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Review Article

Clinical effectiveness and reliability of linezolid in the treatment of pulmonary tuberculosis complicated with severe pneumonia: a meta-analysis

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Abstract: Objective: To systematically evaluate the clinical effect and reliability of linezolid in the treatment of pulmonary tuberculosis complicated with severe pneumonia. Methods: A comprehensive search was conducted to screen the published literature on linezolid therapy in pulmonary tuberculosis complicated with severe pneumonia in PubMed, Embase, Web of Science, Cochrane Library, and published databases of China National Knowledge Infrastructure. After screening the internal data of the literature, the quality of the literature was assessed uniformly. RevMan5.3 was used for meta-analysis. Results: The search identified 1202 clinical patients in 24 articles. Meta-analysis results revealed that linezolid treatment was associated with better bacterial clearance rate (OR=3.66 [2.41, 5.58], P<0.001) and superior total clinical effective rate (OR=5.80 [3.92, 8.58], P<0.001) in patients. The linezolid treatment resulted in lower levels of serum inflammatory factors TNF-α (WMD=-10.75 [-13.63, -7.87], P<0.001), IL6 (WMD=-10.16 [-13.50, -6.82], P<0.001), and IL8 (WMD=-8.31 [-10.41, -6.21], P<0.001). There was no obvious distinction in the occurrence of adverse reactions between the linezolid group and the control group (OR=1.34 [0.86, 2.08], P=0.19). Conclusion: Linezolid combined with conventional anti-tuberculosis treatment has a better bacterial clearance rate and clinical total effective rate than conventional anti-tuberculosis programs with reliable safety.

Keywords: Linezolid, pulmonary tuberculosis complicated with severe pneumonia, effectiveness, reliability, meta-analysis

Introduction

Pulmonary tuberculosis (PT) is an infectious disease caused by Mycobacterium tuberculosis. PT damages multiple organs of the patients, with the most common in lung [1]. Patients with pulmonary tuberculosis show typical clinical symptoms including cough, low-grade fever, and expectoration. PT patients commonly suffer declined immunity and are prone to infections by other bacteria, resulting in severe pneumonia. The overall difficulty of the treatment and fatality rate is high [2].

Linezolid is an antibiotic of the oxazolidinone family. The specific mechanism of action is the inhibition of protein synthesis in bacteria. It reduces bacterial growth and controls infection. In recent years, many scholars have studied the clinical effectiveness of linezolid in pulmonary tuberculosis complicated with severe pneumonia. The clinical effectiveness and reliability of linezolid in the therapy of pulmonary tuberculosis complicated with severe pneumonia have not been systematically assessed in evidence-based medicine [3]. This study aimed to verify the effectiveness and reliability of linezolid in the treatment of pulmonary tuberculosis complicated with severe pneumonia by a meta-analysis.

Materials and methods

Literature search

A comprehensive search was conducted to screen the published literature on linezolid thera-

py in pulmonary tuberculosis complicated with severe pneumonia. The literature searched included PubMed, Embase, Web of Science, Cochrane Library, China Biomedical Documentation, and CNKI, up to March 2022. The search strategy was joint theme keywords and free words: (((pulmonary tuberculosis) OR (pulmonary tuberculosis complicated with severe pneumonia)) OR (pulmonary tuberculosis)) AND (linezolid). The search languages were Chinese and English.

Inclusion and exclusion criteria

Inclusion criteria: RCT studies that investigated the patients with clinically diagnosed pulmonary tuberculosis and severe pneumonia, provided relevant clinical data in terms of overall clinical effectiveness, bacteria clearance rate, inflammatory factors, and adverse reactions. The therapy regimen of the experimental group used linezolid.

Exclusion criteria: Repeated literature; reviews; conference reports, books, case reports, or letters; failure to extract data in a timely manner or insufficient data.

Literature screening and data extraction

For the retrieved literature, Wanfeng Wu and Li Li initially read the titles and abstracts. They preliminarily screened out 366 articles in accordance with the established relevant inclusion and exclusion criteria. After reading the full text, the researchers screened out 24 articles that were included in the meta-analysis. Ambiguities or disagreements were solved by consulting a third person. Li Li and Shaojun Duan were responsible for data extraction and cross-checking. A third researcher reviewed the results. The extracted data from the included studies included publication year, author, country, patient sample size, study site, intervention measures, and outcome variables.

Literature quality assessment

Shaojun Duan and Yunyun Wang analyzed the quality of the included studies based on the Newcastle-Ottawa Scale (NOS). Articles with a score ≥6 were included in this study.

Statistical analysis

RevMan was used for the meta-analysis. For enumeration data, odds ratio (OR) and 95% confidence intervals were used to describe the effect of linezolid on various observing indicators. For the measured data, weighted mean distinction (WMD) and 95% confidence interval were used. I^2 test and *P* value were used to analyze the heterogeneity among multiple studies. If $I^2>50$ or $P<0.1$, it implied that the included studies had an obvious heterogeneity. A random effect model was selected to analyze the results. If an obvious heterogeneity was not concluded, a fixed effect model was used. The funnel plot was used for the evaluation of publication bias with a test level of $\alpha=0.05$.

Results

Literature retrieval and screening

A total of 576 studies were identified after a literature search. There were 148 studies removed for duplicate literature. After the check of the title and abstract, 366 articles met the inclusion criteria. There were 217 articles unavailable for clinical data. These included 149 reviews, case reports, conference abstracts, or monographs. We reviewed the full text of the remaining 62 articles. These included 15 articles that were excluded for no study endpoint, 18 articles that were excluded due to insufficient data, and 5 articles that were excluded for NOS scores below 6. After these exclusions, 24 articles involving 1202 clinical patients were eligible for this study. The flow chart of the literature screening process was shown in **Figure 1**. The basic characteristics of the included literature was shown in **Table 1**.

Bacterial clearance rate

Seven studies analyzed the effect of linezolid on bacterial clearance. The meta-analysis found that there was no obvious heterogeneity among the included studies ($I^2=16\%$, $P=0.31$). A fixed-effects model was used for analysis. The results revealed that the bacterial clearance rate in the linezolid experimental group was obviously higher than that in the control

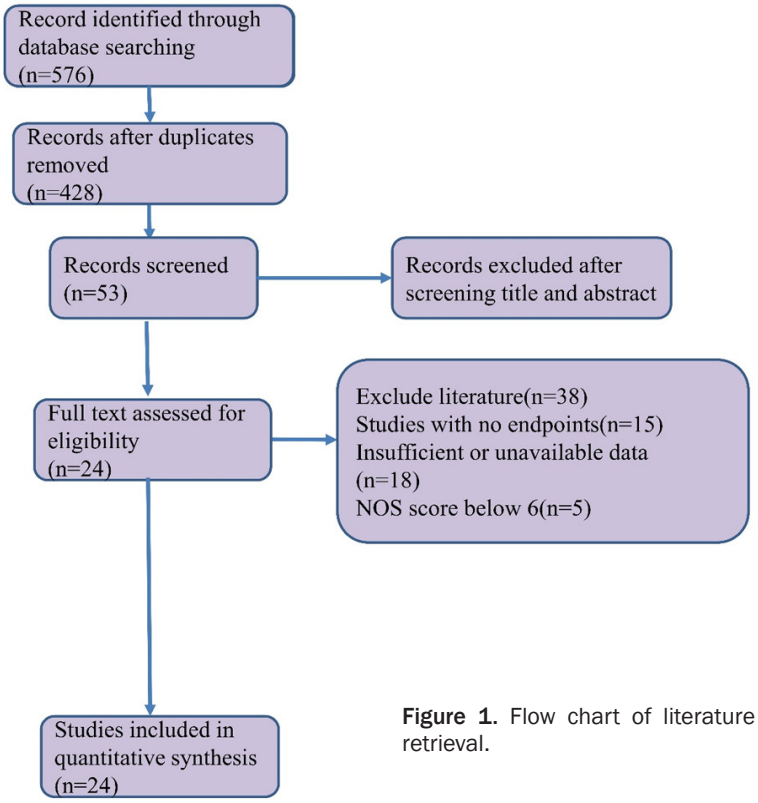

Figure 1. Flow chart of literature retrieval.

group (OR=3.66 [2.41, 5.58], P<0.001) (**Figure 2**).

Serum inflammatory factors

Ten studies analyzed the effect of linezolid on the serum levels of TNF-α. There was no obvious heterogeneity among the included studies (I^2=0%, P=0.52). A fixed-effect model was selected for data analysis. The results showed that the bacterial clearance rate in the linezolid experimental group was obviously higher than that in the control group (WMD=-7.84 [-10.41, -5.27], P<0.001) (**Figure 3**).

Six studies investigated the effect of linezolid on the serum level of IL6. There was an obvious heterogeneity among the included studies (I^2=98%, P<0.01). A random effect model was carried out for data analysis. The results revealed that serum IL6 in the linezolid experimental group was significantly lower than that in the control group (WMD=-8.10 [-11.57, -4.63], P<0.001) (**Figure 4**).

Six studies examined the effect of linezolid on serum IL8. There was an obvious heterogeneity among the included studies (I^2=94%, P<0.01). A random effect model was selected for the analysis. The results revealed that serum IL8 in the linezolid experimental group was obviously lower than that in the control group (WMD=-8.08 [-10.68, -5.49], P<0.001) (**Figure 5**).

Six studies analyzed the effect of linezolid on PCT levels in patients. There was no obvious heterogeneity among the included studies (I^2=0%, P=0.97). A fixed effect model was used for analysis. The results revealed that the PCT level of the linezolid experimental group was obviously lower than that in the control group (WMD=-108.17 [-113.07, -103.27], P<0.001) (**Figure 6**).

Six studies analyzed the effect of linezolid on white blood cell counts in patients. There was no obvious heterogeneity (I^2=0%, P=0.53). A fixed effect model was used for analysis. The results revealed that the number of white blood cells (10^8/L) in the linezolid experimental group was obviously higher than that in the control group (WMD=62.09 [60.42, 65.38], P<0.001) (**Figure 7**).

Total clinical effectiveness

Thirteen studies assessed the therapy effect of linezolid on patients with pulmonary tuberculosis and severe pneumonia by calculating the total clinical response rate. There was no obvious heterogeneity among the included studies (I^2=0%, P=0.88). A fixed effect model was applied. The meta analysis results revealed that the total effective rate of patients in the linezolid group was obviously higher than that in the control group (OR=5.80 [3.92, 8.58], P<0.001) (**Figure 8**).

Adverse reactions

A total of 13 studies recorded the adverse reaction rates during the treatment of pulmonary

Table 1. General characteristics of included publications

Author	Study Site	Sample Size	Control Group	Test Group	Observation	Adverse	NOS
Zhang Qiuhua [7]	Huizhou, Guangdong	50/50	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 14d	C	4/1	7
Huang Yiming [8]	Wuzhou, Guangxi	25/25	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 14d	C; B	6/3	8
Shi haiyan [9]	Jiamusi, Heilongjiang	42/42	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 14d	A; B; D	--	6
Wen Yunjie [10]	Cixi, Zhejiang	30/30	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 14d	A; B; C	5/2	6
Pan Lei [5]	Hangzhou, Zhejiang	49/49	Isoniazid/Rifapentine/Ethambutol	Intravenous linezolid, q12h, 28d	A; B; C; D	6/5	8
Zhu Guochuan [11]	Taiyuan, Shanxi	37/37	Isoniazid	Intravenous linezolid, q12h, 14d	A	2/3	7
Wen Ming [12]	Changsha, Hunan	34/16	Isoniazid/Rifapentine/Ethambutol	Intravenous linezolid, q12h, 28d	A	2/1	7
Guan Zhiwei [13]	Lingbao, Henan	32/32	Isoniazid/Rifapentine/Ethambutol	Intravenous linezolid, q24h, 28d	A; B	3/2	6
Jiang Yezhou [5]	Changsha, Hunan	31/31	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 14d	A; B; D	4/3	7
Li Zhuo [14]	Jinzhou, Liaoning	54/54	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q24h, 14d	A; B	5/3	8
Tsering Zhuoga [15]	Tibet	33/33	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q8h, 14d	A	2/3	7
Yang Nan [6]	Jinzhou, Liaoning	80/80	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 28d	A; B; C	2/1	7
Gao Yuan [16]	Xinxiang, Henan	46/46	Isoniazid/Rifapentine/Ethambutol	Intravenous linezolid, q12h, 28d	A; B	5/3	8
Shi Yunfang [17]	Jincheng, Shanxi	27/27	Isoniazid/Rifapentine/Ethambutol	Intravenous linezolid, q12h, 14d	A; B; C	1/1	6
Li Dong [18]	Yili, Xinjiang	40/40	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 28d	A; B; C	--	6
Anger [19]	USA	8/8	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 28d		1/1	7
De Lorenzo [20]	Italy	6/6	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 28d		--	6
Fortun [21]	Spain	5/5	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 28d		--	6
Migliori [22]	Germany	5/6	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, q12h, 28d		--	7
Nam [23]	South Korea	22/22	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, Q24h, 14d		1/2	8
Schecter [24]	USA	15/15	Isoniazid/Rifampicin/Ethambutol	Intravenous linezolid, Q24h, 14d		1/2	7
Singla [25]	India	15/14	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 28d		1/2	8
Udwadia [26]	India	9/9	Isoniazid	Intravenous linezolid, Q24h, 14d		--	7
Villar [27]	Portugal	8/8	Isoniazid/Rifampicin/Pyrazinamide	Intravenous linezolid, q12h, 28d		--	7

Note: Observation index: A, total clinical effective rate; B, serum inflammatory factors; C, bacterial clearance rate; D, immune function protein adverse reactions.

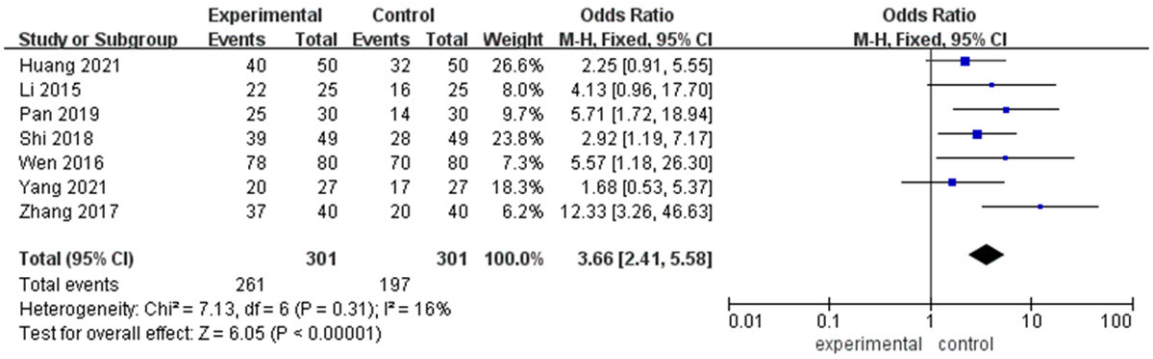

Figure 2. Meta-analysis of the effect of linezolid on bacterial clearance rate in tuberculosis patients with severe pneumonia.

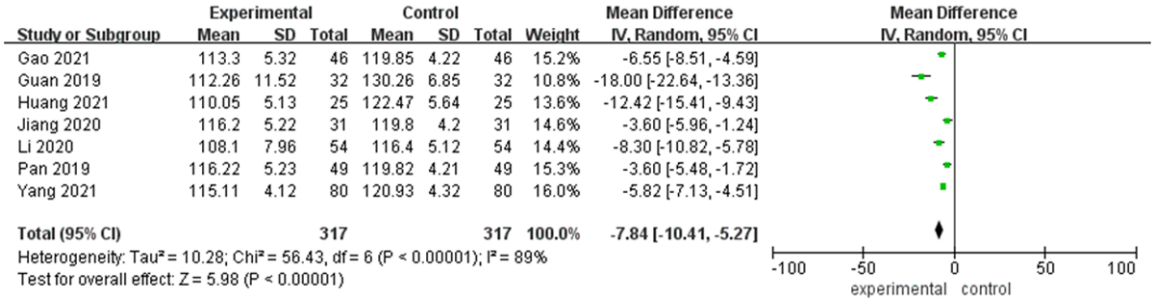

Figure 3. Meta-analysis of the effect of linezolid on serum TNF-α level in tuberculosis patients with severe pneumonia.

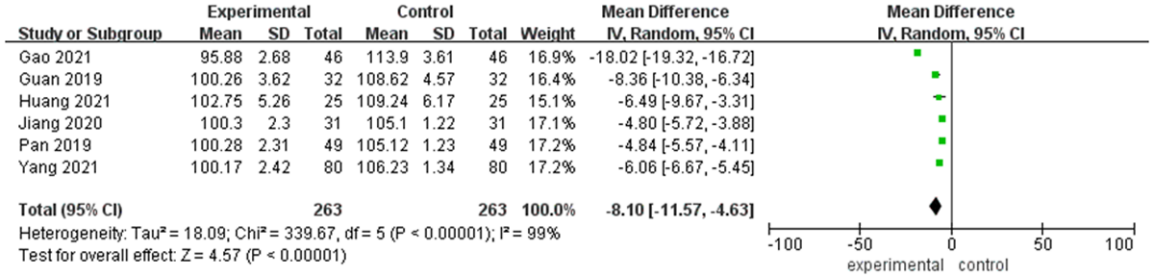

Figure 4. Meta-analysis of the effect of linezolid on serum IL6 level in tuberculosis patients with severe pneumonia.

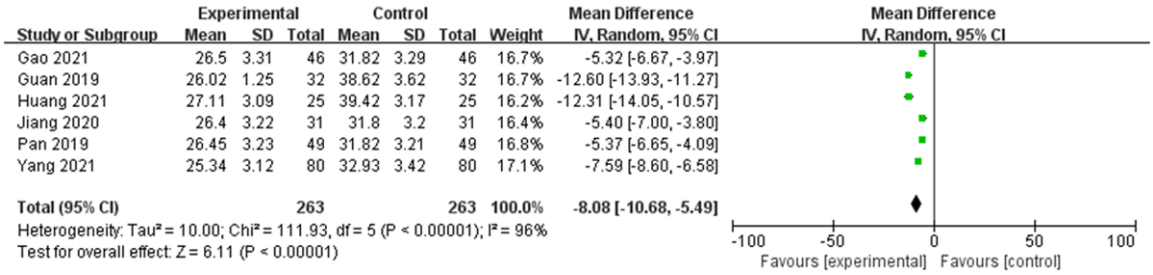

Figure 5. Meta-analysis of the effect of linezolid on serum IL8 level in tuberculosis patients with severe pneumonia.

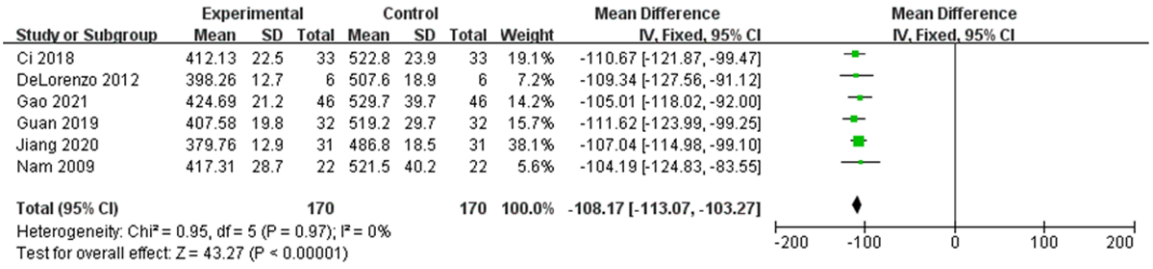

Figure 6. Meta-analysis of the effect of linezolid on the level of PCT in tuberculosis patients with severe pneumonia.

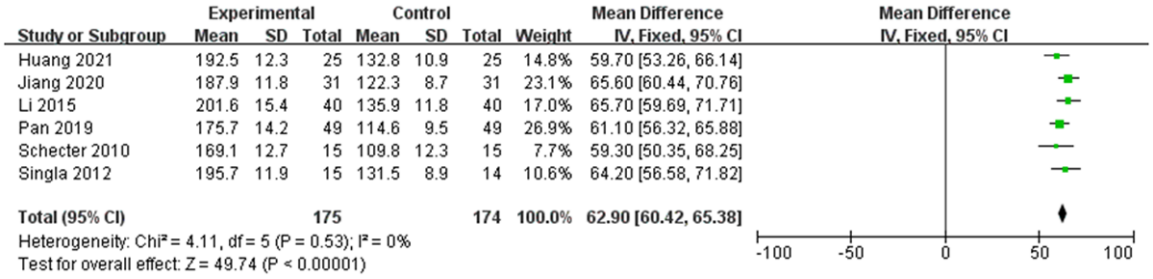

Figure 7. Meta-analysis of the effect of linezolid on white blood cell count in tuberculosis patients with severe pneumonia.

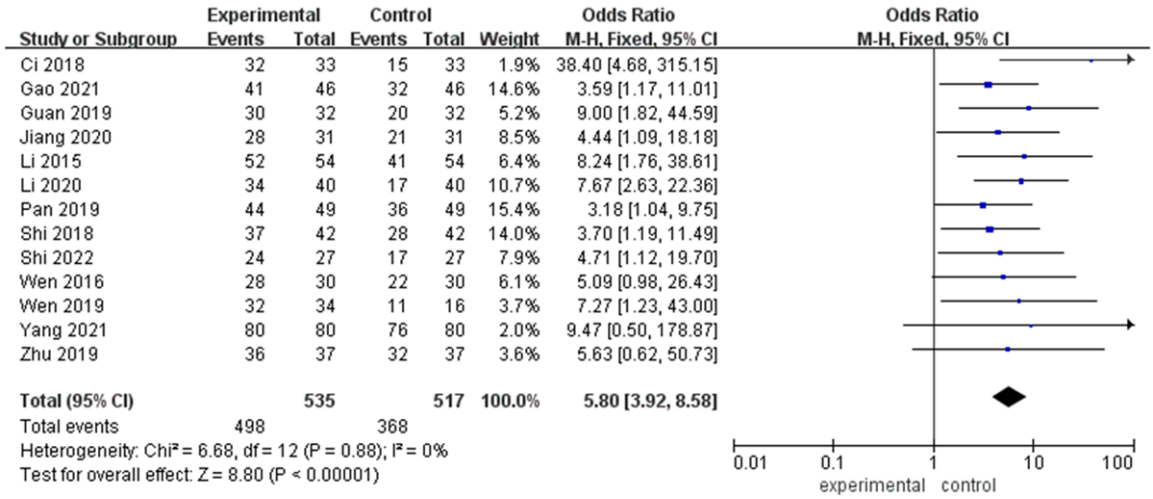

Figure 8. Meta-analysis of the total effective rate of patients in the linezolid trial group and the control group.

tuberculosis complicated with severe pneumonia. The meta-analysis found that there was no obvious heterogeneity among the included studies (I^2=0%, P=0.99). A fixed effect model was applied. The results revealed that there was no obvious distinction in the incidence of adverse reactions between the linezolid experimental and the control group (OR=1.53 [0.95, 2.47], P=0.08) (**Figure 9**).

Sensitivity and heterogeneity analysis

A perceptual analysis was implemented by Stata. The data of each study included in the analysis were eliminated sequentially. Their influence on the combined total effect results was observed. The analysis revealed that after excluding each of the studies, the combined effect size did not change significantly. This

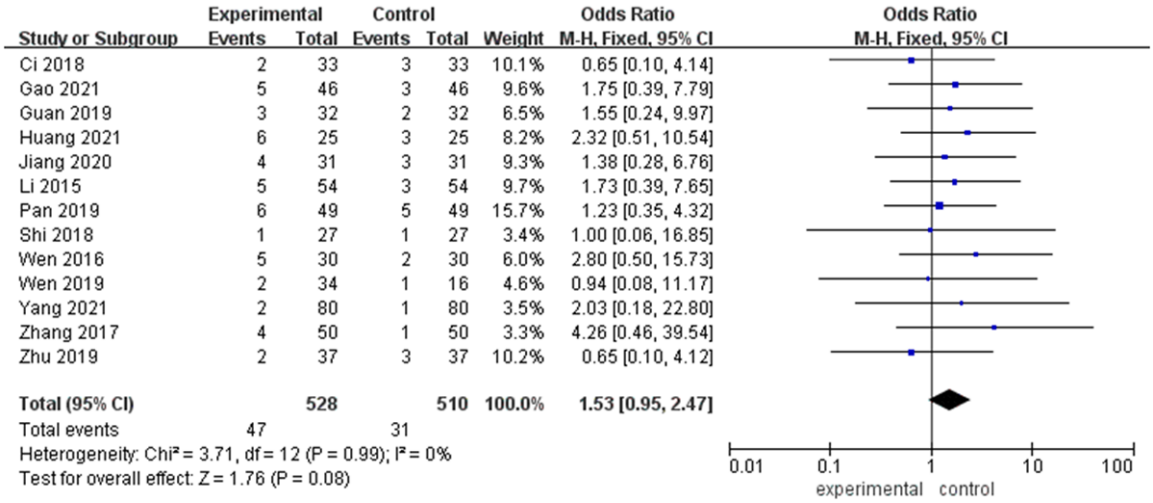

Figure 9. Meta-analysis of adverse reaction rates in linezolid trial group and control group.

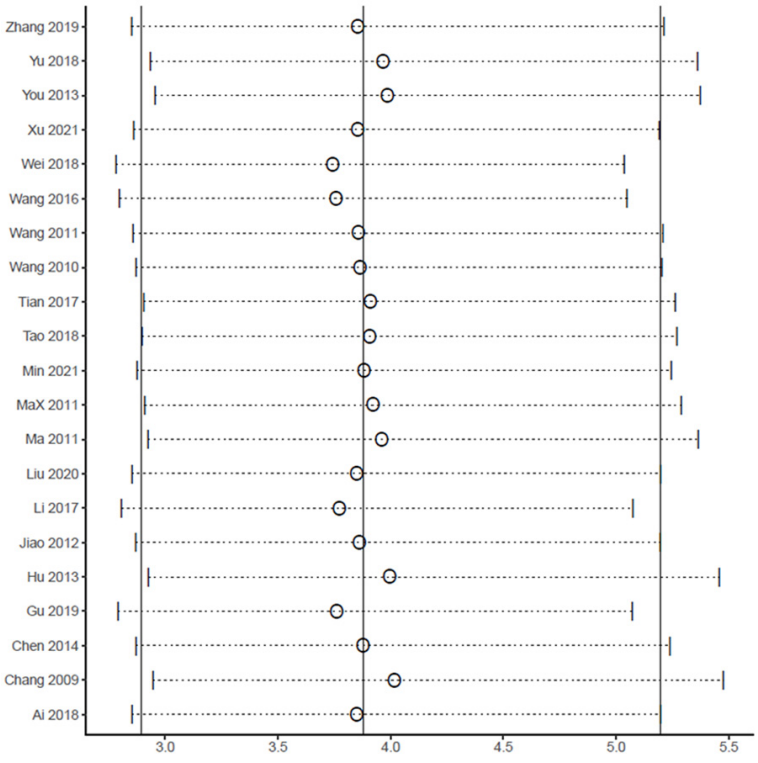

Figure 10. Sensitivity and heterogeneity analysis of included studies.

suggested that the results of this study were stable. The distinctions among the included literature were small, and the results were more reliable (**Figure 10**).

Publication bias

A funnel plot analysis was performed to analyze the publication bias of the included studies. It was found that the scattered dots in the figure were symmetrically distributed, indicating that the included research had no obvious publication bias (**Figure 11**).

Discussion

Pulmonary tuberculosis is a slow-onset disease caused by infection of Mycobacterium tuberculosis. Patients experience many complications. For patients with severe pulmonary infection in clinical practice, external ventilation and circulation equipment are needed to support the overall clinical diagnosis and therapy. Antibiotics are the mainstay in clinical treatment of pulmonary tuberculosis and severe pneumonia. Based on the 50S ribosomal subunit of bacterial, linezolid hinders the synthesis of related proteins in bacteria, achieving a broad-spectrum antibacterial effect [4]. Pan et al. [5] conducted a relevant study on 98 patients with severe pulmonary tuberculosis in clinical practice. The study showed that combining essential tuberculosis therapy with linezolid improved the primary treatment efficacy and serum inflammatory factors. and It enhanced the patient's immunity with reliable safety. Yang et al. [6] analyzed the

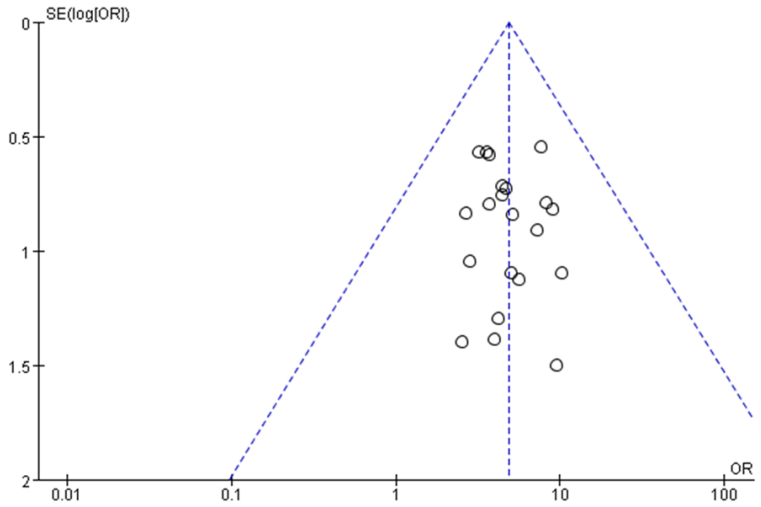

Figure 11. Publication bias was analyzed by funnel plot.

clinical data of 160 patients with severe pneumonia and suggested that concurrent linezolid treatment decreased the level of related serum inflammatory factors and improved the overall effective rate without increasing the adverse reactions. In this study, a comprehensive meta-analysis was taken to quantitatively and objectively evaluate the effectiveness and reliability of linezolid in patients with pulmonary tuberculosis complicated with severe pneumonia. This study provided reliable evidence-based medical support for clinical practice.

This study found that the overall effective rate of linezolid combined with conventional therapy was better than that of the conventional therapy. In terms of inflammation, the serum levels of TNF-α, IL6, and IL8 in patients taking linezolid combined with conventional therapy were lower than those in the conventional therapy group. The incidence of adverse reactions showed no apparent differences between the linezolid group and others, suggesting that linezolid was safe for patients with tuberculosis complicated with severe pneumonia.

This study had certain limitations: the detection methods of serum inflammatory factors used in various studies were different. This resulted in specific heterogeneity in the outcomes. Some of the data were derived from the calculation of the obtained data. This was insufficient. The overall research in this paper deviated from the original data. There was not much available data.

The preliminary results of this study showed that linezolid combined with the conventional anti-tuberculosis therapy mode is better than the conventional therapy in terms of bacterial clearance rate and total clinical effectiveness.

Disclosure of conflict of interest

None.

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References

[1] Kang W, Yu J, Du J, Yang S, Chen H, Liu J, Ma J, Li M, Qin J, Shu W, Zong P, Zhang Y, Dong Y, Yang Z, Mei Z, Deng Q, Wang P, Han W, Wu M, Chen L, Zhao X, Tan L, Li F, Zheng C, Liu H, Li X, A E, Du Y, Liu F, Cui W, Wang Q, Chen X, Han J, Xie Q, Feng Y, Liu W, Tang P, Zhang J, Zheng J, Chen D, Yao X, Ren T, Li Y, Li Y, Wu L, Song Q, Yang M, Zhang J, Liu Y, Guo S, Yan K, Shen X, Lei D, Zhang Y, Yan X, Li L and Tang S. The epidemiology of extrapulmonary tuberculosis in China: a large-scale multi-center observational study. PLoS One 2020; 15: e0237753.

[2] Oh S, Trifonov L, Yadav VD, Barry CE 3rd and Boshoff HI. Tuberculosis drug discovery: a decade of hit assessment for defined targets. Front Cell Infect Microbiol 2021; 11: 611304.

[3] Brown AN, Drusano GL, Adams JR, Rodriquez JL, Jambunathan K, Baluya DL, Brown DL, Kwara A, Mirsalis JC, Hafner R and Louie A. Preclinical evaluations to identify optimal linezolid regimens for tuberculosis therapy. mBio 2015; 6: e01741-01715.

[4] Hashemian SMR, Farhadi T and Ganjparvar M. Linezolid: a review of its properties, function, and use in critical care. Drug Des Devel Ther 2018; 12: 1759-1767.

[5] Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, Mendel CM, Egizi E, Moreira J, Timm J, McHugh TD, Wills GH, Bateson A, Hunt R, Van Niekerk C, Li M, Olugbosi M

and Spigelman M. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020; 382: 893-902.
[6] Yeager SD, Oliver JE, Shorman MA, Wright LR and Veve MP. Comparison of linezolid step-down therapy to standard parenteral therapy in methicillin-resistant staphylococcus aureus bloodstream infections. Int J Antimicrob Agents 2021; 57: 106329.
[7] Zhang QH. Effect of linezolid on patients with pulmonary tuberculosis complicated with severe pneumonia. Chin J Urban Rural Enterprise Hyg 2017; 32: 103-104.
[8] Huang YM. Effect and safety analysis of linezolid adjuvant therapy on inflammatory status in patients with pulmonary tuberculosis complicated with severe pneumonia. Mod Med Health Res 2021; 5: 54-56.
[9] Guan J, Fu R, Ruan EB, Liang Y, Qu W, Wang GJ, Wang XM, Liu H, Wu YH, Song J, Wang HQ, Xing LM and Shao ZH. Clinical analysis of 102 blood disease patients with gram positive cocci infection treated with linezolid. Zhonghua Xue Ye Xue Za Zhi 2010; 31: 527-530.
[10] Dheda K, Limberis JD, Pietersen E, Phelan J, Esmail A, Lesosky M, Fennelly KP, Te Riele J, Mastrapa B, Streicher EM, Dolby T, Abdallah AM, Ben-Rached F, Simpson J, Smith L, Gumbo T, van Helden P, Sirgel FA, McNerney R, Theron G, Pain A, Clark TG and Warren RM. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study. Lancet Respir Med 2017; 5: 269-281.
[11] Grudinina SA, Zubkov MM, Krotova LA, Kurdiukova IuP, Kutsenko MA, Marinin VF, Sidorenko SV, Sinpal'nikov AI, Solomatin AS, Sterkhova GV, Fesenko OV, Fomina IG and Chuchalin AG. Comparison of linezolid and vancomycin in nosocomial pneumonia: results of the multicenter double-blind study. Antibiot Khimioter 2002; 47: 12-17.
[12] Wang Y, Zhang HJ and Song AJ. Evaluation on efficacy and safety of vancomycin and linezolid for treatment of pulmonaryinfections. Chin J Nosocomiol 2015; 25: 2734-2736.
[13] Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, Via LE, Goldfeder LC, Kang E, Jin B, Park H, Kwak H, Kim H, Jeon HS, Jeong I, Joh JS, Chen RY, Olivier KN, Shaw PA, Follmann D, Song SD, Lee JK, Lee D, Kim CT, Dartois V, Park SK, Cho SN and Barry CE 3rd. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012; 367: 1508-1518.
[14] Didilescu C and Craiova UM. Present and future in the use of anti-tubercular drugs. Pneumologia 2011; 60: 198-201.
[15] Agyeman AA and Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob 2016; 15: 41.
[16] Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, Wu M, Zen L, Sun H, Liu Y, Gu J, Lin F, Wang X and Zhang Z. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015; 45: 161-170.
[17] Luchetti G, Roncaioli JL, Chavez RA, Schubert AF, Kofoed EM, Reja R, Cheung TK, Liang Y, Webster JD, Lehoux I, Skippington E, Reeder J, Haley B, Tan MW, Rose CM, Newton K, Kayagaki N, Vance RE and Dixit VM. Shigella ubiquitin ligase IpaH7.8 targets gasdermin D for degradation to prevent pyroptosis and enable infection. Cell Host Microbe 2021; 29: 1521-1530, e1510.
[18] Pang Y, Zong Z, Huo F, Jing W, Ma Y, Dong L, Li Y, Zhao L, Fu Y and Huang H. In vitro drug susceptibility of bedaquiline, delamanid, linezolid, clofazimine, moxifloxacin, and gatifloxacin against extensively drug-resistant tuberculosis in Beijing, China. Antimicrob Agents Chemother 2017; 61: e0900-17.
[19] Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM and Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. J Antimicrob Chemother 2010; 65: 775-783.
[20] De Lorenzo S, Centis R, D'Ambrosio L, Sotgiu G and Migliori GB. On linezolid efficacy and tolerability. Eur Respir J 2012; 39: 770-772.
[21] Fortún J, Martín-Dávila P, Navas E, Pérez-Elías MJ, Cobo J, Tato M, De la Pedrosa EG, Gómez-Mampaso E and Moreno S. Linezolid for the treatment of multidrug-resistant tuberculosis. J Antimicrob Chemother 2005; 56: 180-185.
[22] Migliori GB, Eker B, Richardson MD, Sotgiu G, Zellweger JP, Skrahina A, Ortmann J, Girardi E, Hoffmann H, Besozzi G, Bevilacqua N, Kirsten D, Centis R and Lange C. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. Eur Respir J 2009; 34: 387-393.
[23] Nam HS, Koh WJ, Kwon OJ, Cho SN and Shim TS. Daily half-dose linezolid for the treatment of intractable multidrug-resistant tuberculosis. Int J Antimicrob Agents 2009; 33: 92-93.
[24] Schecter GF, Scott C, True L, Raftery A, Flood J and Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2010; 50: 49-55.
[25] Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK and Behera D. Linezolid: an effective, safe and cheap drug for patients fail-

ing multidrug-resistant tuberculosis treatment in India. Eur Respir J 2012; 39: 956-962.
[26] Udwadia ZF, Sen T and Moharil G. Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective. Eur Respir J 2010; 35: 936-938.
[27] Villar M, Sotgiu G, D'Ambrosio L, Raymundo E, Fernandes L, Barbedo J, Diogo N, Lange C, Centis R and Migliori GB. Linezolid safety, tolerability and efficacy to treat multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2011; 38: 730-733.