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Original Article

Evaluation of the treatment efficacy of systemic care combined with thymopentin and 2HRZE/4HR for primary tuberculosis

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Abstract: Objective: To investigate the efficacy of systemic care combined with thymopentin and 2HRZE/4HR in the treatment of primary tuberculosis. Methods: The clinical data of 93 patients with primary tuberculosis were retrospectively collected and divided into two groups based on the intervention method. Group A (n=46) was treated only with 2HRZE/4HR, and group B (n=47) was treated with the 2HRZE/4HR combined with thymopentin. Meanwhile, both groups received systematic care. The lesion absorption rate, sputum conversion rate (SCR), T lymphocyte subpopulation count, immunoglobulin level, lung function index, changes in sputum supernatant levels of cytokines before and after treatment, and the occurrence of adverse reactions were compared. Results: Group B exhibited higher complete absorption rate of foci and lower basic absorption rate than group A ($P < 0.05$). The SCRs of group B after 2, 4 and 6 months of intervention were higher than those of group A ($P < 0.05$). Compared with group A, group B had lower $CD8^+$ level and higher $CD4^+$ and $CD3^+$ levels ($P < 0.05$). Group B also had higher levels of IgA, IgG, and IgM than group A after intervention ($P < 0.05$). Group B had higher levels of FEV1, PEF, and FVC than group A after intervention ($P < 0.05$). In contrast to group A, group B had lower IL-4 levels and higher TNF-γ levels ($P < 0.05$). The incidence rate of adverse events in group B was not significantly different from that in group A ($P > 0.05$). Conclusion: Systemic care combined with 2HRZE/4HR was effective for treatment of primary tuberculosis, which is beneficial for improving the immunity, SCR, and the inflammatory status, with low incidence of adverse events and a high safety level.

Keywords: Systemic care, thymopentin, 2HRZE/4HR, primary care, tuberculosis, efficacy

Introduction

Tuberculosis is a chronic infectious disease with a high prevalence that can invade multiple organs, with pulmonary tuberculosis infection as the most common type [1]. The source of infection is bacteria. Following human tuberculosis infection, one becomes ill when there is an increase in cell-mediated metamorphosis or when the body's immunity is significantly reduced [2, 3]. If an accurate diagnosis can be obtained in time and treatment is carried out in a scientific and rational manner, most patients will eventually be cured [4].

Pharmacotherapy is the main modality of clinical treatment of tuberculosis, and its role is to shorten the infectious period and reduce the morbidity, infection, and mortality rates [5]. For patients with primary tuberculosis, standardized treatment is the mainstay to control the progression [6]. The 2HRZE/4HR is a commonly used chemotherapy regimen for the treatment of tuberculosis. Although this regimen can effectively kill Mycobacterium tuberculosis, it will inevitably damage white blood cells, impairing the immune function and increasing the risk of microbial infection [7, 8]. Thymopentin is an immunomodulator with a high clinical application rate, which can reasonably regulate the proportion of T-lymphocyte subpopulations and promote the activation, maturation, development and proliferation of each subpopulation to keep Th1/Th2 in a balanced state [9, 10]. Thymopentin has significant immunomodulatory effects and can effec-

tively improve the prognosis of patients after administration. In addition to drug therapy for patients with tuberculosis, scientific and reasonable nursing intervention is essential to ensure an ideal treatment effect [11]. Systematic care is a holistic, scientific, and systematic nursing model, emphasizing the continuity and humanization of nursing. When applying systematic care to tuberculosis treatment, the quality of life was improved [12].

This study explored the regimen of 2HRZE/4HR combined with thymopentin in the treatment of primary tuberculosis, and combined it with systematic care, aiming to improve the prognosis of patients and enhance the immunity of the body.

Materials and methods

Baseline data

We retrospectively retrieved the clinical data of 93 patients with primary tuberculosis in our hospital and grouped them based on the intervention mode. There were 46 patients in group A who were only treated with 2HRZE/4HR, and 47 patients in group B who were treated with 2HRZE/4HR combined with thymopentin, while both groups were strengthened with systemic care. (1) Inclusion criteria. The consent form was signed by patients and their families; positive results from sputum smear; active TB foci were observed in the lungs by chest X-ray; normal communication skills; without contraindications to the drugs. This study was approved by the ethics committee of The First People's Hospital of Fuyang Hangzhou. (2) Exclusion criteria: inability to strictly comply with medical advice; treatment with immunosuppressants or immune-boosting agents within 3 months prior to enrollment; combined with severe cardiac, liver, kidney, and other organic diseases; combination of other bacterial or fungal infections of the lungs; and allergies.

Methods

Group A: During the intensive phase, they were given 0.75 g of ethambutol (GuojiziH33021602, Hangzhou Minsheng Pharmaceutical Co., 0.25 g*100 tablets), 1.5 g pyrazinamide (H21022354, Shenyang Hongqi Pharmaceutical Co., specification: 0.25 g), 0.45 g rifampicin (H31020346, Shanghai Xinyi Tianping Pharmaceuticals Ltd., Specifications: 0.15 g), 0.3 g isoniazid (H21022350, Shenyang Hongqi Pharmaceutical Co., Ltd., specification: 0.1 g*100 tablets), q.i.d for 2 consecutive months. When the patient was in the consolidation phase they were given, q.i.d 0.45 g of rifampin, 0.3 g of isoniazid, q.i.d for 4 consecutive months of treatment.

Group B: The dosing of 2HRZE/4HR was the same as group A. Patients were also given enteric-coated capsules (H20000301, Haco White Swan Pharmaceutical Group Co.), b.i.d 5 mg for 6 months.

The two groups were given systematic care (1) Psychological intervention. After patients were admitted to the hospital, the nurses actively communicated with them, assessed their needs, provided them with psychological and physiological support, and alleviated their sense of helplessness and fear; instructed their families to give them psychological support to alleviate their sense of guilt and inferiority; correct their misconceptions about the disease, and help build their confidence in treatment. (2) Disease knowledge guidance: The medication knowledge guidance was strengthened. The importance and necessity of strict compliance was explained. Considering the patients' individual condition, targeted health education was strengthened, including the types of drugs, doses, methods and related matters/details needing attention. Their families were responsible for monitoring drugs compliance. (3) Life guidance: Patients were instructed to develop healthy lifestyles/habits, quit smoking and drinking, avoid inhaling all kinds of irritating gases, have a light diet rich in vitamins and protein, avoid overheating, strong stimulating or spicy food during hemoptysis. When their condition is in a stable state, breathing exercises were given like tai chi and jogging and other physical exercises were performed according to their actual conditions. (4) Disinfection and isolation guidance: Patients were instructed to avoid spitting everywhere and not to sneeze or cough in front of others; The bedpans, chopsticks, basins and towels and other personal items were separately used; Patients' books, clothes and bedding were exposed to the sun, and the room was kept ventilated and airy. (5) Continuing care: When patients were discharged from the

Table 1. Comparison of clinical data [n (%)]/($\bar{x}$ ± s)

Baseline data		Group A (n=46)	Group B (n=47)	t/X^2	P
Gender	Male	39 (84.78)	41 (87.23)	0.116	0.733
	Female	7 (15.22)	6 (12.77)		
Age (years)		45.98±3.17	46.02±3.12	0.061	0.951
Duration (year)		0.58±0.05	0.56±0.09	1.321	0.190

Table 2. Comparison of lesion absorption rate between the two groups [n (%)]

Grouping	Cases	Complete absorption	Significant absorption	Basic absorption	No change or worsening
Group A	46	29 (63.04)	10 (21.74)	7 (15.22)	0 (0.00)
Group B	47	43 (91.49)*	2 (4.26)*	5 (10.64)	0 (0.00)
X^2		10.760	6.323	0.434	--
P		0.001	0.011	0.510	--

Note: *indicates comparison with group A. P < 0.05; -indicates none.

Table 3. Comparison of SCR between the two groups [n (%)]

Grouping	Cases	2 months	4 months	6 months
Group A	46	30 (65.22)	31 (67.39)	33 (71.74)
Group B	47	42 (89.36)*	43 (91.49)*	46 (97.87)*
X^2		8.610	8.305	12.416
P		0.003	0.004	0.000

Note: *indicates comparison with group A. P < 0.05.

Table 4. Comparison of the occurrence of adverse reactions [n (%)]

Grouping	Cases	Abnormal liver function	Gastrointestinal reactions	The incidence
Group A	46	3 (6.52)	4 (8.70)	7 (15.22)
Group B	47	4 (8.51)	4 (8.51)	8 (17.02)
X^2				0.056
P				0.813

hospital, they left their contact information such as for QQ, telephone or WeChat, so that medical and nursing staff can contact them to remind them to take their medication and return to the hospital for re-examination on time.

Outcomes measurement

(1) Absorption of foci [13]: After 6 months of treatment, if the foci were completely absorbed, it was classified as complete absorption; if the foci shrink by 1/2 compared to the pre-treatment, the cavity is obstructively or completely closed, it was classified as significant absorption; if the foci shrink by 1/2 compared to the pre-treatment and the cavity becomes smaller, it was classified as basic absorption; if the foci were not absorbed or instead increase in size, it was classified as no change or worsening.

(2) Criteria for sputum conversion [14]: If the results of three consecutive sputum smears were negative, sputum conversion is indicated, and the rates of sputum conversion in the two groups of patients after 2, 4 and 6 months of treatment were compared.

(3) Immune function indexes [15]: Before and after treatment, 3 ml of morning fasting venous blood was drawn from patients of both groups, and T-lymphocyte subsets $CD8^+$, $CD4^+$, $CD3^+$ were measured by multicolor flow cytometry, and immunoglobulin IgA, IgG, and IgM levels were measured by turbidimetric assay.

(4) Pulmonary function indexes [16]: The pulmonary function indexes Forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), and forced vital capacity (FVC) were measured by pulmonary function analyzer.

(5) Cytokine levels of sputum supernatant [17]: Before and after treatment, 1 ml of deep sputum was collected from both groups, and TNF-γ (tumor necrosis factor-γ) and IL-4 (interleukin-4) were measured by enzyme-linked immunosorbent assay.

(6) The incidence of adverse reactions in the two groups was compared.

Statistical methods

SPSS 22.0 was used for data analysis. Graphpad Prism 8 software was used to create plots. Measurement data were expressed as mean ± standard deviation, and *t* test was used

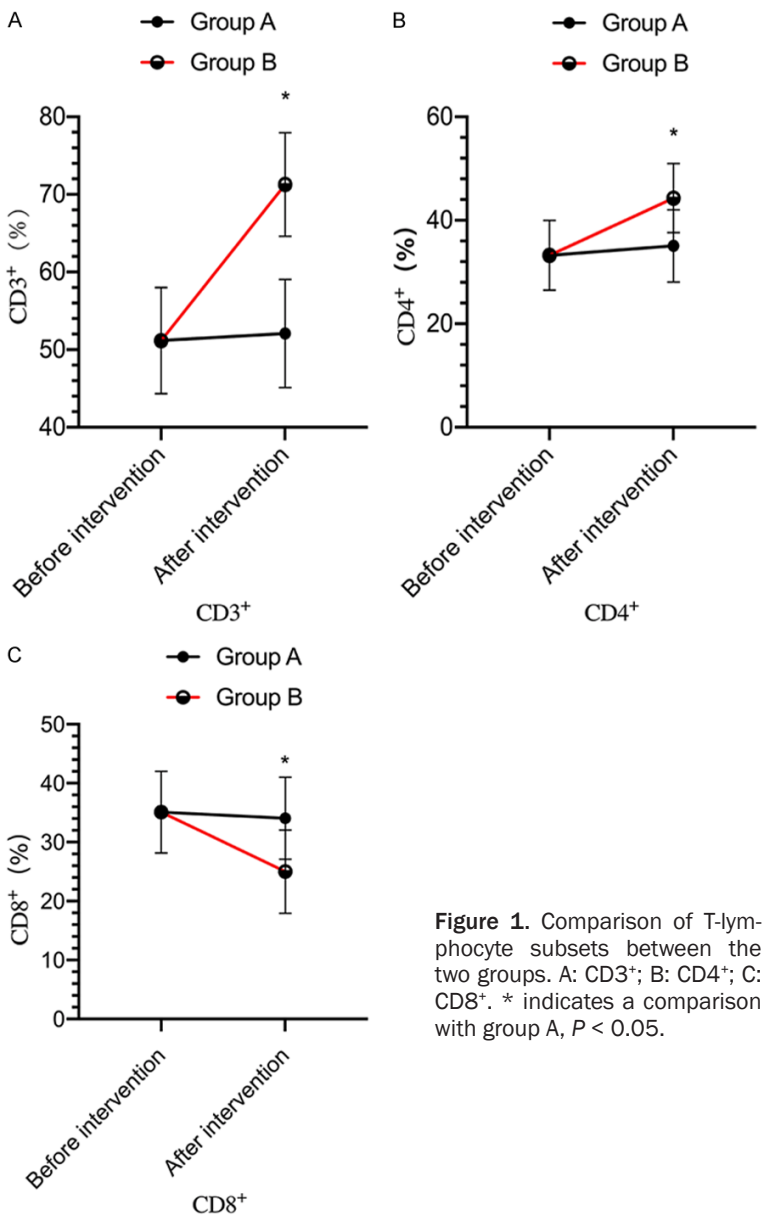

Figure 1. Comparison of T-lymphocyte subsets between the two groups. A: $CD3^+$; B: $CD4^+$; C: $CD8^+$. * indicates a comparison with group A, $P < 0.05$.

for normally distributed data, while Mann-Whitney U test was used for non-normally distributed data; Count data were expressed as [n (%)], and chi-aquared test was used for comparison of count data. $P < 0.05$ suggested that statistical significance existed.

Results

Comparison of baseline data

There was no statistical significance ($P > 0.05$) (**Table 1**) when comparing the two groups in terms of gender, age, and disease duration.

Comparison of foci absorption, SCR and adverse effects between the two groups

After treatment, the complete absorption rate of foci in group B was 91.49%, higher than 63.04% in group A. The basic absorption rate was 4.26%, lower than 21.74% in group A ($P < 0.05$). There was no significant difference in the rate of significant absorption, no change or worsening between the two groups ($P > 0.05$) (**Table 2**). Patients in group B had a SCR of 89.36% after 2 months of intervention, higher than 65.22% in group A. The SCR after 4 months of intervention was 91.49%, higher than 67.39% in group A. The SCR after 6 months of intervention was 97.87%, higher than 71.74% in group A ($P < 0.05$) (**Table 3**). There were 4 cases of abnormal liver function and 4 cases of gastrointestinal reactions in group B, and the corresponding cases were 3 and 4 respectively, in group A. The incidence rate of adverse reactions in group B was 17.02%, which was not significantly different from 15.22% in group A ($P > 0.05$) (**Table 4**).

Comparison of T lymphocyte subpopulations

Compared with the pre-intervention, the $CD8^+$ level decreased, and $CD4^+$ and $CD3^+$ levels increased in both groups after intervention ($P < 0.05$). $CD8^+$ was lower and $CD4^+$ and $CD3^+$ were higher ($P < 0.05$) after intervention in group B compared to group A (**Figure 1**).

Comparison of immunoglobulin levels

Compared with the pre-intervention levels, the levels of immunoglobulins in the two groups increased after intervention ($P < 0.05$). In contrast to group A, the levels of IgA, IgG and IgM were higher in group B ($P < 0.05$) (**Figure 2**).

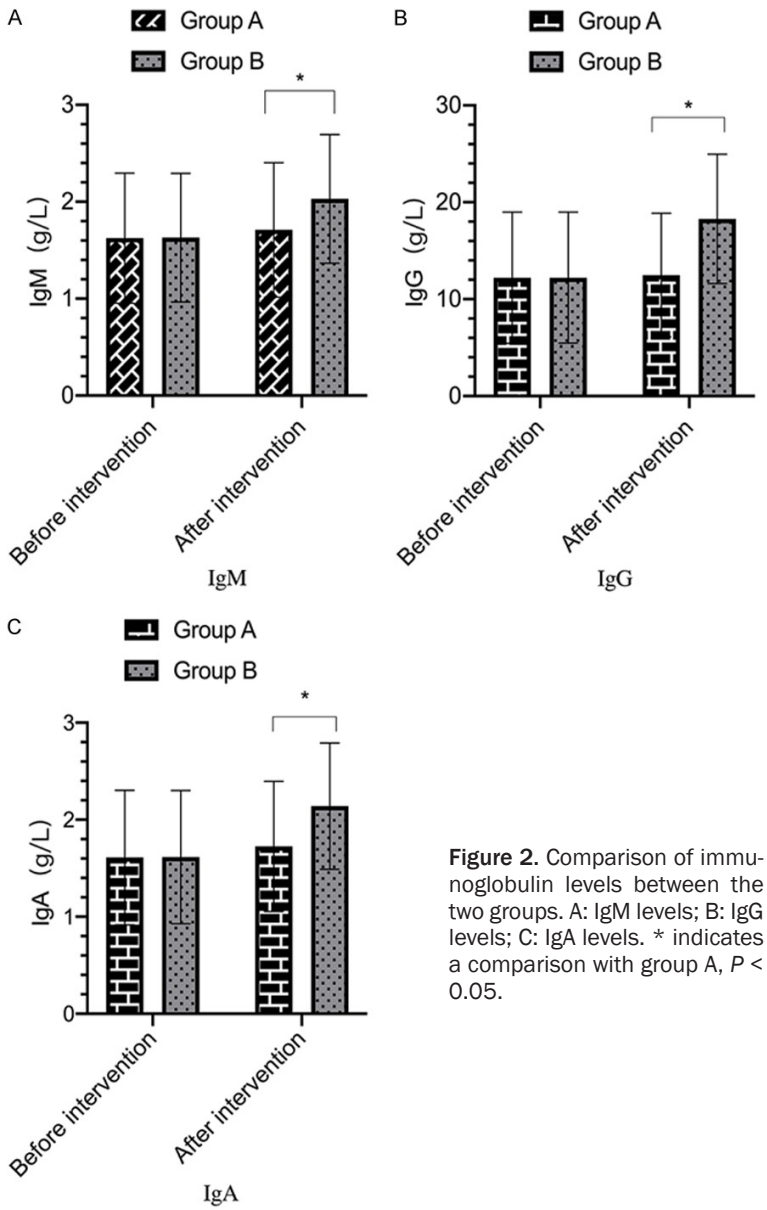

Figure 2. Comparison of immunoglobulin levels between the two groups. A: IgM levels; B: IgG levels; C: IgA levels. * indicates a comparison with group A, $P < 0.05$.

Comparison of lung function indexes

In comparison with the pre-intervention, the levels of each pulmonary function index in the two groups increased after intervention ($P < 0.05$). The levels of FEV1, PEF, and FVC were higher in group B than in group A ($P < 0.05$) (**Figure 3**).

Comparison of cytokine levels in sputum supernatant

The levels of cytokine levels in sputum supernatant did not differ before intervention between two groups ($P > 0.05$). Compared with the pre-intervention, the levels of IL-4 decreased and TNF-γ increased in both groups after intervention ($P < 0.05$). Compared with group A, the levels of IL-4 were lower and TNF-γ were higher ($P < 0.05$) in group B after intervention (**Figure 4**).

Discussion

The bacteria that cause tuberculosis often develop resistance to antimicrobial drugs and thus tuberculosis exhibits a long disease duration, and also has a high relapse rate. Studies show that 32.8% of patients with primary treatment of sputum-positive tuberculosis experience recurring episodes of symptoms, and the resistance rate to anti-TB drugs is about 46.4% [18, 19]. When treating primary tuberculosis, the choice of treatment options is very important, and we need to find highly sensitive and effective anti-TB drugs to treat patients.

The 2HRZE/4HR regimen is usually prescribed to treat tuberculosis. Although this regimen can kill the tuberculosis bacillus, it can also damage normal white blood cells and weaken the body's immunity, which affects the treatment effects and prognosis [20, 21]. Meanwhile, the combination of multiple chemotherapeutic drugs may also lead to multiple adverse reactions, and some patients may even discontinue the treatment due to intolerance [22]. In view of this, the present study showed that complete lesion absorption rate and SCR were higher in the combined treatment group than in the group treated with 2HRZE/4HR alone, and all the lung function indicators were better in the combined treatment group than in the group treated with 2HRZE/4HR alone, suggesting thymopentin combined with the 2HRZE/4HR enhances the

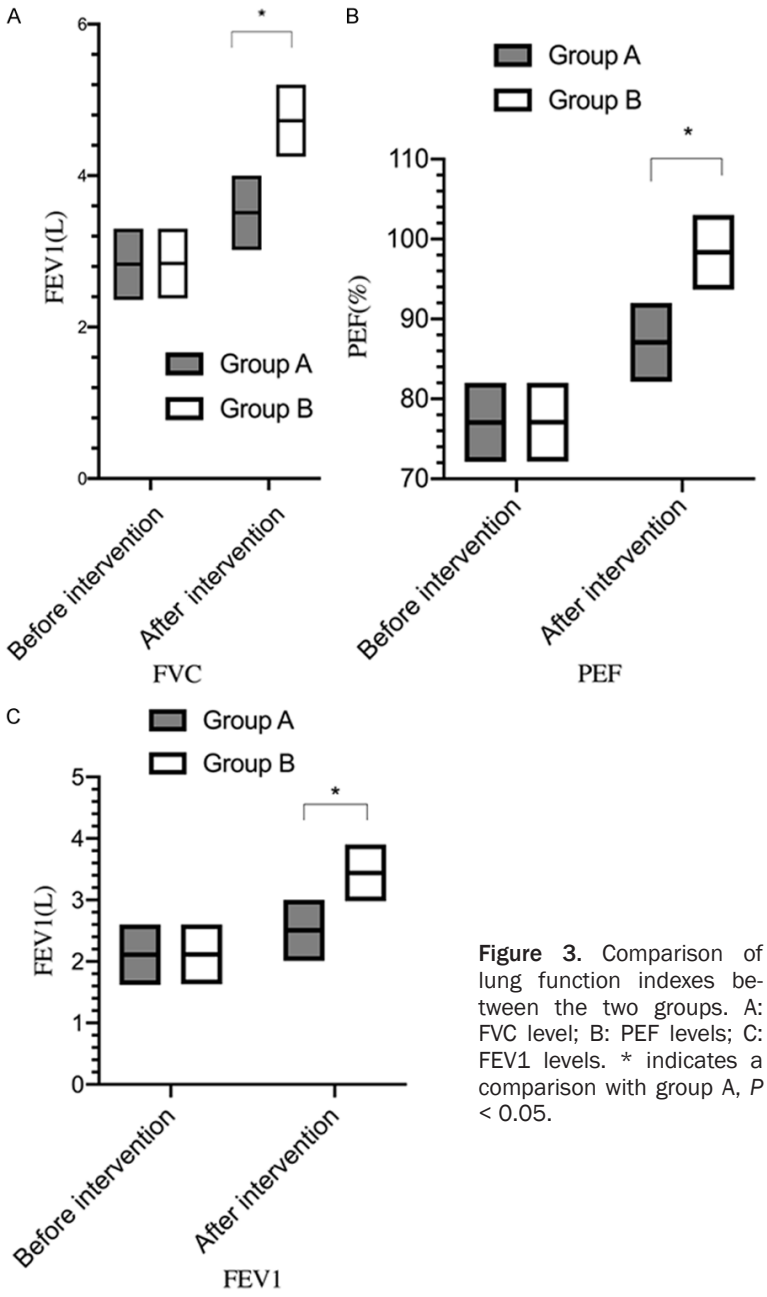

Figure 3. Comparison of lung function indexes between the two groups. A: FVC level; B: PEF levels; C: FEV1 levels. * indicates a comparison with group A, $P < 0.05$.

clinical efficacy and improves the lung function of patients. Since the incidence of adverse events was not significantly different between the two groups, this further proves the safety of the combined regimen. We speculated that thymopentin is an immunomodulator that enhances the phagocytic activity of macrophages and immunity, resulting in increased serum superoxide dismutase activity and natural killer cell activity [23]. This drug also enhances the therapeutic effect of the 2HRZE/4HR regimen, inhibits the tuberculosis bacillus and promotes the conversion of sputum bacteria, resulting in less pathological damage to the lungs. $CD8^+$, $CD4^+$, and $CD3^+$ indicated the immune function, and their levels are closely correlated with the long-term prognosis of primary tuberculosis and the clearance rate of the pathogenic bacteria. Compared to healthy subjects, patients with primary tuberculosis generally have higher levels of $CD8^+$ and lower levels of $CD4^+$ and $CD3^+$. IgA, IgG, and IgM levels are also important indicators to measure immune function, and they are relatively low in patients with primary tuberculosis [24]. In this study, the $CD4^+$, $CD3^+$ levels, IgA, IgG, and IgM levels were higher while $CD8^+$ levels were lower in the combined treatment group than in the group treated with 2HRZE/4HR alone, suggesting that the combination of thymopentin with 2HRZE/4HR regimen is beneficial for improving immunity. The reason may be that thymopentin can induce the transformation of stem cells into T cells, promote the activation, maturation and differentiation of T lymphocytes and their subpopulations, so that the human body's immune function can be improved and the impaired cellular immune function can be corrected. A variety of cytokines play an important role in the immunopathological process of tuberculosis, and are closely related to the clinical prognosis, and severity of the disease. In the present study, the combined treatment group had lower IL-4 levels and higher TNF-γ levels after intervention, suggesting that the combination therapy could improve the inflammatory status. TNF-γ is a multifunctional immunomodulatory protein, mainly secreted by T lymphocytes. IL-4 is a Th2 cytokine that plays a key role in humoral immunity, inhibiting the expression of Th1 cells and promoting the differentiation and proliferation of Th2 cells [25, 26]. Thymopentin and 2HRZE/

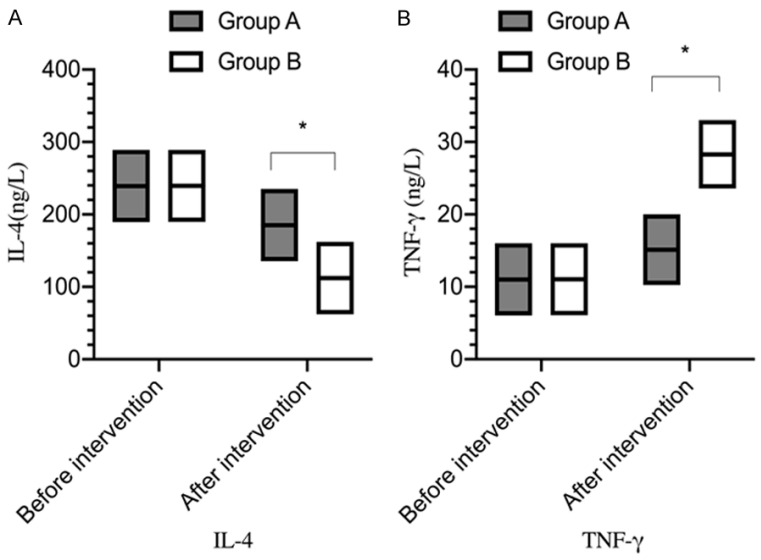

Figure 4. Comparison of cytokine levels between the two groups. A: IL-4 levels; B: TNF-γ levels. * indicates a comparison with group A, $P < 0.05$.

4HR exert a combined effect to improve immune function and therefore cytokine levels [27]. The present study showed that the 2HRZE/4HR and thymopentin regimen achieved a satisfactory therapeutic effect, which is also closely related to the efficacy of systematic care. In this study, we provided systematic care for TB patients in terms of psychology, medication, lifestyle, diet, disinfection and isolation, which can help correct patients' misconceptions about the disease and ensure ideal treatment results by strictly following medical advice. The core of systematic care is the continuity of nursing intervention, which can help to monitor patients' strict compliance with medication and improve their prognosis after discharge from the hospital [28].

In summary, the systemic care combined with thymopentin and 2HRZE/4HR is effective in treating primary tuberculosis, improving immunity, SCR, and inflammation.

Although this study has achieved some results, there is a limitation of small sample size, which needs to be further investigated in the future by expanding the sample size.

Disclosure of conflict of interest

None.

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