

Clinical Effects of Traditional Chinese Medicine + Azithromycin in the Treatment of Mycoplasma Pneumonia

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Objective: To explore the clinical effect of Traditional Chinese Medicine (TCM) plus azithromycin in the treatment of Mycoplasma pneumonia (MP).

Methods: This was a retrospective study including the clinical data of 119 patients with MP treated at Taihe County Hospital of Traditional Chinese Medicine from April 2021 to November 2023. According to treatment records, 58 cases were treated with conventional therapy and azithromycin (azithromycin group), and 61 cases were treated with conventional therapy, azithromycin, and Xiaoxianxiong decoction and Weijing decoction and acupoint application (TCM + azithromycin group). The treatment outcomes, levels of inflammatory status indicators before and after treatment, respiratory function status, and incidence of adverse reactions were analyzed between the two groups.

Results: The overall effective rate of TCM + azithromycin group was significantly higher than that of azithromycin group ($P < 0.05$). After treatment, the serum C-reactive protein (CRP), procalcitonin (PCT), and white blood cell count (WBC) levels in both groups significantly decreased compared to before treatment, and the TCM + azithromycin group was significantly lower than the azithromycin group ($P < 0.05$). After treatment, partial pressure of carbon dioxide (PaCO_2) in both groups significantly decreased compared to before treatment, while oxygen partial pressure (PaO_2) and oxygenation index (OI) significantly increased compared to before treatment; Moreover, the TCM + azithromycin group had significantly lower PaCO_2 and higher PaO_2 and OI than the azithromycin group ($P < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

Conclusion: Compared with treatment with azithromycin alone, intervention with TCM + azithromycin can significantly improve the respiratory function of patients with MP, reduce the degree of inflammatory response, and enhance the overall treatment effect without increasing the incidence of adverse reactions.

Core Tip: This study indicates that intervention with traditional Chinese medicine and azithromycin can significantly improve the respiratory function of MP patients, reduce the degree of inflammatory response, improve overall treatment efficacy, and is safe.

Keywords: Traditional Chinese Medicine, Xiaoxianxiong decoction, Weijing decoction, acupoint application, azithromycin, mycoplasma pneumonia

Introduction

MP is known as primary atypical pneumonia.^{1,2} The main clinical manifestations include fever, anorexia, cough, chills, sore throat, and substernal pain. X-rays often show unilateral lesions.¹⁻³ If patients do not receive timely and effective intervention, they may progress to severe pneumonia, and in severe cases, multiple organ dysfunction syndrome, and septic shock may occur.³⁻⁵

Currently, clinical interventions for pneumonia are often implemented through measures such as reducing fever, promoting sputum excretion, and combating infection, which can alleviate the clinical symptoms of patients to varying degrees.^{6,7} However, the overall effect is difficult to achieve clinical expectations, and long-term medication can easily

lead to drug resistance and related adverse reactions.^{6–8} As TCM continues to gain recognition and acceptance, the focus of clinical research on pneumonia treatment has shifted to the combination of traditional Chinese and Western medicine. TCM believes that the onset of MP is due to improper diet, loss of spleen function, difficulty in transforming water and grains into essence, accumulation of phlegm and turbidity, storage in the lungs, and obstruction of the lungs. Therefore, the treatment of MP should focus on broadening the chest, regulating qi, clearing heat and resolving phlegm.^{9,10} Acupoint application is an important technique for treating internal and external diseases in TCM. It can stimulate specific acupoints, regulate the circulation of blood and qi, drive away cold and wind, regulate qi and promote internal circulation.¹¹ Xiaoxianxiong decoction is a representative formula of TCM for removing phlegm. Weijing decoction is a classic formula for pulmonary abscess. Both have the effects of removing blood stasis and pus, clearing the lungs and resolving phlegm.^{12,13}

At present, clinical research has been conducted on the application value of acupoint application, Xiaoxianxiong decoction, and Weijing decoction in the treatment of MP. However, the clinical efficacy of Xiaoxianxiong decoction, Weijing decoction, acupoint application, and azithromycin in the treatment of MP has not been widely confirmed. Therefore, this study aimed to retrospectively analyze the clinical data of patients with MP in our hospital to clarify the combined efficacy of TCM and azithromycin in the treatment of MP.

Materials and Methods

General Information

This was a retrospective study including the clinical data of 119 patients with MP treated at the Taihe County Hospital of Traditional Chinese Medicine from April 2021 to November 2023. According to the treatment records in the clinical data, they were divided into two groups: azithromycin group (conventional treatment + azithromycin treatment) and TCM + azithromycin group (conventional treatment + azithromycin treatment + Xiaoxianxiong decoction and Weijing decoction and acupoint application).

Inclusion Criteria

- Patients diagnosed with MP: Fever and cough; Decreased breath sounds and/or dry or wet rales; Chest X-ray showed enlarged hilar lymph nodes, interstitial pulmonary infiltration, and lobar pulmonary consolidation; Positive IgM antibody specific to *M. pneumoniae*; Increased white blood cell count in laboratory tests;¹
- Complete clinical data;
- Patients accepted conventional treatment + azithromycin treatment or TCM + azithromycin group treatment;
- Age \geq 18 years old.

Exclusion Criteria

- Individuals with functional impairments in important organs;
- Individuals with systemic infectious diseases;
- Malnourished individuals;
- Individuals with immune system disorders;
- Individuals with other respiratory system diseases;
- Individuals on long term use of immunosuppressive agents, antibiotics, or hormone therapy.

Routine Treatment

After admission, patients in both groups were given routine interventions such as nebulizer inhalation, rehydration, antipyretic, and antiasthmatic treatment. Oxygen inhalation could be used if necessary. The patients' blood routine, liver function indicators, and electrocardiogram were monitored in real time. On this basis, the two groups were given different medication regimens.

Azithromycin group: Based on the routine treatment, patients were also treated with azithromycin (0.125 g/dose, Shenyang First Pharmaceutical Factory of Northeast Pharmaceutical Group Company) 0.5 g/dose intravenously, once a day, for 2 weeks.

TCM + azithromycin group: Based on the routine treatment, patients were also treated with azithromycin and TCM. The treatment of azithromycin was same as that of the Azithromycin group. For TCM treatment, a combination of Xiaoxianxiong decoction, Weijing decoction, and acupoint application medication was adopted. The mixture of 6g roasted licorice, 10g Platycodon grandiflorus, 10g Scutellaria baicalensis, 15g Gualou peel, 15g Fructus Aurantii, 15g Pinellia ternata, 8g peach kernel, 20g Houttuynia cordata, 20g Coix seed, 20g winter melon kernel, and 20g reed root were decocted in water, and finally 400mL of juice was collected, which was taken in the morning and evening in divided doses. Procedures for acupoint application was as follows: Ephedra, almond, and white mustard seeds were each taken 15g, ground into powder, and made into paste with 1 spoon of honey. The patients were instructed to take a comfortable position, and the above medication was evenly applied to the acupoints Fengmen, Dingchuan, Zhongfu, and Feishu. 5 times per week, 6 hours per time, for 2 weeks.

Patient Baseline Data and Relevant Indicators Before and Two weeks After Treatment

1) Treatment effect: Symptoms such as difficulty breathing, fever, and cough disappear or were basically relieved, and the disappearance of lung shadows was considered as cure; Symptoms such as difficulty breathing, fever, and cough were alleviated, and lung shadows were reduced but not disappeared was considered as effective; and failure to meet the above criteria was considered as invalid. Overall effective rate = (cured + effective)/total number of patients. 2) Inflammatory status: About 3 mL of fasting venous blood was extracted and centrifuged to obtain the supernatant for detection. The levels of CRP, PCT, and white WBC were measured by enzyme-linked immunosorbent assay (ELISA). 3) Respiratory function status: PaCO₂, PaO₂, and OI were detected through a fully automatic blood gas analyzer. 4) Adverse reactions: The adverse reactions including vomiting, nausea, dizziness, and gastrointestinal discomfort.

Statistical Methods

The data analysis was conducted using SPSS 22.0 software (IBM, Armonk, New York, USA) and PRISM8.0 software (GraphPad, San Diego, USA). The measurement data were represented as mean ± standard deviation (SD) and *t*-test was used to compare two independent samples between groups. For categorical variables, frequency distribution was provided and expressed as a percentage. Chi square tests were used to compare categorical variables between the two groups, such as gender distribution and the presence of diabetes. *P*<0.05 is considered to be statistically significant.

Results

A total of 119 patients (71 males and 48 females) met the inclusion criteria were included. Age range of the patients was from 18 to 54 years old, with a mean of 29.66 ± 8.93 years old. There were 58 cases in the Azithromycin group and 61 cases in the TCM + azithromycin group. Figure 1 was the flow diagram of participants. There was no significant difference in sex, age, BMI, disease duration, history of smoking or drinking, and history of hypertension or diabetes between the two groups (*P*>0.05) (Table 1).

The overall effective rate of the TCM + azithromycin group (58/61, 95.08%) was significantly higher than that of the Azithromycin group (48/58, 82.76%) (*P*<0.05) (Table 2).

Before treatment, there was no significant difference in serum CRP, PCT, and WBC levels between the two groups (*P*>0.05). After treatment, the serum CRP, PCT, and WBC levels in both groups significantly decreased compared with those before treatment, and they were significantly lower in the TCM + azithromycin group than in the Azithromycin group (*P*<0.05) (Figure 2).

Before treatment, there was no significant difference in the levels of PaCO₂, PaO₂, and OI between the two groups (*P*>0.05). After treatment, PaCO₂ in both groups significantly decreased compared with those before treatment, while PaO₂ and OI significantly increased compared with those before treatment; And the TCM +

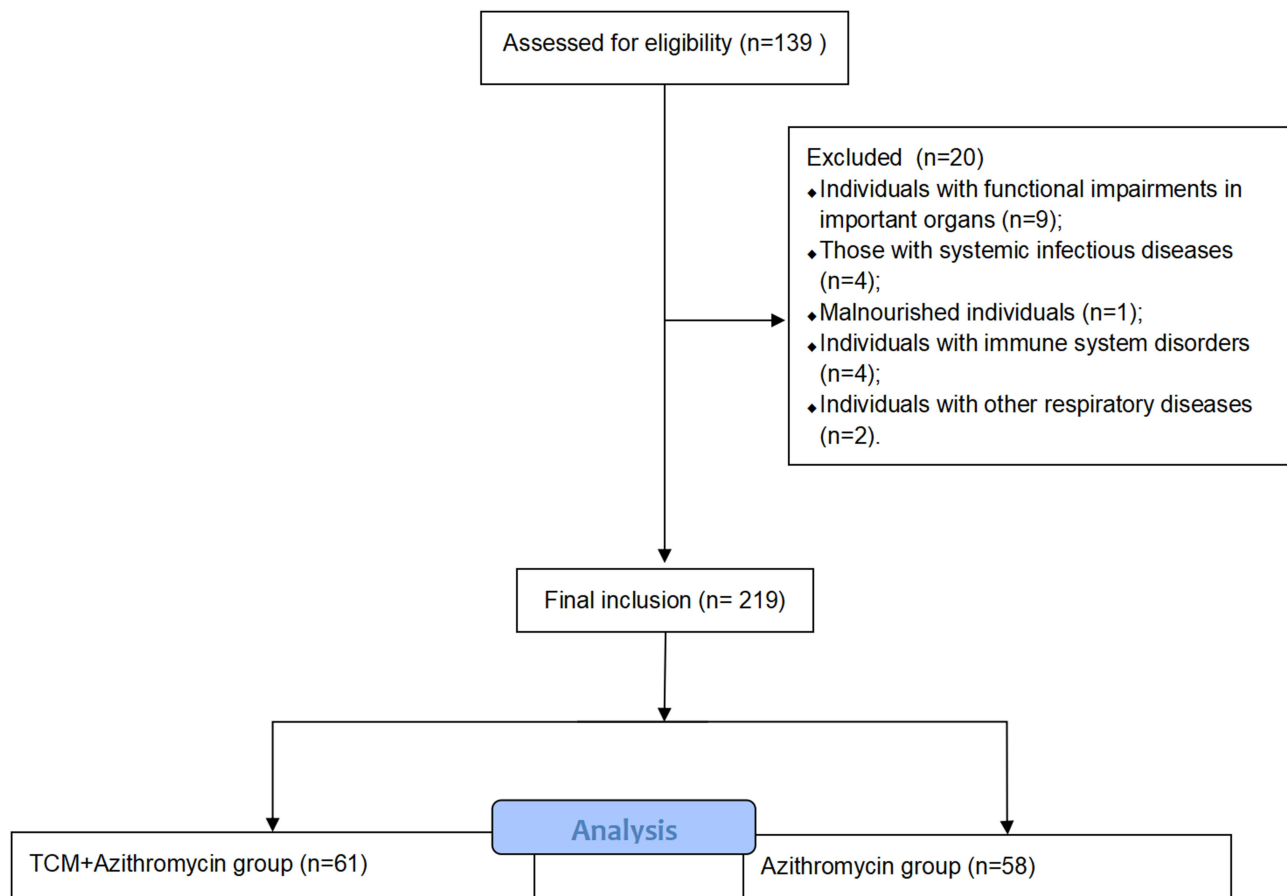


Figure 1 Guidelines Flow Diagram.

azithromycin group had lower PaCO₂ than the Azithromycin group, and higher PaO₂ and OI than the Azithromycin group ($P < 0.05$) (Figure 3).

There was no significant difference in the incidence of adverse reactions between the TCM + azithromycin group (4/61, 6.56%) and the Azithromycin group (2/58, 3.45%) ($P > 0.05$) (Table 3).

Table 1 Comparison of Baseline Data Between Two Groups

Item	TCM + Azithromycin Group (n=61)	Azithromycin Group (n=58)	t/χ^2	P
Male (Yes)	36 (59.02)	35 (60.34)	0.022	0.883
Age (years)	28.93±9.15	30.41±8.69	0.903	0.368
BMI (kg/m ²)	22.64±4.09	23.02±3.88	0.519	0.605
Disease duration (days)	5.08±1.14	5.11±1.10	0.146	0.884
History of smoking (Yes)	29 (47.54)	24 (41.38)	0.457	0.499
History of drinking (Yes)	35 (57.38)	38 (65.52)	0.831	0.362
History of hypertension (Yes)	17 (27.87)	13 (22.41)	1.492	0.222
History of diabetes (Yes)	7 (11.48)	4 (6.90)	0.743	0.389
Severity of the patients (n)				
Mild pneumonia	15 (24.59)	20 (34.48)	3.307	0.191
Moderate pneumonia	30 (49.18)	30 (51.73)		
Severe pneumonia	16 (26.23)	8 (13.79)		

Table 2 Comparison of Treatment Effects Between Two Groups

Group	n	Cure	Effective	Invalid	Overall effective rate
TCM + azithromycin group	61	43 (70.49)	15 (24.59)	3 (4.92)	58 (95.08)
Azithromycin group	58	32 (55.17)	16 (27.59)	10 (17.24)	48 (82.76)
χ^2					4.640
P					0.031

Discussion

This study showed that compared with treatment with azithromycin alone, intervention with TCM + azithromycin treatment for MP can significantly improve the patient's respiratory function and reduce the degree of inflammation in the

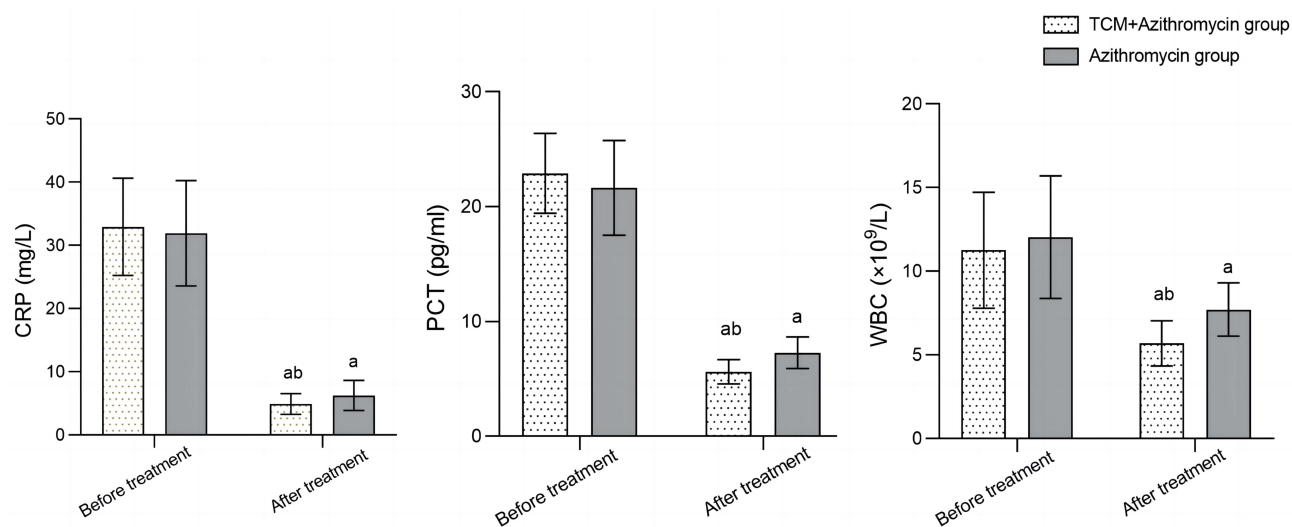


Figure 2 Comparison of inflammatory status indicators before and after treatment between two groups; Compared to before treatment in the same group, ^a $P < 0.05$; Compared to the Azithromycin group, ^b $P < 0.05$.

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count.

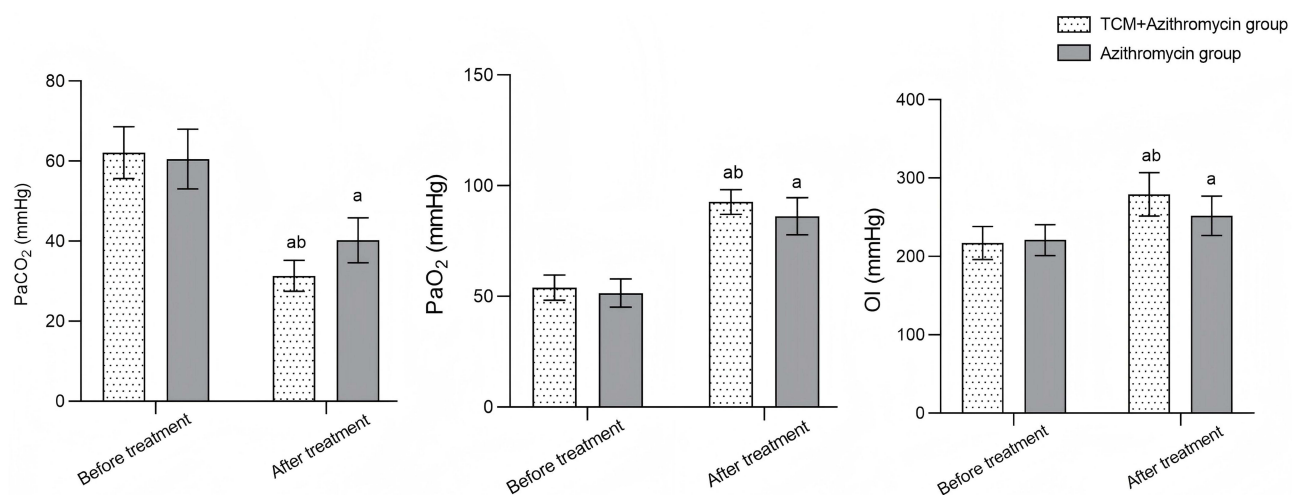


Figure 3 Comparison of respiratory function status between two groups before and after treatment; Compared to before treatment in the same group, ^a $P < 0.05$; Compared to the Azithromycin group, ^b $P < 0.05$.

Abbreviations: PaCO₂, partial pressure of carbon dioxide; PaO₂, oxygen partial pressure; OI, oxygenation index.

Table 3 Comparison of Incidence Rates of Adverse Reactions Between Two Groups

Group	n	Vomiting	Nausea	Dizzy	Digestive Discomfort	Overall Incidence Rate
TCM + azithromycin group	61	0 (0.00)	2 (3.28)	1 (1.64)	1 (1.64)	4 (6.56)
Azithromycin group	58	1 (1.72)	1 (1.72)	0 (0.00)	0 (0.00)	2 (3.45)
χ^2						0.127
P						0.722

body. With the continuous attention and recognition of TCM, the combination of traditional Chinese and Western medicine has gradually become a trend in the treatment of pneumonia.^{7,9,10} Studies have also explored the application of TCM in pneumonia.^{9,10,13-15} The application value of TCM decoctions in pneumonia has also been explored. As Wu Xiongfei et al¹⁴ found in their research on severe pneumonia, comprehensive intervention was implemented with Xiaoxianxiong decoction on the basis of bronchoalveolar lavage. The results confirmed that it can effectively down-regulate the levels of CRP, PCT and other indicators, improve lung function, and reduce the 28 day mortality rate to 6.98%. Yang Yan et al¹⁵ intervened in elderly patients with severe pneumonia by using Qian Jin Wei Jing Tang on the basis of bronchoscopy lavage, and the results also showed that after treatment, the patient's blood gas status, clinical symptoms, and respiratory function were significantly improved, and the overall effective rate of disease treatment could be increased to 94.23%. The above studies have respectively confirmed the application value of Xiaoxianxiong decoction and Weijing decoction in pneumonia.^{14,15} However, in clinical practice, it has been found that pneumonia has many pathogenic factors and complex pathological mechanisms. A single prescription may not fully cover the pathological mechanisms and treatment principles of the disease. Ma Qiang¹⁶ found that the overall effective rate of using Xiaoxianxiong decoction combined with Weijing decoction to treat pulmonary infections can reach 90.70%, which can more effectively improve the patient's lung function and blood gas status compared to conventional Western medicine treatment. The present study showed that the overall effective rate of patients treated with TCM + azithromycin for MP was as high as 95.08%, which was higher than 82.76% of patients in the azithromycin group treated only with Western medicine; the levels of inflammatory factors and respiratory function status indicators were better in the azithromycin group than in the azithromycin group, and there was no significant difference in the incidence of adverse reactions between the groups. The results of the current study are consistent with the previous research conclusions, which indicated that the treatment of pneumonia with TCM + azithromycin is feasible and effective.

In addition, Sun Yingxue et al¹⁷ intervened in patients with MP by applying TCM syndrome differentiation acupoints on the basis of routine treatment. They found that the clinical symptoms of the patients were significantly relieved, the levels of inflammatory factors decreased, the time for clinical symptom relief was better than that of patients who only received Western medicine treatment, and the overall effective rate of treatment can reach 97.78%. The research results of Li R et al¹⁸ showed that the antipyretic rate of 1229 patients treated with acupoint application was 1.82 times higher than that of patients who did not receive acupoint application. Other studies have shown that the overall effective rate of acupoint application for treating patients with respiratory diseases is significantly improved, and it can also effectively improve the patient's immune function and reduce the frequency of acute disease attacks.^{19,20} Liu S et al²¹ conducted a network meta-analysis of 55 studies, and the results showed that six commonly used Chinese herbal formulas, namely Weijing decoction, Xin Xing Shi Gan decoction, Yue Jia Ban Xia decoction, Qing Qi Hua Tan decoction, Ding Chuan decoction, and Sang Bai Bai decoction, were used in combination with conventional drug therapy to treat acute exacerbation of chronic obstructive pulmonary disease. They were superior in improving arterial blood gas and efficacy compared to drug therapy alone. Among the treatment plans adopted in this study, Xiaoxianxiong decoction and Weijing decoction have significant effects on broadening the chest and dispersing nodules, clearing heat and resolving phlegm, and TCM has advantages such as fewer toxic side effects and multi target effects; Acupoint application can apply drugs to the surface of the body, passing through the skin to the site of the disease. The drug concentration is gentle and long-lasting, which can avoid the first pass effect on the liver and has high safety.^{22,23} During the intervention period, this study also found that TCM + azithromycin can exert a synergistic effect through oral administration and external application, which helps to promote symptom improvement and further enhance treatment effectiveness. TCM's internal

and external treatment of diseases has the advantages of rapid onset and direct access to the affected area. In acupoint application therapy, by applying drugs to the target acupoints, it can ensure the absorption of drugs through the skin, stimulate the meridians and acupoints, regulate the blood and gas circulation of the meridians, improve organ function, and achieve a synergistic effect of meridian guidance and drug efficacy.^{24,25}

Limitations

This was a single center retrospective study with a small sample size. The data of this study needs to be confirmed through further research on expanding and specific patient cohorts. In addition, the macrolide resistance rate of MP in the participants was not evaluated, which may affect the therapeutic effect of azithromycin. Moreover, whether TCM has the effect of killing *M. pneumoniae* was not studied, which may help to further understand the role of TCM in the treatment of *M. pneumoniae* and could be explored in future research. It is necessary to further validate the benefits of TCM + azithromycin treatment in patients with MP in prospective large-scale controlled studies, including those with other etiologies.

Conclusion

Compared with simple treatment with azithromycin, intervention with TCM + azithromycin can significantly improve the respiratory function of patients with MP, reduce the degree of inflammatory response in the body, enhance the overall treatment effect, and have comparable safety. Although these findings may provide insights into the clinical effects of TCM + azithromycin in the treatment of MP, the findings from a single center sample may not be representative of the entire MP populations, and further research is needed to validate the conclusions in the current study.

Abbreviations

TCM, Traditional Chinese Medicine; MP, Mycoplasma pneumonia; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; PaCO₂, partial pressure of carbon dioxide; PaO₂, oxygen partial pressure; OI, oxygenation index; ELISA, enzyme-linked immunosorbent assay; SD, standard deviation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The informed consent was waived by the ethics committee of Taihe County Hospital of Traditional Chinese Medicine for the observational and retrospective nature. Our study was approved by the Ethics Review Board of Taihe County Hospital of Traditional Chinese Medicine (No.: THZYL2024058; Date: 23-April, 2024). All data were stored securely, and confidentiality was maintained throughout the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest that could be perceived as prejudicing the impartiality of the reported research.

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