

Original Article

Influence of anti-tuberculosis drugs plus cycloserine on sputum negative conversion rate, adverse reactions and inflammatory factors in multi-drug resistant tuberculosis

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Abstract: Objective: The aim of this investigation was to determine the influence of anti-tuberculosis (anti-TB) drugs plus cycloserine (CS) on the sputum negative conversion rate, adverse reactions and inflammatory factors in the treatment of multidrug-resistant tuberculosis (MDR-TB). Methods: Seventy patients with MDR-TB who were referred to Nanjing Hospital Affiliated with Nanjing University of Traditional Chinese Medicine from April 2017 to April 2020 were assigned into the research group (RG; 38 cases) for anti-TB drugs plus CS, and the control group (CG; 32 cases) for conventional anti-TB drugs. The two groups were compared in their sputum negative conversion rate, incidence of adverse reactions, and foci absorption rate after 6, 12 and 24 months of treatment. The levels of inflammatory factors; tumor necrosis factor (TNF- α), interleukin-6 (IL-6) and interferon- γ (IFN- γ), both pre- and post-treatment were detected. Also, pre- and post-treatment, pulmonary function (PF) indexes (forced expiratory volume in 1 s/forced vital capacity, FEV1/FVC; FEV1; peak expiratory flow, PEF), and the scores of anxiety and depression (self-rating anxiety/depression scale, SAS/SDS), as well as Pittsburgh Sleep Quality Index (PSQI) were compared. Results: After 6, 12 and 24 months of treatment, the sputum negative conversion rate and foci absorption rate were higher in the RG than in the CG (both $P < 0.05$). The RG presented with fewer adverse reactions, lower TNF- α , IL-6 and IFN- γ levels, higher FEV1, FEV1/FVC and PEF, and lower SAS, SDS and PSQI scores than the CG, post treatment (all $P < 0.05$). Conclusions: While helping to raise the sputum negative conversion rate, improve prognosis, and reduce adverse reactions, anti-TB drugs plus CS can also inhibit the release of inflammatory factors, improve PF and alleviate negative emotion and sleep disorders.

Keywords: Cycloserine, multidrug-resistant tuberculosis, sputum negative conversion rate, adverse reactions, inflammatory factors

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium TB infection, with pulmonary TB being the most pervasive type [1, 2]. Multi-drug resistant tuberculosis (MDR-TB) refers to TB that is at least resistant to both isoniazid and rifampicin [3, 4]. Due to irregular chemotherapy, HIV infection, poverty and the biological characteristics of Mycobacterium TB, MDR-TB is rapidly increasing and spreading all over the world [5, 6]. Studies

have shown that inflammatory factors play an important role in the control of Mycobacterium tuberculosis. For example, tumor necrosis factor (TNF- α) and interleukin-6 (IL-6) have strong pro-inflammatory activity and can aggravate tissue damage through pro-inflammatory effects [7]. MDR-TB has become a serious social and public health problem due to the prolonged course of disease, high treatment cost, poor curative effect and high mortality rate, which seriously affects the physical and mental health as well as the life and safety of pa-

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tients [8]. As mentioned earlier, the mortality rate of MDR-TB is very high in clinical treatment, and it is difficult to use conventional treatments to achieve a high treatment efficacy. Meanwhile, the treatment cost is also overwhelmingly high, so most patients have to give up treatment as they cannot bear the large cost [9-11]. Thus, finding a suitable, safe and effective treatment has important implications [12].

Cycloserine (CS) is a broad-spectrum antibiotic, which is a D-alanine analogue. It can inhibit alanine racemase and synthetase, which in turn affects the formation of cell wall mucopeptides and reduces the cell wall resistance of Mycobacterium TB, thus playing a role of sterilization and bacteriostasis [13]. Given the drug resistance of first-line TB drugs, second-line TB drugs play an increasingly vital role in the treatment of drug-resistant TB [14]. CS, is a second-line oral anti-TB drug, and it has outstanding anti-TB effects and many other merits [15]. It has low drug resistance rates, without cross resistance with other anti-TB drugs. Apart from that, the drug has strong tissue penetration and wide distribution, and is distributed in various tissues and body fluids. Moreover, the toxic side effects of CS on the liver are relatively mild, so that it can be used even if the liver function of patients is damaged [16, 17]. Nowadays, combined medication has become a crucial medication scheme for epidemic treatment [18]. Nevertheless, there are only a few studies on CS plus anti-TB drugs in the treatment of MDR-TB [19].

In this study, we administered CS plus anti-TB drugs to patients with MDR-TB, so as to explore the influence of this treatment regimen on the sputum negative conversion rate, adverse reactions and inflammatory factors in patients.

Materials and methods

General information

Seventy patients who were referred to the Nanjing Hospital Affiliated to Nanjing University of Traditional Chinese Medicine from April 2017 to April 2020, with MDR-TB were assigned into the research group (RG) for anti-TB drugs plus CS, and the control group (CG) for conventional anti-TB drugs. The RG consisted of 38 patients (21 males and 17 females,

mean age 46.86 ± 7.14 years ranging between 30-68 years), while the CG was composed of 32 patients (20 males and 12 females, mean age 47.69 ± 8.06 years ranging between 35-70 years).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria of MDR-TB [20]; (2) The Ethics Committee of Nanjing Hospital Affiliated with Nanjing University of Traditional Chinese Medicine, approved this study, and all patients and their families were informed and signed the fully informed consent.

Exclusion criteria: (1) Patients who were allergic to the study medication; (2) Patients with severe organ diseases such as in the heart, liver and kidney, or those with malignant tumors and end-stage diseases; (3) Patients with cognitive impairment, language or hearing impairment; (4) Patients with mental illness or family history of mental illness.

Treatment methods

The CG was treated with conventional anti-TB drugs: Patients in an intensive phase were given pyrazinamide (PZA) 1.6 g/d + amikacin (AMK) 0.75 g/d + levofloxacin (LEV) 0.75 g/d + protionamide (0.5 g/d for body mass <60 kg and 0.75 g/d for body mass ≥ 60 kg) + p-aminosalicylic acid (PAS) 8.0 g/d for 6 months. Patients in a consolidation phase were administered with the following drugs for 18 months: PZA 1.6 g/d + LEV 0.75 g/d + protionamide (0.5 g/d for body mass <60 kg and 0.75 g/d for body mass ≥ 60 kg) + PAS 8.0 g/d.

The RG was treated with CS plus anti-TB drugs: Patients in an intensive phase were treated with PZA 1.6 g/d + AMK 0.75 g/d + LEV 0.75 g/d + protionamide (0.5 g/d for body mass <60 kg and 0.75 g/d for body mass ≥ 60 kg) + CS (0.5 g/d for body mass <60 kg and 0.7 g/d for body mass ≥ 60 kg) for 6 months, while those in a consolidation phase were given PZA 1.6 g/d + LEV 0.75 g/d + protionamide (0.5 g/d for body mass <60 kg and 0.75 g/d for body mass ≥ 60 kg) + CS (0.5 g/d for body mass <60 kg and 0.7 g/d for body mass ≥ 60 kg) for 18 months.

All patients took vitamin B6 orally at 150 mg/d simultaneously during treatment.

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Endpoints

(1) Sputum negative conversion rate: The sputum negative conversion rates after 6, 12 and 24 months of treatment were compared between the two groups.

(2) Foci absorption rate: The foci absorption rate was compared with the evaluation criteria for the efficacy as follows: Significant absorption: X-ray examination shows that the cavity in the focus area was closed, and the absorption was $>2/3$. Absorption: the cavity in the lesion area was obviously reduced, and the absorption was less than $2/3$. Ineffective: there was no significant change in the size and cavity of the lesion area. Deteriorated: the focus area and cavity were enlarged.

(3) Incidence of adverse reactions: The incidence of adverse reactions during treatment was compared between the two series.

(4) Inflammatory factors: Serum tumor necrosis factor- α (TNF- α), interleukin (IL)-6 and interferon (IFN)- γ levels were measured by ELISA before and after treatment strictly following the kit instructions of human TNF- α ELISA, human IL-6 ELISA and human IFN- γ ELISA (Shanghai Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-1446, JK-(a)-0023 and JK-ELISA-01321).

(5) Pulmonary function (PF) indexes: Forced expiratory volume in 1 s (FEV1), FEV1/forced vital capacity (FVC) and peak expiratory flow (PEF) were recorded and compared before and after treatment.

(6) SAS and SDS scores: Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) [21] evaluated the anxiety and depression of patients in the two series before and after treatment, with 50-70 points corresponding to mild anxiety, 71-90 corresponding to moderate anxiety, and >90 corresponding to severe anxiety on a 100-point scale. With a total score of 100 points, the score and corresponding depression evaluation was 50-70 points for mild depression, 71-90 for moderate depression, and >90 for severe depression. The severity of anxiety and depression was in positive association with the corresponding score.

(7) Pittsburgh Sleep Quality Index (PSQI) score: PSQI [22] was applied for sleep quality assess-

ment of patients before and after treatment. There are 7 components (each scoring 0-3 points) and 18 items in the scale, and the cumulative score is the total score of PSQI, which ranges from 0 to 21. Very good sleep quality: 0-5 points; Good sleep quality: 6-10 points; Fair sleep quality: 11-15 points; Poor sleep quality: 16-21 points.

Statistical methods

Statistical analysis and figure illustration were performed by SPSS 24.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7 respectively. Recorded as [n (%)], the counting data were compared by Chi-square test between groups and analyzed by continuity correction Chi-square in case that the theoretical frequency in Chi-square test was less than 5. Expressed as means \pm standard deviation ($\bar{x} \pm sd$), the measurement data between groups were compared by independent sample t-test, and the intra-comparison pre- and post-treatment was made by paired T-test. The data at different time points within the group were analyzed by one-way ANOVA, and the subsequent pairwise comparisons were carried out by SNK-q method. Differences with p -values <0.05 were considered significant.

Results

General information

Significant statistical differences were absent with respect to patient general clinical baseline data such as gender, age, body mass index (BMI), course of disease, marriage, residence, educational background, smoking history, drinking history, hypertension history, and diabetes history ($P>0.05$) (Table 1).

Comparison of sputum negative conversion rate

The RG present with remarkably higher sputum negative conversion rates than the CG after 6, 12 and 24 months post treatment ($P<0.05$) (Table 2).

Comparison of foci absorption rate

The post-treatment foci absorption rate was 97.37% in the RG, which was notably higher than 68.75% in the CG ($P<0.01$) (Table 3).

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Table 1. Comparison of general information between the two groups ([n (%)], $\bar{x} \pm \text{sd}$)

| Classification | Research group (n=38) | Control group (n=32) | t/ χ^2 value | P value |
|---------------------------|-----------------------|----------------------|-------------------|---------|
| Gender | | | 0.374 | 0.540 |
| Male | 21 (55.26) | 20 (62.50) | | |
| Female | 17 (44.74) | 12 (37.50) | | |
| Age (years old) | 46.86 \pm 7.14 | 47.69 \pm 8.06 | 0.456 | 0.649 |
| BMI (kg/m ²) | 23.56 \pm 3.24 | 23.04 \pm 3.02 | 0.689 | 0.492 |
| Course of disease (month) | 11.04 \pm 1.08 | 10.85 \pm 1.12 | 0.720 | 0.473 |
| Marital status | | | 0.537 | 0.463 |
| Married | 28 (73.68) | 21 (65.62) | | |
| Single or widowed | 10 (26.32) | 11 (34.38) | | |
| Residence | | | 0.130 | 0.717 |
| Urban | 15 (39.47) | 14 (43.75) | | |
| Rural | 23 (60.53) | 18 (56.25) | | |
| Educational background | | | 0.320 | 0.571 |
| \geq High school | 18 (47.37) | 13 (40.62) | | |
| < High school | 20 (52.63) | 19 (59.38) | | |
| History of smoking | | | 0.160 | 0.689 |
| Yes | 22 (57.89) | 17 (53.12) | | |
| No | 16 (42.11) | 15 (46.88) | | |
| History of drinking | | | 0.576 | 0.447 |
| Yes | 11 (28.95) | 12 (37.50) | | |
| No | 27 (71.05) | 20 (62.50) | | |
| History of hypertension | | | 0.472 | 0.491 |
| Yes | 8 (21.05) | 9 (28.12) | | |
| No | 30 (78.95) | 23 (71.88) | | |
| History of diabetes | | | 0.015 | 0.900 |
| Yes | 10 (26.32) | 8 (25.00) | | |
| No | 28 (73.68) | 24 (75.00) | | |

Table 2. Comparison of sputum negative conversion rate between the two groups [n (%)]

| Groups | At 6th month after treatment | At 12th month after treatment | At 24th month after treatment |
|-----------------------|------------------------------|-------------------------------|-------------------------------|
| Research group (n=38) | 25 (65.79) | 35 (92.11) | 38 (100.00) |
| Control group (n=32) | 13 (40.63) | 19 (59.38) | 23 (71.88) |
| χ^2 | 4.433 | 10.550 | 12.260 |
| P | 0.035 | 0.001 | <0.001 |

Comparison of incidence of adverse reactions

The RG (18.42%) showed a noticeably lower incidence of adverse reactions than in the CG (53.13%) post treatment ($P < 0.01$) (Table 4).

Comparison of inflammatory factors

TNF- α , IL-6 and IFN- γ levels differed insignificantly between the two series before treat-

ment, while after treatment, these parameters reduced notably and were noticeably lower in the RG than in the CG ($P < 0.001$) (Figure 1).

Comparison of PF indexes

Significant differences were absent in FEV1, FEV1/FVC and PEF between the two series before treatment, while after treatment, these parameters increased significantly and were dramatically higher in the RG than in the CG ($P < 0.001$) (Figure 2).

Comparison of SAS, SDS and PSQI scores

No significant differences were observed in SAS, SDS and PSQI scores between the two groups before treatment, but after treatment, the three scale scores declined observably, with lower parameters in the RG than in the CG ($P < 0.001$) (Figures 3, 4).

Discussion

The incidence of MDR-TB is increasing annually, and the clinical treatment effect is poor, with low sputum negative conversion rates and severe lung tissue destruction, which have become the Gordian knot in the clinical treatment of pulmonary TB [23, 24]. Accordingly, finding new treatment schemes and drugs to improve clinical efficacy and avoid drug resistance is a pressing issue [25].

In the current research, we applied the regimen of CS plus anti-TB drugs to patients with MDR-TB and discussed its application effect, hoping to provide useful references for clinical practice.

In this study, a significantly higher sputum negative conversion rate was determined in the RG after 6, 12 and 24 months of treatment as compared to in the CG. This indicates that CS

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Table 3. Comparison of foci absorption rate between the two groups [n (%)]

| Groups | Significant absorption | Absorption | Ineffective | Deteriorated | Total absorptivity |
|-----------------------|------------------------|------------|-------------|--------------|--------------------|
| Research group (n=38) | 27 (71.05) | 10 (26.32) | 1 (2.63) | 0 (0.00) | 37 (97.37) |
| Control group (n=32) | 9 (28.13) | 13 (40.63) | 10 (31.25) | 0 (0.00) | 22 (68.75) |
| χ^2 | - | - | - | - | 10.740 |
| P | - | - | - | - | 0.001 |

Table 4. Comparison of incidence of adverse reactions between the two groups [n (%)]

| Groups | Gastrointestinal reaction | Hypothyroidism | Drug-induced liver injury | Central nervous system symptoms | Mental illness | Total incidence |
|-----------------------|---------------------------|----------------|---------------------------|---------------------------------|----------------|-----------------|
| Research group (n=38) | 1 (2.63) | 0 (0.00) | 1 (2.63) | 3 (7.90) | 2 (5.26) | 7 (18.42) |
| Control group (n=32) | 6 (18.75) | 4 (12.50) | 5 (15.62) | 1 (3.13) | 1 (3.13) | 17 (53.13) |
| χ^2 | - | - | - | - | - | 9.286 |
| P | - | - | - | - | - | 0.002 |

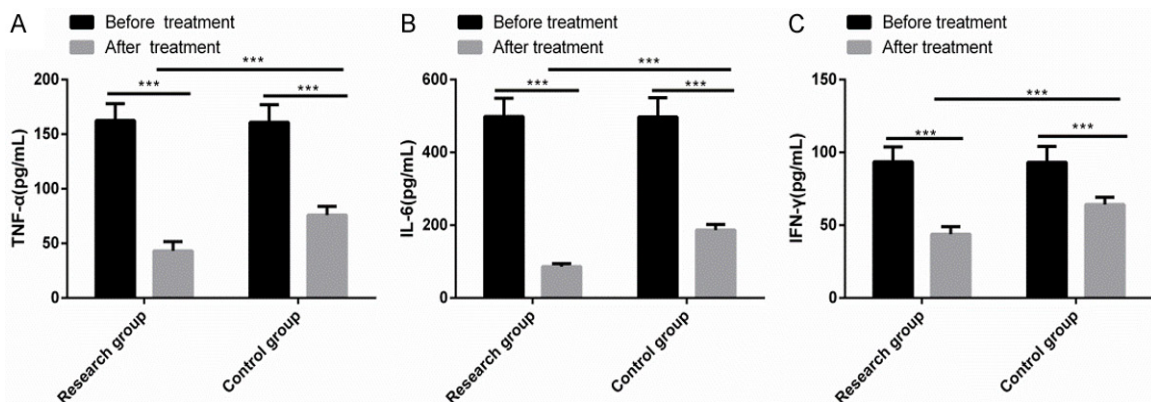


Figure 1. Comparison of inflammatory factors. TNF- α (A), IL-6 (B) and IFN- γ (C) levels differed insignificantly between the two series before treatment, while after treatment these parameters reduced notably and were noticeably lower in the RG than in the CG ($P < 0.001$). Note: *** $P < 0.001$.

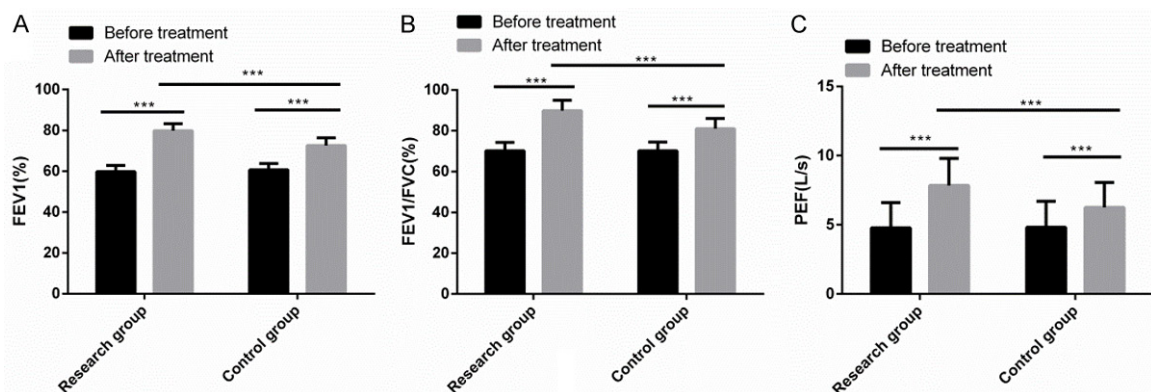


Figure 2. Comparison of pulmonary function indexes. There was no significant difference in FEV1, FEV1/FVC and PEF between the two groups before treatment. After treatment, FEV1, FEV1/FVC and PEF increased significantly, and levels in the research group were significantly higher than those in the control group. Note: *** $P < 0.001$.

plus anti-TB drugs can effectively improve the sputum negative conversion rate of patients,

which is related to the antibacterial pharmacological action of CS, that is, high sensitivity and

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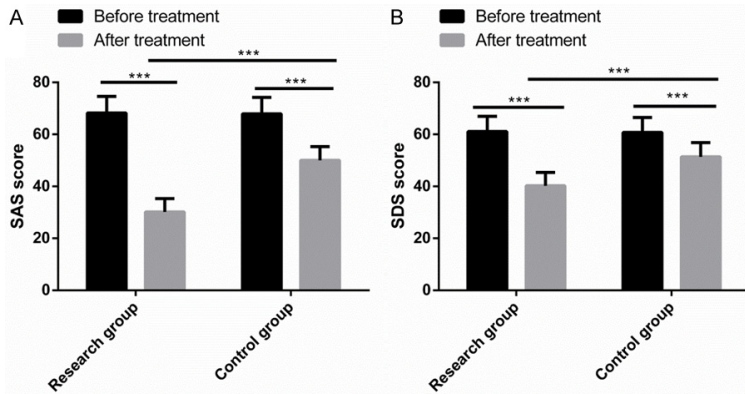


Figure 3. Comparison of SAS, SDS and PSQI scores. Before treatment, there was no significant difference in SAS score (A) and SDS score (B). After treatment, SAS, SDS decreased significantly, and the three scale scores in the research group were significantly lower than those in the control group. Note: *** $P < 0.001$.

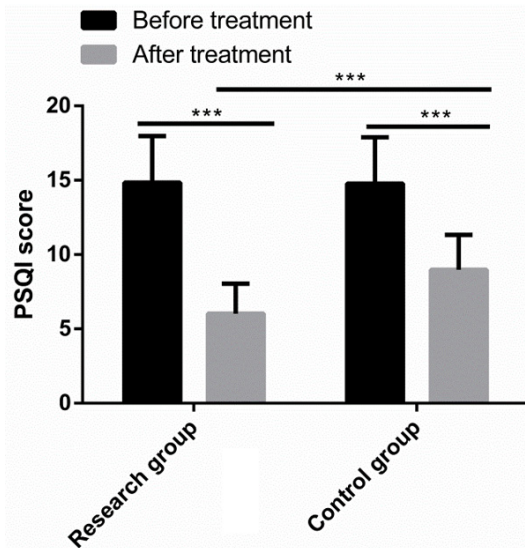


Figure 4. Comparison of PSQI scores. Before treatment, there was no significant difference in PSQI scores between the two groups. After treatment, PSQI scores decreased significantly in both groups, and were lower in the research group than in the control group. Note: *** $P < 0.001$.

difficulty in developing drug resistance. Li Y et al. [26] found that CS in the treatment of MDR-TB can enormously improve the sputum negative conversion rate in the consolidation phase and enhance the treatment effect of patients, which is in line with our research results. Van der Walt ML et al. [27] reported that compared with those receiving ethambutol or terizidone, patients receiving CS had evidently higher sputum negative conversion rates, lower adverse reactions, higher treatment compliance and

better clinical efficacy. Besides, our research determined distinctly higher foci absorption rates and a lower incidence of adverse reactions in the RG than in the CG, suggesting that CS plus anti-TB drugs can promote foci absorption and cavity healing, and reduce the adverse reaction rate of patients. This is related to the strong tissue penetration and relatively small toxic side effects of CS, which is similar to the research results of Van der Walt ML et al. As PF of MDR-TB patients is an essential index for efficacy and prognosis evaluation

of patients [28], we also evaluated the PF of patients. Significantly elevated FEV1, FEV1/FVC and PEF were found in the RG after treatment, which were also higher than those in the CG, indicating that CS plus anti-TB drugs can effectively enhance the PF of patients. In the research of Wang J et al. [29], it was observed that CS significantly enhanced the efficacy and the PF of patients with MDR-TB, but the adverse reactions in the central nervous system in patients deserves attention, which is in line with our research results. What's more, inflammatory factors TNF- α , IL-6 and IFN- γ were determined to be evidently decreased in the RG after treatment and were also lower than those in the CG, indicating that CS plus anti-TB drugs can validly inhibit inflammatory reactions. Basingnaa et al. [30] revealed that in patients with MDR-TB, TNF- α , IL-6 and IFN- γ levels declined dramatically after anti-TB treatment, which agrees with our research results. Most MDR-TB patients will suffer from anxiety and depression, which will adversely affect their sleep quality [31]. In our investigation, the scores of SAS, SDS, and PSQI decreased statistically in the RG after treatment and were distinctly lower than those in the CG, demonstrating that CS plus anti-TB drugs can greatly relieve the patients' anxiety and depression and improve their sleep quality. Similarly, Khanal S et al. [32] found that patients with MDR-TB had a high risk of anxiety, depression and sleep disorders, which could be effectively alleviated by social psychological support.

To sum up, while effectively improving the sputum negative conversion rate, ameliorating the

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prognosis, and reducing adverse reactions, CS plus anti-TB drugs for MDR-TB patients can inhibit the release of inflammatory factors, improve PF, and palliate anxiety, depression and sleep disorders. However, there are still some shortcomings to be addressed. For example, we can further analyze the influencing factors of patients' treatment compliance, and expand the sample size to explore the credibility of clinical efficacy and adverse reactions. In the future, we will conduct research from the above perspectives.

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Disclosure of conflict of interest

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