.81, 12.71), 7.21% (6.28, 8.15), respectively, and could also reduce the level of CD8⁺ T lymphocytes after 2–3 months and 6–9 months of treatment. The WMD (95% CI) were -4.06% (-4.96, -3.13), -3.52%, (-4.07, -2.98), respectively, and the differences were all statistically significant.

Conclusion: Thymopentin adjuvant treatment for drug-resistant PTB can promote the therapeutic effect and improve the immune indexes in patients with drug-resistant PTB.

Keywords: thymopentin, drug resistance, pulmonary TB, immunity, meta-analysis

Introduction

Tuberculosis (TB), especially drug-resistant TB, is an infectious disease seriously endangering human health. In 2019, it was estimated that there were approximately 465,000 new patients with drug-resistant TB/rifampicin-resistant TB worldwide, accounting for 44% of the total cases of TB.¹ Drug-resistant TB has a complex treatment regimen, long course of treatment, and poor efficacy, which makes global TB control an enormous challenge.²

Studies have shown that the level of CD4⁺ in peripheral blood of patients with multiple drug-resistant tuberculosis (MDR-TB) and its production of γ -IFN are significantly lower than those of patients with non-drug-resistant tuberculosis,

while the level of IL-4 produced by CD4⁺ is significantly higher.^{3,4} With the aggravation of pulmonary tuberculosis, CD4⁺ in peripheral blood decreased, CD8⁺ increased and CD4⁺/CD8⁺ decreased. It is also reported that the cytotoxicity of CD8⁺ in patients with MDR-TB is significantly increased, the Th1 type cellular immune response is weakened, while the activity of regulatory T cells is enhanced, and the cellular immune response is shifted to Th2 type.⁵ Similarly, studies have shown that the wider the void scope of tuberculosis patients, the lower the peripheral blood CD4⁺ and CD4⁺/CD8⁺, and the higher the CD8⁺. This indicates that with the enhancement of CD8⁺ and its cytotoxic activity, tissue damage is further aggravated, and the scope of lung cavity is gradually increased.⁶

MDR-TB patients have certain immune characteristics. However, the cellular immune mechanism of TB, especially drug-resistant TB, is perplexing. In view of the current literature reports, it is indicated that the severity of drug-resistant tuberculosis is closely related to the level of immune cells in patients. Giving these patients immune intervention is expected to improve the curative effect of patients. In recent years, the immunotherapy of drug-resistant pulmonary TB (PTB) has attracted much attention. Effective immunotherapy can kill intracellular bacteria and persistent bacteria by stimulating the immune cells [T cells, natural killer cells (NK)] in the body.⁷ Literature has reported that many immune agents have achieved good efficacy in the treatment of drug-resistant tuberculosis.⁸ Thymopentin, as an immunomodulator, is a synthetic 5-peptide fragment. The fragment is a peptide chain fragment composed of five amino acids of thymic hormone isolate, which has all the functions of thymopoietin II.⁹ After entering the body, it can enhance the production of thymic T lymphocytes, promote the differentiation and maturation of T lymphocytes, improve the production level of a variety of lymphokines and interferon, and regulate and enhance the cellular immune function of the body.¹⁰ In China, thymopentin has been used by clinicians in the treatment of TB, especially in drug-resistant TB, but there is no further medical evidence for its application. Therefore, this study systematically reviewed the relevant literature on thymopentin in treating drug-resistant PTB to provide evidence for clinical treatment.

Information and Methods

1. Relevant studies were retrieved from PubMed, Embase, Cochrane Library, Chinese Biomedical Literature Database, CNKI, and Wanfang database. The English retrieval words included the following: “thymopentin,” “TB,” “drug-resistant,” “mono-drug-resistant,” “poly-drug-resistant,” “multidrug-resistant,” “pre-extensively drug-resistant,” “extensively-drug-resistant,” “rifampicin-resistant,” “MDR-TB,” “XDR-TB,” or “RR-TB.” The Chinese retrieval words include 胸腺五肽,” “结核,” “耐药,” “单耐药,” “多耐药,” “广泛耐 multidrug,” or “耐药 multidrug”.

The relevant diagnostic criteria for drug-resistant tuberculosis cited in the literature are consistent with the global tuberculosis report 2020.¹ The retrieval range of time is from the building of the databases to June 2021. In addition, the references of all the included literature were retrieved to find more qualified studies. All documents were managed by Endnote software. Following the blind principle, two researchers independently screened the literature to evaluate the eligibility of the studies. Data were extracted using standard data extraction tables, and cross-checks were performed to minimize the bias and randomization error in data analysis.

2. Inclusion and exclusion criteria: The type of study to be included must be a randomized controlled trial (RCT), and the subjects were diagnosed with drug-resistant PTB. The subjects in the observation group were treated with anti-tuberculous drugs + thymopentin. Exclusion criteria: Only the data of the latest or most comprehensive research literature were included in the literature published repeatedly or with the same data source. Review, case reports, animal studies, and in vitro studies were not included in the analysis.

3. Data extraction and quality evaluation: The extracted outcome indicators mainly include the following: focal absorption rate, the time to cough symptoms remission, the sputum culture-negative rate at 2–3 months, 6–9 months, and the end of the whole course of treatment, and values of CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells at 2–3 months and 6–9 months after treatment. According to the Cochrane evaluation manual, Review Manager 5.4 software was used for risk assessment and quality evaluation of included studies.

4. Statistical analysis: Data were statistically analyzed using statistical software STATA 11.0. First, the heterogeneity test was conducted. The heterogeneity was tested by Cochran's Q test and I² test. If P < 0.05 or I² > 50%, the random effect model was adopted. If P > 0.05 or I² < 50%, the fixed-effects model was adopted. Risk ratio (RR) and 95% confidence interval (CI) were used to evaluate the therapeutic effect of binary variables. Standardized mean difference

(SMD) or weighted mean difference (WMD) was used to analyze continuous variables according to whether the units of specific indicators were unified. The inspection level of the meta-analysis was set as $\alpha = 0.05$, and 95% CI was calculated for all analyses. An Egger's test was used to evaluate the publication bias, and the literature that biased the evaluation quality was eliminated through sensitivity analysis.

Results

Basic Situations of Included Literature

A total of 409 pieces of literature were retrieved. Duplicate and irrelevant literature, case reports, reviews, and animal experiments were removed. Finally, 23 pieces of literature involving 2061 patients were included in the study. The results are presented in Figure 1.

Characteristics and Quality Evaluation of Included Literature

A total of 23 RCT studies were included, all of which were Chinese literature, and no relevant literature reports from other countries were retrieved. The basic characteristics of the included literature are presented in Table 1.^{11–33} The quality of the literature was evaluated by examining the angles of the random grouping method, allocation concealment,

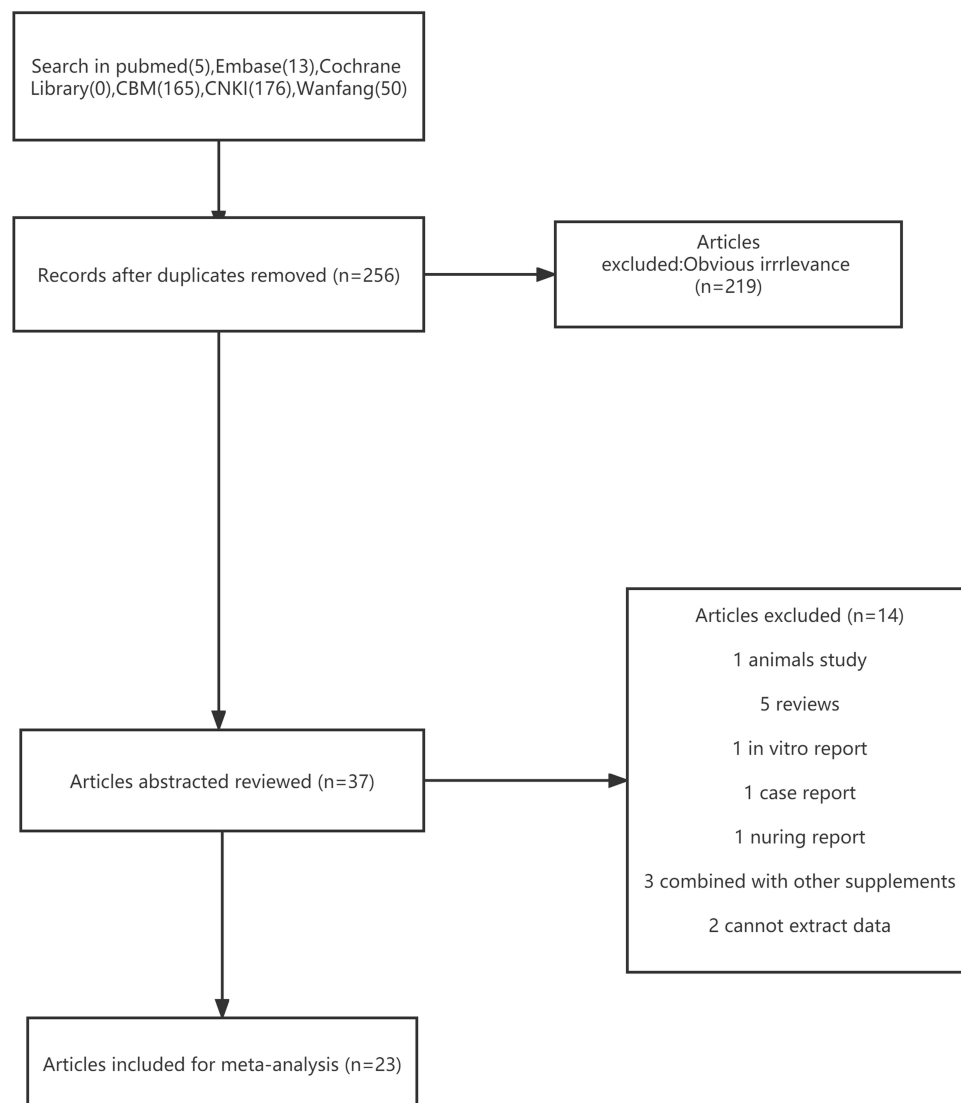


Figure 1 Literature retrieval flow chart.

Table I Basic Situations of Included Literatures

Author	Year of Publication	Control Group Case	Combined Thymopentin Treatment Group Case	Usage of Thymopentin	Male: Female Reference Group/ Reserch Group	Age Group/Research Group	Outcome Indicator
Maimati ¹¹	2017	50	50	1 mg/time/d, Intramuscular injection, 15 times	31:19/32:18	41.68±4.52/41.62±4.54	③④
Chen ¹²	2021	40	40	1 mg/time/d, NA, 30 times	25:15/24:16	40.85±4.24/40.79±4.76	⑤⑥⑧⑩
Chen ¹³	2014	50	50	1 mg/time/2d, Intramuscular injection, 120 times	29:21/28:22	73.6±2.8/73.5±2.9	④⑤⑦⑨⑪
Guan ¹⁴	2008	30	31	1 mg/time/2d, Intramuscular injection, 90 times	19:11/19:12	49.7/48.3	③
He ¹⁵	2020	42	42	80mg/time/d, NA, 16 times	27:15/29:13	41.6±4.4/42.2±4.3	③
Ji ¹⁶	2015	40	40	1 mg/time/d, NA, 240 times	27:13/26:14	65.12±2.53/64.13±3.42	④
Kang ¹⁷	2020	41	41	1 mg/time/d, NA, 90 times	23:18/21:20	38.51±9.32/39.21±8.94	①②⑪
Li ¹⁸	2021	50	50	10mg/time/d, NA, NA	27:23/28:22	39.5±3.1/39.7±2.9	③
Li ¹⁹	2017	35	35	1 mg/time/d, NA, 180times	18:17/19:16	70.5±4.2/71.3±4.0	④⑦⑨⑪
Li ²⁰	2020	38	38	1 mg/time/2d, Intramuscular injection, 120 times	23:15/24:14	53.87±2.69/53.76±2.71	⑤⑨⑪
Li ²¹	2013	32	33	1.6mg/time, 2time/Week, NA, 6 times	20:12/18:15	40/43	③
Liu ²²	2014	29	29	1 mg/time/d, Intramuscular injection, 180 times	18:11/19:10	43.3±11.5/42.1±10.3	①②③
Liu ²³	2018	69	69	NA, Intravenous injection, NA	42:27/40:29	42.3±2.6/42.5±2.7	③④
Liu ²⁴	2016	100	100	1 mg/time/d, NA, 90 times	68:32/64:36	38.32±9.33/37.54±8.43	⑥⑧⑩
Mao ²⁵	2020	30	30	1 mg/time/d, NA, 180 times	18:12/17:13	48.72±4.15/49.13±4.02	⑪
Ouyang ²⁶	2019	31	31	1 mg/time/d, NA, 180 times	19:12/21:10	46.01±8.2/45.33±8.5	⑥
Qi ²⁷	2007	35	32	1 mg/time/d, NA, 30 times	NA	NA	①④
Wang ²⁸	2021	40	40	1 mg/time/d, NA, 60 times	21:19/22:18	41.28±3.89/42.16±3.27	①④⑥⑩
Yang ²⁹	2019	53	53	1 mg/time/d, NA, 60 times	33:20/34:19	43.5±3.3/43.6±3.7	③④
Yu ³⁰	2020	44	44	1 mg/time /d, NA, 180 times	26:18/25:19	47.22±8.01/48.13±7.89	②④
Yu ³¹	2016	40	40	1 mg/time/2d, NA, 120 time	23:17/25:15	55.16±10.36/55.03±10.22	⑤⑨⑪
Zhang ³²	2011	34	34	1 mg/time/2d, NA, 45 times	29:5/28:6	42.5±14.2/43.0±13.6	①②③⑤⑦⑨⑪
Zou ³³	2017	67	89	1 mg/time/d, NA, 60 times	38:29/50:39	39.54±5.13/40.52±5.34	①⑧⑩⑥

Notes: ① Sputum culture negative rate after 2–3 months of treatment. ② Sputum culture negative rate after 6–9 months of treatment. ③ Sputum culture negative rate after the whole course of treatment. ④ Focal absorption rate of PTB. ⑤ The time to cough symptom remission. ⑥ The CD3⁺ T cell level after 2–3 months of treatment. ⑦ The CD3⁺ T cell level after 6–9 months of treatment. ⑧ The CD4⁺ T cell level after 2–3 months of treatment. ⑨ The CD4⁺ T cell level after 6–9 months of treatment. ⑩ The CD8⁺ T cell level after 2–3 months of treatment. ⑪ The CD8⁺ T cell level after 6–9 months of treatment.

blinding method, integrity of result data, blinding method for participants and researchers, selective reporting bias, and other bases of RCT. The results are presented in [Figure 2](#).

Meta-Analysis of the Sputum Culture-Negative Rate

The comparison of the sputum culture-negative rate between the combined thymopentin treatment group and control group at 2–3 months ([Figure 3A](#)) and 6–9 months ([Figure 3B](#)) of treatment and the end of the whole course of treatment ([Figure 3C](#)) were reported by six, four, and ten independent studies, respectively. The heterogeneity analysis revealed that in all studies, I^2 was $<50\%$, and all heterogeneity analyses were conducted using a fixed-effect model analysis. Meta-analysis revealed that compared with conventional therapy, the sputum culture-negative rate was significantly increased after 2–3 months and 6–9 months of treatment. At the end of the combined thymopentin treatment, the RR (95% CI) was 1.44 (1.26–1.64), 1.47 (1.21–1.78), and 1.27 (1.18–1.36), respectively. The differences were all statistically significant ($P < 0.05$ for all), suggesting that thymopentin combined with anti-TB drugs can improve the sputum culture-negative rate in patients with drug-resistant PTB.

Meta-Analysis of the Time to Cough Symptom Remission

Six studies reported the comparison of the time to cough symptom remission between the combined thymopentin treatment group and the control group. The heterogeneity analysis revealed that I^2 was $<31.8\%$, which was conducted using fixed-effect model analysis ([Figure 4A](#)). Compared with conventional therapy, the time to cough symptom remission of the combined thymopentin treatment was shortened, the WMD (95% CI) = -9.46 d (-10.36 to -8.57), the difference was statistically significant ($P < 0.001$), suggesting that thymopentin combined with anti-TB drugs can shorten the time to cough symptom remission in patients with drug-resistant PTB.

Meta-Analysis of the Focal Absorption Rate of PTB

Nine studies reported the focal absorption rate between the combined thymopentin treatment group and the control group. The heterogeneity analysis revealed that $I^2 = 23.5\%$, which was conducted using fixed-effect model analysis ([Figure 4B](#)). The results revealed that compared with conventional therapy, in the combined thymopentin treatment group the focal absorption rate was higher, RR (95% CI) = 1.36 (1.25–1.47). The difference was statistically significant ($P < 0.001$), suggesting that thymopentin combined with anti-TB drugs can improve the focal absorption rate in patients with drug-resistant PTB.

Meta-Analysis of Levels of T Lymphocyte Subsets in Peripheral Blood After Treatment

(1) The comparison of peripheral blood $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T cell levels of drug-resistant PTB in the combined thymopentin treatment group and control group at 2–3 months after treatment was reported by five, three, and four studies, respectively. The heterogeneity analysis revealed that I^2 was $>50\%$, which was conducted using the random-effects model analysis. The results reveal that compared with the control group, after 2–3 months of combined thymopentin treatment, the WMD (95% CI) of $CD3^+$ T cells, $CD4^+$ T cells, and $CD8^+$ T cells were 9.96% (7.84–12.08), 10.26% (7.81–12.71), and -4.06% (-4.96 to -3.13), respectively. The differences were statistically significant ($P < 0.05$ for all, [Figure 5A, C, and E](#)). (2) The comparison of peripheral blood $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T cell levels of drug-resistant PTB in the combined thymopentin treatment group and control group at 2–3 months after treatment was reported by three, five, and seven studies, respectively. The results reveal that compared with the control group, after 6–9 months of combined thymopentin treatment, the WMD (95% CI) of $CD3^+$ T cells, $CD4^+$ T cells, and $CD8^+$ T cells were 4.68% (3.36–6.00), 7.21% (6.28–8.15), and -3.52% (-4.07 to -2.98), respectively. The differences were statistically significant ($P < 0.05$ for all, [Figure 5B, D, and F](#)). The above results revealed that thymopentin combined with anti-TB drugs could improve the immune indexes in patients with drug-resistant PTB.

Publication Bias and Sensitivity Analysis

Egger's test and funnel plot analysis were carried out for 11 indexes. The result revealed that there were publication biases in the sputum culture-negative rate after 2–3 months of treatment ($t = 5.49$, $P = 0.005$), the sputum culture-negative rate after the whole course of treatment ($t = 4.78$, $P = 0.001$), the focal absorption rate ($t = 8.64$, $P < 0.001$), and

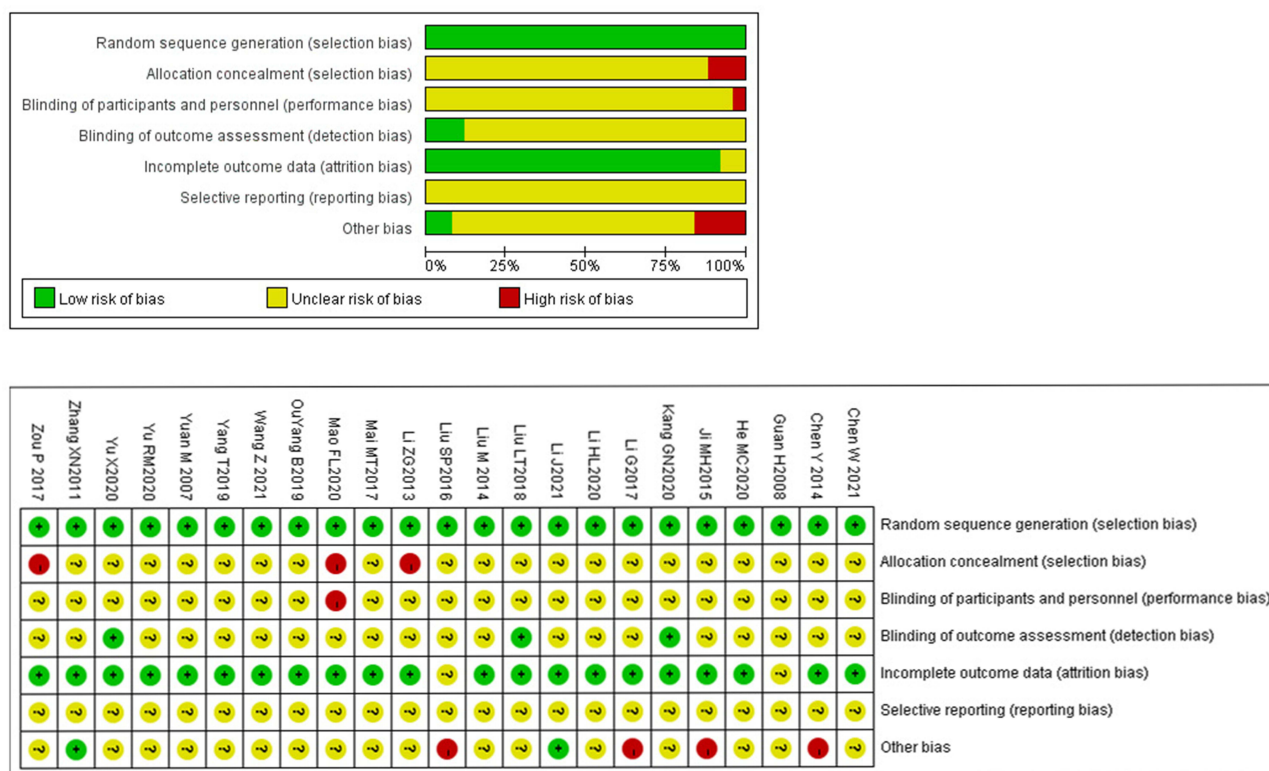


Figure 2 Quality evaluation of included literatures.

the CD4⁺ T cell level ($t = 7.83$, $P = 0.004$) after 6–9 months of treatment. There was no publication bias in other indexes by Egger's test ($P > 0.1$ for all). Related literature was excluded according to sensitivity analysis results. The sputum culture-negative rate and focal absorption rate after the whole course of treatment were not significantly different from those before the exclusion, suggesting that the sensitivity of this meta-analysis was low, and the results were relatively reliable. The sputum culture-negative rate at the end of 2–3 months (Figure 6) and the change in CD4⁺ T cell level at the end of 6–9 months in the patients receiving adjuvant treatment of drug-resistant PTB with thymopentin should not be analyzed after excluding related literature because of its small sample size (Figure 7).

Discussion

In recent years, it has been realized that TB is not only an infectious disease but also an immune disease. *Mycobacterium tuberculosis* infection interacts with the host immune system. The occurrence, development, and prognosis of TB are closely related not only to the number and virulence of invasive *mycobacterium tuberculosis* but also to the immune state and immune response of the host.³⁴ *Mycobacterium tuberculosis* infection can destroy the antigen-presenting function of macrophages and reduce the activation of effector T cells so that *mycobacterium tuberculosis* can escape immune surveillance.³⁵ CD3⁺ molecule can be expressed on all mature T cells, that is, T lymphocytes (CD3⁺ T cells). CD3⁺ T cells and T cell receptor (TCR) form TCR-CD3⁺ complex, which activates T cells by transduction of activation signals generated by TCR recognition antigen. CD3⁺ T cells contain subsets of CD4⁺ T cells and CD8⁺ T cells. A previous study revealed that peripheral blood CD4⁺ T and NK cells decreased and CD8⁺ T cells increased in patients with TB, especially in advanced or diffuse TB.³⁶ CD4⁺ T lymphocytes secrete anti-TB immune protective mediators, such as IL-2, TNF- α , and INF- γ . It can activate the ability of macrophages to inhibit or kill *mycobacterium tuberculosis*. Therefore, it is considered an important functional cell for anti-TB and immune protection.³⁷ Activation of CD8⁺ T lymphocytes can participate in the protective immune response against TB. The cells infected by *mycobacterium tuberculosis* can be recognized by CD8⁺ T cells to produce bactericidal components such as perforin, granulysin, and granzyme, so that the *mycobacterium tuberculosis* in the cells are swallowed and killed by nearby macrophages.³⁸ CD8⁺ T lymphocytes gather

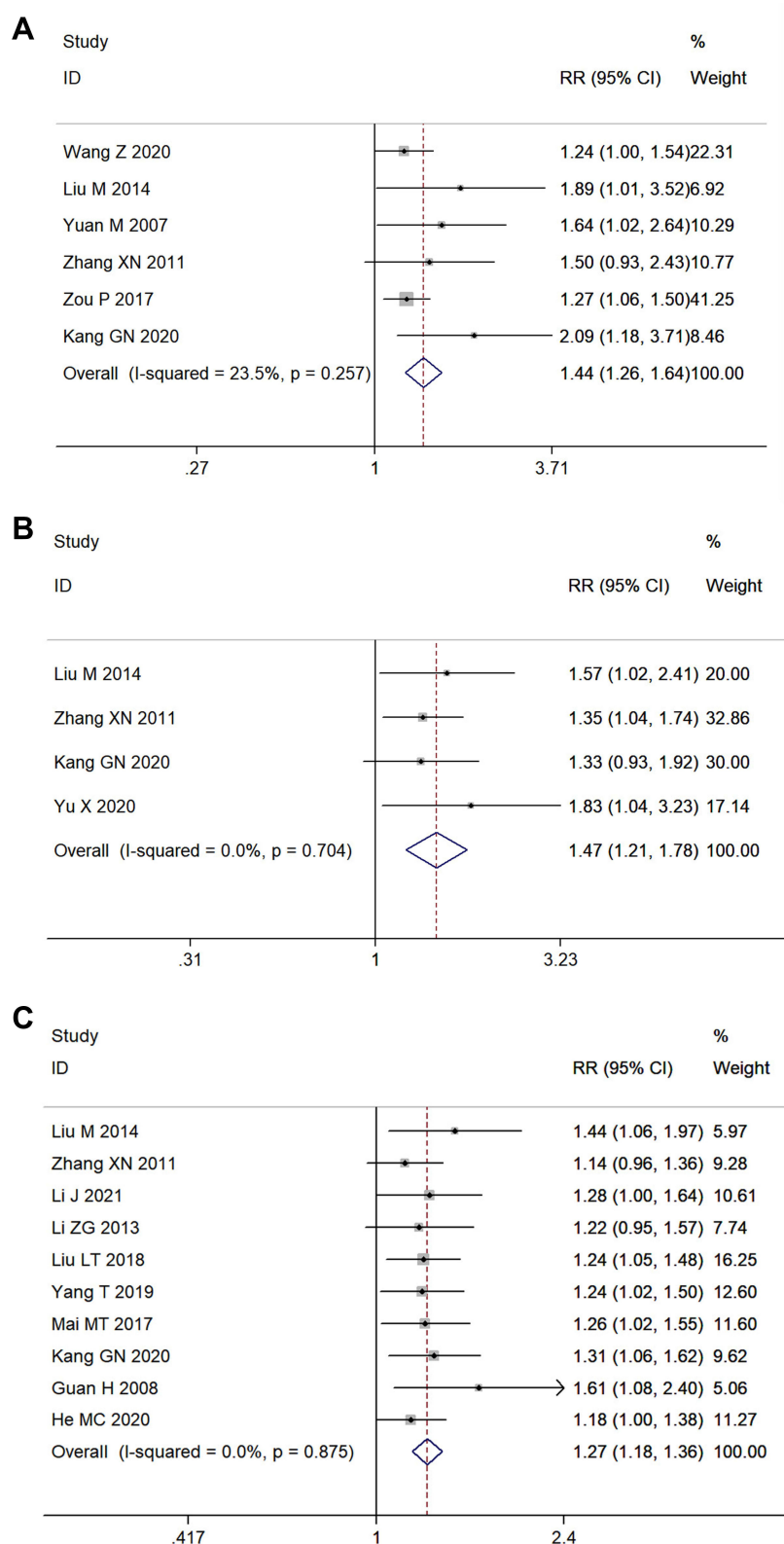


Figure 3 (A) Comparison forest plots of the sputum culture negative rate after 2–3 months of treatment. (B) Comparison forest plots of the sputum culture negative rate after 6–9 months of treatment. (C) Comparison forest plots of the sputum culture negative rate after the whole course of treatment.

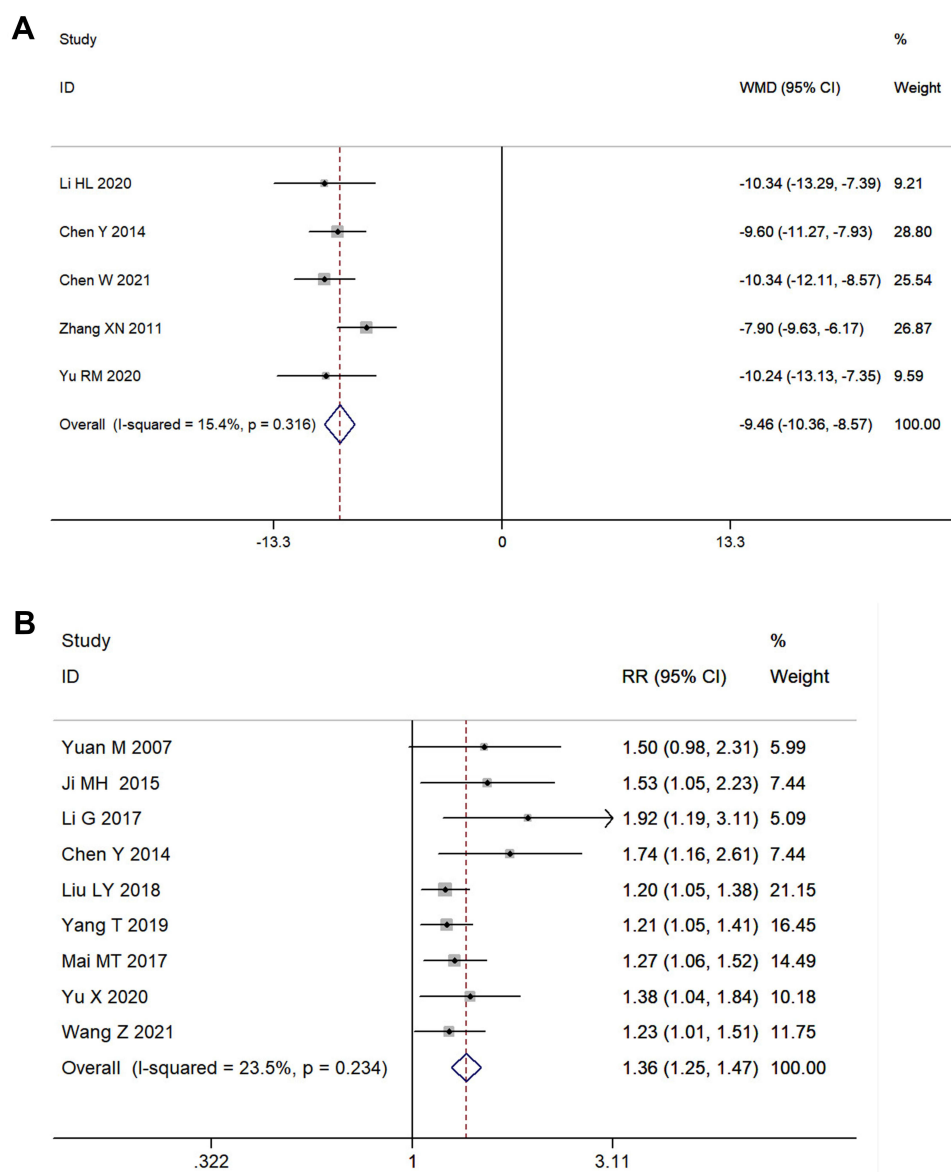


Figure 4 (A) Comparison forest plots of the time to cough symptom remission. **(B)** Comparison forest plots of focal absorption rate of PTB.

near the focus of *mycobacterium tuberculosis* infection. The more extensive the lesions are, the higher the level of CD8⁺ T lymphocytes. Therefore, we can infer that the quantity and function of CD4⁺ T cells and CD8⁺ T cells are closely related to the anti TB immunity, the occurrence and development of tuberculosis. The use of immune agents that promote the differentiation and maturation of T lymphocytes in the treatment of tuberculosis, especially drug-resistant TB, may promote the recovery of tuberculosis.

Thymopentin has been used clinically as an immunomodulator in the treatment of drug-resistant PTB. However, its clinical application has not been supported by large-scale clinical data. In this study, a meta-analysis of 23 RCT studies of thymopentin in the treatment of drug-resistant PTB was conducted. The result revealed that CD3⁺ T cell and CD4⁺ T cell levels in patients with drug-resistant PTB treated with thymopentin were higher than those in the non-immunotherapy group at 2–3 and 6–9 months after treatment, and the differences were statistically significant. The levels of peripheral blood CD8⁺ T cells in the thymopentin treatment group were lower than those in the control group after 2–3 months and 6–9 months of treatment, suggesting that thymopentin may increase the levels of CD3⁺ T cells and CD4⁺ T cells and

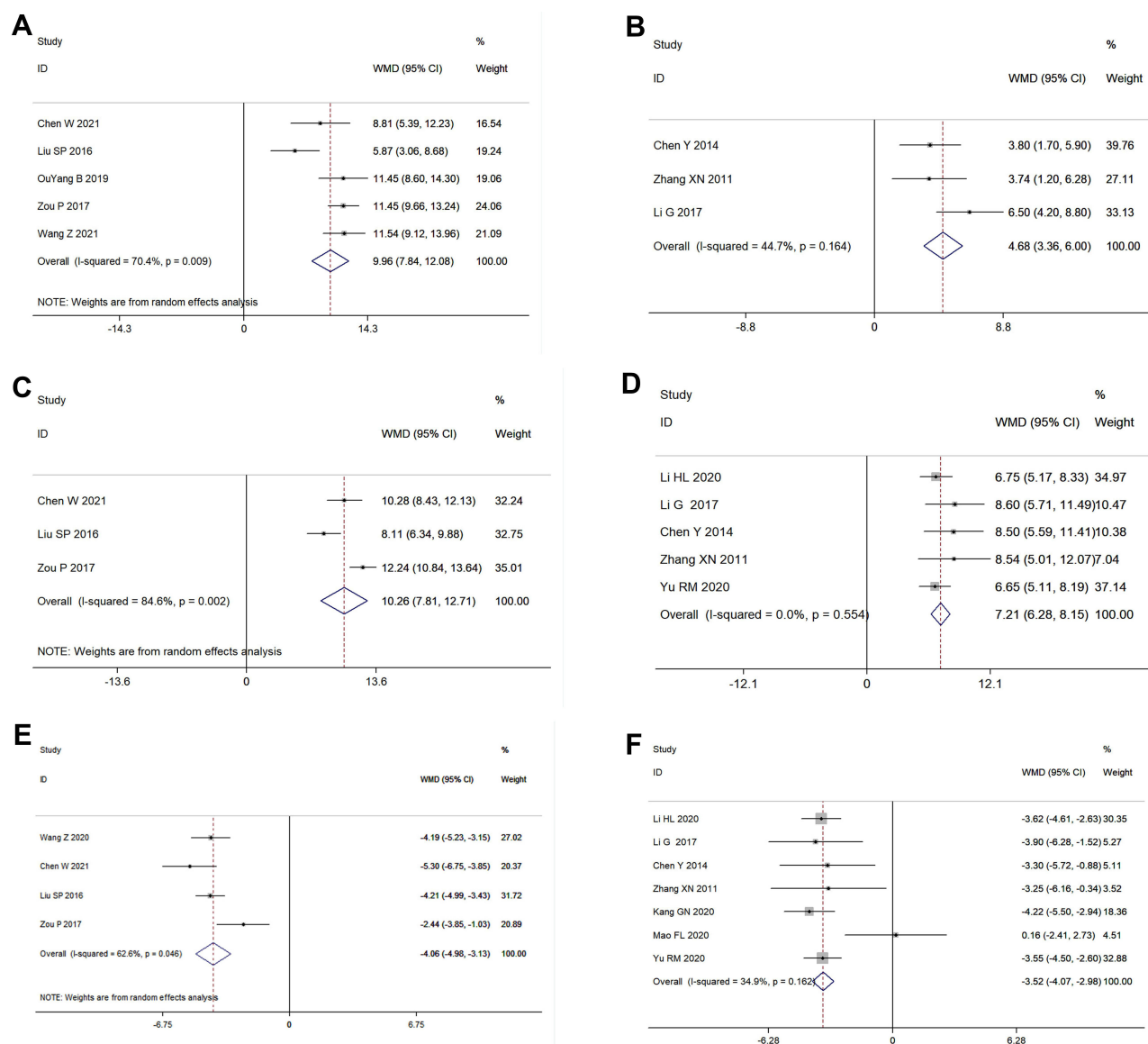


Figure 5 (A) Comparison forest plots of CD3⁺ T cell level after 2–3 months of treatment. (B) Comparison forest plots of CD3⁺ T cell level after 6–9 months of treatment. (C) Comparison forest plots of CD4⁺ T cell level after 2–3 months of treatment. (D) Comparison forest plots of CD4⁺ T cell level after 6–9 months of treatment. (E) Comparison forest plots of CD8⁺ T cell level after 2–3 months of treatment. (F) Comparison forest plots of CD8⁺ T cell level after 6–9 months of treatment.

reduce the level of CD8⁺ T cells in patients with drug-resistant PTB. The results of this meta-analysis revealed that the addition of thymopentin based on conventional anti-TB drugs could increase the immune response, and regulate the proportion of T lymphocytes, thus playing a positive role in the treatment of TB.

This meta-analysis also revealed that combined thymopentin treatment in treating drug-resistant PTB could improve the sputum culture-negative rate and the focal absorption rate and effectively shorten the time to cough symptom remission. The differences were all statistically significant. This is consistent with the results of other related studies, such as thymopentin in the treatment of newly smear-positive PTB,³⁹ retreatment smear-positive PTB,¹⁰ and PTB with diabetes mellitus, suggesting that thymopentin plays a positive role in the treatment of PTB.⁴⁰

When using thymopentin, some patients may have adverse reactions such as nausea, fever, dizziness, chest tightness and weakness. A few patients have occasional drowsiness, and the vast majority do not need to stop taking the drug. In addition, patients with chronic hepatitis B may have a temporary rise in alanine aminotransferase (ALT) level. If there is no sign of liver failure, they can still continue to use the thymopentin.

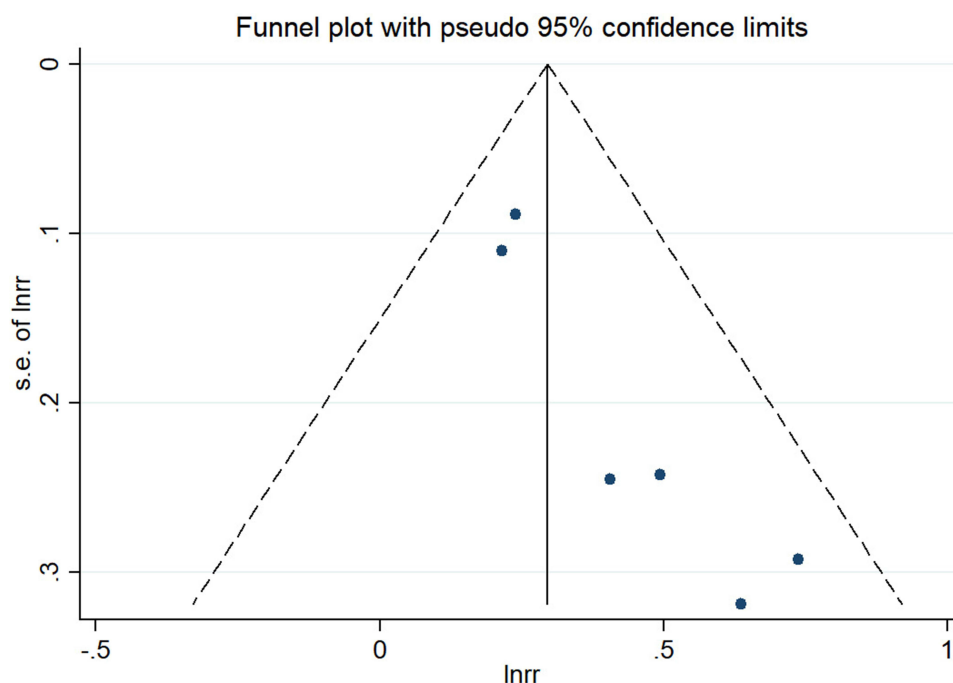


Figure 6 Funnel plots of the sputum culture negative rate after 2–3 months of treatment.

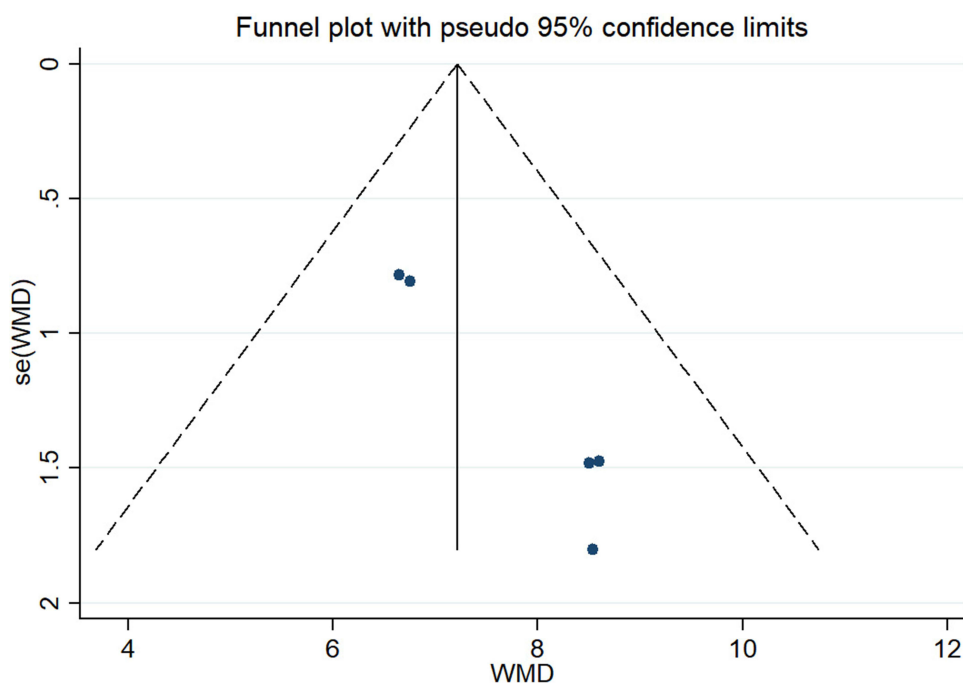


Figure 7 Funnel plots of CD4⁺ T cell level after 6–9 months of treatment.

Conclusion

In summary, thymopentin has a positive effect in the treatment of drug-resistant PTB and can assist in the treatment of drug-resistant PTB. However, there are also some limitations in this meta-analysis, which are mainly reflected in the following aspects: (1) Among the followed-up individuals, the administration method of thymopentin was not completely consistent. In most patients, it was an intravenous injection of 1 mg/d for 15 days. (2) There were differences in

the treatment regimen of drug-resistant TB. (3) The treatment duration, patient type, and study design of drug-resistant TB were different in the studies. (4) The limited quality of included literature, the small number of included literature and publication bias of some data, and the absence of foreign journals increased the limitations of the research results.

Although thymopentin plays a positive role in the treatment of drug-resistant PTB with anti-tuberculosis drugs. In terms of the combination of antituberculous drugs in the treatment of drug-resistant pulmonary tuberculosis, the treatment course of thymopentin is 15 days, which is the customary usage of clinicians. It is mainly used with reference to the instructions. The instructions suggest that thymopentin treat tumors for 15–30 days as a course of treatment. How to use thymopentin in the treatment of pulmonary tuberculosis, especially drug-resistant pulmonary tuberculosis, how many courses of treatment and how many days each course of treatment. In the next step, large sample clinical research is needed to further explore these problems.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Eighth Medical Center of PLA General Hospital in China (No.202109101430).

Acknowledgments

We are particularly grateful to all the people who have given us help on our article.

Funding

This work was supported by grants from the Serious Infectious Diseases Special Foundation of China [No. 2017ZX10201301-007-001] and Major science and technology projects of Beijing [No. Z171100001017187].

Disclosure

The authors declare that they have no competing interests.

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