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RESEARCH ARTICLE

Clinical efficacy of comprehensive therapy based on traditional Chinese medicine patterns on patients with pneumoconiosis: a pilot double-blind, randomized, and placebo-controlled study

Jiansheng Li (✉)[1,2], Hulei Zhao[1,2,3], Yang Xie[1,2,3], Jieya Li[4], Qingwei Li[5], Xuexin Chen[6], Weiyu Zhang[1,2,3]

[1]Collaborative Innovation Center for Chinese Medicine and Respiratory Diseases Co-constructed by Henan Province & Education Ministry of China, Henan University of Chinese Medicine, Zhengzhou 450046, China; [2]Henan Key Laboratory of Chinese Medicine for Respiratory Disease, Henan University of Chinese Medicine, Zhengzhou 450046, China; [3]Department of Respiratory Diseases, The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, China; [4]Department of Pneumoconiosis, Henan Hospital for Occupational Diseases, Zhengzhou 450052, China; [5]Department of Respiratory Diseases, Jiaozuo Coal Industry Group Co., Ltd. Central Hospital, Jiaozuo 454000, China; [6]Department of Pneumoconiosis, Yima Coal Industry Group Co., Ltd. General Hospital, Yima 472300, China

Abstract **Effective therapy options for pneumoconiosis are lacking. Traditional Chinese medicine (TCM) presents a favorable prospect in the treatment of pneumoconiosis. A pilot study on TCM syndrome differentiation can evaluate the clinical efficacy and safety of TCM and lay a foundation for further clinical research. A double-blind, randomized, and placebo-controlled trial was conducted for 24 weeks, in which 96 patients with pneumoconiosis were randomly divided into the control and treatment groups. Symptomatic treatment was conducted for the two groups. The treatment group was treated with TCM syndrome differentiation, and the control group was treated with placebo. The primary outcomes were the six-minute walking distance (6MWD) and the St. George Respiratory Questionnaire (SGRQ) score. The secondary outcomes were the modified British Medical Research Council Dyspnea Scale (mMRC), Chronic Obstructive Pulmonary Disease Assessment Test (CAT), Hospital Anxiety and Depression Scale (HADS), and pulmonary function. Only 83 patients from the 96 patients with pneumoconiosis finished the study. For the primary outcome, compared with the control groups, the treatment group showed a significantly increased 6MWD (407.90 m vs. 499.51 m; 95% confidence interval (CI) 47.25 to 135.97; P <0.001) and improved SGRQ total score (44.48 vs. 25.67; 95% CI −27.87 to −9.74; P <0.001). The treatment group also significantly improved compared with the control group on mMRC score (1.4 vs. 0.74; 95% CI −1.08 to −0.23; P =0.003), CAT score (18.40 vs. 14.65; 95% CI −7.07 to −0.43; P =0.027), and the total symptom score (7.90 vs. 5.14; 95% CI −4.40 to −1.12; P <0.001). No serious adverse events occurred. This study showed that TCM syndrome differentiation and treatment had a favorable impact on the exercise endurance and quality of life of patients with pneumoconiosis.**

Keywords pneumoconiosis; randomized controlled trials; traditional Chinese medicine

Introduction

Pneumoconiosis refers to a group of occupational lung diseases characterized by diffuse fibrosis of the lung tissues. This disease is caused mainly by long-term inhalation and deposition of mineral dust, with varying levels of pathogenicity, into the lungs during occupational activities [1–3]. The main symptoms are cough, expectoration, chest pain, and dyspnea. At the beginning of the 21st century, statistics from the National Institute of Occupational Safety and Health show that the incidence of pneumoconiosis has been rapidly increasing [4,5]. According to the statistical bulletin on the development of health and health services in China in 2018, 19 468 cases of occupational pneumoconiosis have been reported, accounting for 82.85% of the 23 497 cases of occupational diseases [6]. The prevalence of silicosis from 2002 to 2016 was 12.7% [7]. At present, more than 870 000 cases of pneumoconiosis have been reported in China, with a mortality as high as 31.2% [8,9]. Pneumoconiosis causes an estimated 184.5 billion RMB economic losses in China

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Correspondence: Jiansheng Li, li_js8@163.com

[10]. The prevention and treatment of pneumoconiosis is a major social and livelihood problem. Whole lung lavages, lung transplantation, and stem cell therapy have certain curative effects in the treatment of pneumoconiosis, but these processes have disadvantages, such as high treatment costs, narrow indications, and invasive procedure [11–14]. Traditional Chinese medicine (TCM) has a good prospect in the treatment of pneumoconiosis. The efficacy of TCM has recently been demonstrated in the treatment of pneumoconiosis which can improve the patients' clinical symptoms, exercise capacity, and quality of life [15,16]. However, the quality of the research using TCM was low and further investigation by well-designed RCT is needed to demonstrate the effect of TCM for pneumoconiosis. A pilot double-blind, randomized, and placebo-controlled study was performed to preliminarily evaluate the clinical efficacy and safety of the differentiation and treatment of pneumoconiosis by TCM and lay a foundation for further larger sample-size and multicenter clinical study.

Methods

Study design

This work is a double-blind, randomized, and placebo-controlled multicenter pilot study in the First Affiliated Hospital of Henan University of Chinese Medicine, Henan Hospital for Occupational Diseases, Jiaozuo Coal Industry Group Co., Ltd. Central Hospital, and Yima Coal Industry Group Co., Ltd. General Hospital. The study consisted of three visits as follows: enrolment and baseline data collection; 12-week data collection; and 24-week data collection. This trial was registered on the Chinese Clinical Trial Registry with the identifier number ChiCTR1800019515.

Sample size

Based on the sample size reported in a previous study and the patient resources available for this pilot study, we recruited a total of 96 patients (approximately 40 patients in each arm and assuming a 20% dropout rate).

Ethics

The clinical trial was conducted according to the principles of the *Declaration of Helsinki* and followed the laws, regulations, and administrative provisions of the Health Commission of Henan Province. This study was approved by the Clinical Research Ethics Committees of the First Affiliated Hospital of Henan University of Chinese Medicine (2018HL-052-01). The participants were informed of the risks and benefits of the study and allowed to voluntarily cease participation at any time for any reason. To protect the privacy of the subjects, each patient was identified with a unique random number, and the patients' names and personal information were kept confidential to everyone, except for the researchers.

Eligibility criteria

We selected all subjects with a diagnosis of pneumoconiosis according to the Diagnosis of Occupational Pneumoconiosis (GBZ 70-2015) [2]. Participants were included if they met all of the following criteria: (1) patients with pneumoconiosis (coal workers' pneumoconiosis) who were in the age range of 18–75 years; (2) complied with TCM syndrome differentiation standards; and (3) signed informed consent forms.

Participants were excluded if they met one of the following criteria: (1) patients who did not get rid of the dust; (2) patients who received bronchoalveolar lavage within 3 years before selection; (3) patients with active tuberculosis, idiopathic pulmonary fibrosis, asthma, bronchiectasis, pulmonary embolism, chronic respiratory failure, or other severe respiratory diseases; (4) acute exacerbations occurred within 1 month before selection; (5) patients with severe cardiovascular and cerebrovascular diseases (i.e., malignant arrhythmia, unstable angina, acute myocardial infarction, HF New York Heart Association classes III to IV, stroke, and cerebral hemorrhage); (6) patients with severe liver and kidney diseases (liver cirrhosis, portal hypertension, dialysis, and kidney transplantation); (7) tumor patients who underwent resection, radiotherapy, and chemotherapy within 5 years before selection; (8) patients with activity difficulties caused by neuromuscular diseases; (9) patients with severe arthritis; (10) patients with severe peripheral vascular disease; (11) pregnant and lactating women; (12) patients with severe cognitive and mental disorders; and (13) clinical investigators who were participating in other interventions within 1 month before selection.

Randomization and blinding

Eligible patients with pneumoconiosis were randomly divided into the treatment and control groups in a 1:1 allocation ratio with a block size of 6. The researchers obtained the drug number through the central randomization system provided by the Jiangsu Famous Medical Technology Co., Ltd. in Nanjing, China and distributed the drug to the patients. The investigators who were responsible for assessing the primary outcomes and the patients were blinded to the study group assignment.

Intervention

For the treatment group, which was given symptomatic treatments, patients were also given Chinese medicine compound based on the differentiated TCM syndrome: Yang Qing Chen Fei Granules, yin deficiency and heat-dryness; Bao Jin Chen Fei Granules, pulmonary qi

deficiency; and Jin Shui Chen Fei Granules, deficiency of pulmonary and renal qi. For the control group, which was administered symptomatic treatments, patients were also given Chinese medicine compound placebo based on the differentiated TCM syndrome: Yang Qing Chen Fei Granules placebo, yin deficiency and heat-dryness; Bao Jin Chen Fei Granules placebo, pulmonary qi deficiency; and Jin Shui Chen Fei Granules placebo, deficiency of pulmonary and renal qi. The appearance, shape, color, and packaging of the Chinese medicine compound placebo were the same as those of the drugs. The TCM granules were compound preparations of TCM, and their components are shown in Table 1. All drugs were made into granules by Sichuan Neo-Green Pharmaceutical Technology Development Co., Ltd. The daily dose of Yang Qing Chen Fei Granules, Bao Jin Chen Fei Granules, and Jin Shui Chen Fei Granules were 11.69, 10.32, and 9.86 g/day, respectively. Each granule was given orally twice a day for 24 weeks.

Study outcomes

The primary outcomes were six-minute walking distance (6MWD) and St. George's Respiratory Questionnaire (SGRQ), and the secondary outcomes were the Modified British Medical Research Council Dyspnea Scale (mMRC), pulmonary function, clinical symptoms, and signed Short Form 36 Health Survey Questionnaire (SF-36), the Chronic Obstructive Pulmonary Disease Assessment Test (CAT), and the Hospital Anxiety and Depression Scale (HADS). Safety was assessed via adverse events and medical examination indices.

Statistical analysis

Primary and secondary outcomes were analyzed using intent-to-treat (ITT) and per-protocol (PP) analyses. The ITT population included all patients who met the inclusion criteria and were randomized. Patients who were lost to follow-up were excluded from the PP analysis. Distribution of data was evaluated using the Shapiro−Wilk test, and thereafter between-group comparisons of baseline data were undertaken using *t*-tests, χ^2 tests, or Mann–Whitney U test. Repeated measures ANOVA were used to evaluate the main effects for group versus time interaction. A two-sided P value < 0.05 was considered statistically significant. Confidence intervals (CIs) were set to 95%. Missing data were imputed by means of the expectation–maximization algorithm. All analyses were conducted using the SPSS 19.0 statistical software.

Results

Between January 2019 and March 2020, 96 patients underwent randomization and received the corresponding intervention. After 24 weeks, 83 patients (86.5% of the initial study population) completed the final visit (Fig. 1). The set population for the ITT analysis was 96, while that of the PP analysis was 83. No between-group differences were noted in the baseline characteristics. No between-group differences at the baseline was also found in the outcome variables (Tables 2 and 3).

Efficacy outcomes

Primary outcomes

The treatment group exhibited an increase of 52.40 m (13.48–91.32 m) in the 6MWD, compared with the control group, which showed a decrease of −29.41 m (−69.77 to 10.94 m) (Table 5). The difference between the groups was statistically significant ($P < 0.001$) (Tables 4 and 5).

The treatment group showed an improvement in the SGRQ total scores of 15.57 units, which was a statistically significant change compared with the baseline ($P < 0.001$). For the domain scores in the treatment group, symptoms improved by 13.53 units ($P = 0.004$), impact by 16.32 units ($P < 0.001$), and activity by 16.56 units ($P < 0.001$). The control group showed no significant changes in the SGRQ total scores and domain scores at 24 weeks compared with the baseline. The difference between the groups was statistically significant for the SGRQ total scores and domain scores ($P < 0.05$) (Tables 4 and 5).

Secondary outcomes

The treatment group had improved mMRC score of −0.63 (from −0.97 to −0.29) and had lower mMRC scores compared with the controls ($P < 0.05$) (Tables 6 and 7). The CAT score decreased in the treatment group but increased in the control group at 24 weeks. The difference between the groups was statistically significant ($P < 0.05$) (Table 7). However, ITT analysis showed no difference

Table 1 Detail of the traditional Chinese medicine formulae

Formula	Traditional Chinese medicine
Yang Qing Chen Fei Granules	Dwarf Lilyturf Tuber, American Ginseng, Figwort Root, Snakegourd Fruit, Thunberg Fritillary Bulb, Red Peony Root, Turmeric Root Tuber
Bao Jin Chen Fei Granules	Ginseng, Milkvetch Root, Fiveleaf GynoStemma, Thunberg Fritillary Bulb, Tree Peony Root Bark, Coix Seed, Officinal Magnolia Bark
Jin Shui Chen Fei Granules	Ginseng, Chinese Magnoliavine Fruit, Epimedium Herb, Rose-Boot, Tendrilleaf Fritillary Bulb, Tree Peony Root Bark, Coix Seed, Perilla Seed

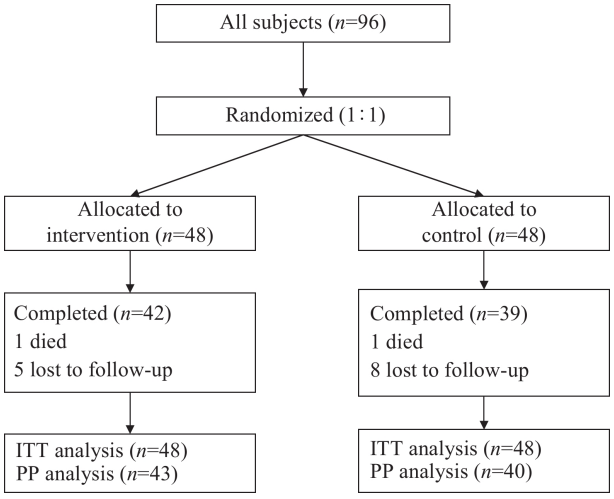

Fig. 1 Flowchart showing the participant's progress through the study.

between the two groups in the CAT score ($P > 0.05$) (Table 6).

The symptom score (including expectoration, wheezing, shortness of breath, and fatigue) and anxiety score decreased more in the treatment group than in the control group after 24 weeks of treatment. The difference was statistically significant ($P < 0.05$; Tables 6–9). Significantly improved SF-36 General Health Score was recorded for the treatment group, and the difference between the groups was statistically significant ($P < 0.05$; Tables 9 and 10). However, no significant between-group differences were found in the SF-36 domain scores of the physical function, role-physical, bodily pain, vitality, social functioning, role-emotional, and mental health at 24 weeks ($P > 0.05$) (Tables 10 and 11). No differences were also found between the two groups in the pulmonary function and depression score ($P > 0.05$) (Tables 6, 7, 11, and 12).

Safety assessment and adverse events

Complete blood counts, renal function, and liver function were evaluated at baseline and after the 24 week treatment for all participants. No differences were observed in these safety indices within each group over time or between the two groups. Three adverse events were reported (treatment group, two events; control group, one event; $P = 1.00$).

Discussion

Pneumoconiosis is a major occupational disease in China and characterized by high incidence, high disability, high mortality, and high economic burden [17]. The disease has a serious impact on health and the quality of life of patients with pneumoconiosis. However, effective therapeutic drugs to limit the progression of pneumoconiosis are lacking. Therefore, pneumoconiosis is not only a

Table 2 Characteristics of the subjects at baseline

Variable	ITT analysis		PP analysis	
	Treatment group (*N*=48)	Control group (*N*=48)	Treatment group (*N*=43)	Control group (*N*=40)
Age, year, mean±SD	53.96±9.01	57.40±10.13	54.40±9.18	57.23±10.75
Disease type				
Anthracosis, *n* (%)	34 (70.83)	34 (70.83)	32 (74.42)	27 (67.50)
Silicosis, *n* (%)	8 (16.67)	9 (18.75)	6 (13.95)	9 (22.50)
Anthracosilicosis, *n* (%)	6 (12.50)	5 (10.42)	5 (11.63)	4 (10.00)
Course of disease, month, median (IQR)	57.00 (31.50,117.00)	65.00 (24.00,156.75)	49.00 (29.00,120.0)	60.00 (24.00,156.75)
Western medicine treatment				
Symptomatic treatment, *n* (%)	15 (31.25)	15 (31.25)	12 (27.91)	12 (30.00)
Cetylcysteine, *n* (%)	10 (22.83)	11 (22.92)	9 (20.93)	8 (20.00)
Tiotropium, *n* (%)	4 (8.33)	10 (22.83)	2 (4.65)	9 (22.50)
Doxofylline, *n* (%)	0 (0.00)	2 (4.17)	0 (0.00)	1 (2.50)
Tetrandrine, *n* (%)	10 (22.83)	12 (25.00)	10 (23.26)	9 (22.50)
Pulmonary function, mean±SD				
FEV1 (L)	2.67±0.95	2.61±1.07	2.76±0.73	2.63±1.17
FVC (L)	3.54±1.24	3.54±1.15	3.59±0.91	3.57±1.25
FEV1/FVC (%)	74.47±10.28	73.17±12.05	76.45±8.07	73.15±13.18
FEV1%	83.05±29.39	80.04±31.74	86.74±21.49	81.18±33.92
PEF (L/s)	7.13±2.61	7.16±2.75	7.36±2.42	7.20±2.90
DLCO (mL/mmHg/min)	7.45±2.50	7.22±1.76	7.75±2.20	7.35±1.73

Table 3 Characteristics of the comorbidity in subjects

Variable	ITT analysis		PP analysis	
	Treatment group (*N*=48)	Control group (*N*=48)	Treatment group (*N*=43)	Control group (*N*=40)
Hypertension disease, *n* (%)	4 (8.33)	4 (8.33)	4 (9.30)	4 (10.00)
Amlodipine, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Captopril, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Nimodipine, *n* (%)	0 (0.00)	1 (2.08)	0 (0.00)	1 (2.50)
Indapamide, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Nifedipine, *n* (%)	2 (4.17)	2 (4.17)	2 (4.65)	2 (5.00)
Valsartan, *n* (%)	0 (0.00)	1 (2.08)	0 (0.00)	1 (2.50)
Chronic obstructive pulmonary disease, *n* (%)	0 (0.00)	1 (2.08)	0 (0.00)	1 (2.50)
Tiotropium, *n* (%)	0 (0.00)	1 (2.08)	0 (0.00)	1 (2.50)
Diabetes, *n* (%)	2 (4.17)	3 (6.25)	2 (4.65)	3 (7.50)
Acarbose, *n* (%)	0 (0.00)	1 (2.08)	0 (0.00)	1 (2.50)
Metformin, *n* (%)	1 (2.08)	2 (4.17)	1 (2.33)	2 (5.00)
Gliclazide, *n* (%)	0 (0.00)	2 (4.17)	0 (0.00)	2 (5.00)
Insulin glargine, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Gastric Ulcer, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Omeprazole, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)
Cimetidine, *n* (%)	1 (2.08)	0 (0.00)	1 (2.33)	0 (0.00)

Table 4 Primary outcome measures for the control and treatment groups (ITT analysis)

Variable	Treatment group (*N*=48)		Control group (*N*=48)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
6MWD, m[b]	439.25±111.96	486.19±109.14	432.53±102.40	407.08±100.12	79.10 (36.66 to 121.55)	13.693	<0.001
SGRQ symptoms score[b]	51.55±24.99	34.22±22.52	53.90±17.97	45.33±21.38	−11.11 (−20.01 to −2.21)	6.143	0.015
SGRQ activity score[b]	46.43±25.60	25.26±23.68	47.98±22.31	42.60±27.34	−17.34 (−27.71 to −6.98)	11.040	0.001
SGRQ impacts score[b]	38.69±28.55	18.63±18.17	44.48±24.60	37.58±25.02	−18.95 (−27.81 to −10.08)	18.014	<0.001
SGRQ total score[b]	43.08±25.80	23.42±19.11	46.43±21.80	40.39±24.06	−16.97 (−25.78 to −8.17)	14.644	<0.001

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

Table 5 Primary outcomes measures for the control and treatment groups (PP analysis)

Variable	Treatment group (*N*=43)		Control group (*N*=40)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
6MWD, m[b]	447.12±108.23	499.51±99.39	437.31±107.66	407.90±103.72	91.61 (47.25 to 135.97)	16.883	<0.001
SGRQ symptoms score[b]	50.47±22.68	36.94±22.25	55.15±17.93	47.75±20.27	−10.811 (−20.13 to −1.49)	5.328	0.024
SGRQ activity score[b]	44.76±23.63	28.20±23.30	46.61±23.87	47.53±25.31	−19.33 (−29.95 to −8.71)	13.125	0.001
SGRQ impacts score[b]	36.59±27.44	20.27±18.53	43.56±26.19	41.18±24.45	−20.92 (−30.35 to −11.49)	19.464	<0.001
SGRQ total score[b]	41.25±24.16	25.67±18.94	45.63±23.37	44.48±22.54	−18.81 (−27.87 to −9.74)	17.025	<0.001

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

Table 6 Secondary outcome measures (mMRC, CAT, and HADS) for the control and treatment groups (ITT Analysis)

Variable	Treatment group (*N*=48)		Control group (*N*=48)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
mMRC score[b]	1.46±0.87	0.90±1.08	1.37±0.98	1.45±1.01	−0.56 (−0.98 to −0.14)	6.881	0.010
CAT score[b]	17.00±9.26	15.42±9.54	18.37±7.65	17.9±6.47	−2.48 (−5.78 to 0.82)	2.221	0.140
HADS-anxiety score[b]	7.00±3.88	4.35±3.56	7.17±3.47	6.06±3.72	−1.71 (−3.19 to −0.23)	5.276	0.024
HADS-depression score[b]	6.50±4.38	5.27±4.04	7.38±3.31	5.56±3.73	−0.29 (−1.28 to 1.87)	0.135	0.714

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

Table 7 Secondary outcome measures (mMRC, CAT, and HADS) for the control and treatment groups (PP analysis)

Variable	Treatment group (*N*=43)		Control group (*N*=40)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
mMRC score[b]	1.37±0.76	0.74±0.93	1.35±1.05	1.40±1.01	−0.66 (−1.08 to −0.23)	9.526	0.003
CAT score[b]	16.33±8.29	14.65±8.52	18.08±8.03	18.40±6.44	−3.75 (−7.07 to −0.43)	5.05	0.027
HADS-anxiety score[b]	6.79±3.78	4.86±3.42	7.00±3.65	6.75±3.38	−1.89 (−3.38 to −0.40)	6.398	0.013
HADS-depression score[b]	6.29±4.10	5.88±3.81	7.22±3.50	6.15±3.50	−0.27 (−1.87 to 1.34)	0.109	0.742

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

Table 8 Secondary outcome measures (clinical symptoms and sign questionnaire score) for the control and treatment groups (ITT analysis)

Variable	Treatment group (*N*=48)		Control group (*N*=48)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
Cough score[b]	1.00 (1.00,2.00)	0.50 (0.00,1.00)	2.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (0.00 to 0.00)	1.771	0.077
Expectoration score[b]	1.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.429	0.015
Wheezing score[b]	2.00 (1.00,2.00)	1.00 (0.00,2.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	3.508	<0.001
Chest tightness score[b]	2.00 (1.00,2.00)	1.00 (0.25,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.408	0.016
Shortness of breath score[b]	1.50 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.380	0.017
Fatigue score[b]	2.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,1.00)	0.00 (−1.00 to 0.00)	2.822	0.005
Cyanosis score[b]	1.00 (0.00,1.00)	0.00 (0.00,1.00)	1.00 (0.00,1.00)	1.00 (0.00,1.00)	0.00 (0.00 to 0.00)	1.117	0.264
Total clinical symptom score[c]	8.83±3.57	5.58±4.20	8.73±3.19	8.06±3.35	−2.48 (−4.02 to −0.94)	10.222	0.002

[a]*P* values are reported for between-group comparison. [b]Mann–Whitney U test. [c]Repeated measures ANOVA.

Table 9 Secondary outcome measures (clinical symptoms and signs questionnaire score) for the control and treatment groups (PP analysis)

Variable	Treatment group (*N*=43)		Control group (*N*=40)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
Cough score[b]	1.00 (1.00,2.00)	0.00 (0.00,1.00)	2.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	1.896	0.058
Expectoration score[b]	1.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (0.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.339	0.019
Wheezing score[b]	2.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	−1.00 (−1.00 to 0.00)	3.331	0.001
Chest tightness score[b]	2.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.033	0.042
Shortness of breath score[b]	1.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (1.00,2.00)	0.00 (−1.00 to 0.00)	2.008	0.045
Fatigue score[b]	2.00 (1.00,2.00)	1.00 (0.00,1.00)	1.00 (1.00,2.00)	1.00 (0.25,1.75)	−1.00 (−1.00 to 0.00)	3.009	0.003
Cyanosis score[b]	1.00 (0.00,1.00)	0.00 (0.00,1.00)	1.00 (0.00,1.00)	1.00 (0.00,1.00)	0.00 (0.00 to 0.00)	1.286	0.198
Total clinical symptom score[c]	8.72±3.38	5.14±3.88	8.60±3.30	7.90±3.60	−2.76 (−4.40 to −1.12)	11.159	<0.001

[a]*P* values are reported for between-group comparison. [b]Mann–Whitney U test. [c]Repeated measures ANOVA.

Table 10 Secondary outcome measures (SF-36) for the control and treatment groups (ITT analysis)

Variable	Treatment group (*N*=48)		Control group (*N*=48)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
Physical function score[b]	75.00 (46.25,85.00)	75.0 0 (55.00,85.00)	60.00 (45.00,85.00)	60 (50.00,80.00)	0.00 (−5.00 to 10.00)	−0.735	0.462
Role physical score[b]	12.50 (0.00,75.00)	0.00 (0.00,100.00)	0.00 (0.00, 75.00)	0.00 (0.00,50.00)	0.00 (0.00 to 0.00)	−1.726	0.084
Bodily pain score[b]	62.00 (52.00,84.00)	74.00 (62.00,100)	62.00 (52.00,74.00)	74.00 (62.00,96.00)	0.00 (0.00 to 10.00)	−1.038	0.229
General health score[b]	37.50 (26.25,50.00)	51.00 (35.00,64.25)	40.00 (26.25,50.00)	35.00 (30.00,45.00)	10.00 (5.00 to 15.00)	−3.159	0.002
Vitality score[b]	50.00 (45.00,63.75)	55.50 (50.00,65.00)	50.00 (45.00,63.75)	50.00 (50.00,60.00)	0.00 (0.00 to 5.00)	0.682	0.495
Social function[b]	62.50 (50.00,87.50)	75.00 (53.13,87.50)	75.00 (50.00,87.50)	62.50 (50.00,87.50)	0.00 (0.00 to 12.50)	−0.992	0.321
Role emotional score[b]	33.00 (0,100.00)	33.30 (0.00,100.00)	0.00 (0.00,66.70)	0.00 (0.00,66.70)	0.00 (0.00 to 0.00)	0.242	0.808
Mental health score[b]	52.00 (48.00,60.00)	52.00 (48.00,56.00)	52.00 (49.00,56.00)	52.00 (52.00,56.00)	0.00 (−4.00 to 0.00)	0.844	0.398
Health change score	25.00 (25.00,50.00)	50.00 (25.00,75.00)	25.00 (20.00,50.00)	50.00 (25.00,50.00)	0.00 (0.00 to 25.00)	−1.137	0.255

[a]*P* values are reported for between-group comparisons. [b]Mann–Whitney U test.

Table 11 Secondary outcome measures (SF-36) for the control and treatment groups (PP analysis)

Variable	Treatment group (*N*=43)		Control group (*N*=40)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
Physical function score[b]	75.00 (55.00,85.00)	80.00 (60.00,85.00)	60.00 (41.25, 88.75)	65.00 (46.25,80.00)	0.00 (−5.00 to 10.00)	−0.549	0.583
Role physical score[b]	25.00 (0.00,75.00)	0.00 (0.00,100.00)	0.00 (0.00, 75.00)	0.00 (0.00,50.00)	0.00 (0.00 to 25.00)	−1.707	0.088
Bodily pain score[b]	62.00 (52.00,84.00)	74.00 (62.00,100.00)	62.00 (52.00,81.50)	74.00 (62.00,100.00)	0.00 (0.00 to 10.00)	0.872	0.383
General health score[b]	40.00 (30.00,50.00)	55.00 (35.00,65.00)	40.00 (21.25, 50.00)	35.00 (30.00,45.00)	10.00 (5.00 to 17.00)	−3.061	0.002
Vitality score[b]	50.00 (45.00,65.00)	55.00 (50.00,65.00)	50.00 (45.00,65.00)	50.00 (50.00,60.00)	0.00 (−5.00 to 5.00)	−0.656	0.512
Social function[b]	62.00 (50.00,87.00)	75.00 (62.00,87.00)	75.00 (50.00,87.00)	62.50 (50.00,87.50)	0.00 (0.00 to 12.50)	−0.961	0.337
Role emotional score[b]	33.30 (0,100.00)	33.30 (0.00,100.00)	0.00 (0.00,91.68)	0.00 (0.00,100.00)	0.00 (0.00 to 0.00)	−0.264	0.792
Mental health score[b]	52.00 (48.00,60.00)	52.00 (48.00,56.00)	52.00 (52.00,59.00)	56.00 (52.00,56.00)	0.00 (−4.00 to 0.00)	0.815	0.415
Health change score	25.00 (25.00,50.00)	50.00 (25.00,75.00)	25.00 (25.00,50.00)	50.00 (25.00,50.00)	0.00 (0.00 to 25.00)	−1.137	0.255

[a]*P* values are reported for between-group comparisons. [b]Mann–Whitney U test.

Table 12 Secondary outcome measures (pulmonary function) for the control and treatment groups (ITT analysis)

Variable	Treatment group (*N*=48)		Control group (*N*=48)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
FEV1 (L)[b]	2.67±0.95	2.65±0.82	2.61±1.07	2.62±0.77	0.03 (−0.29 to 0.36)	0.045	0.832
FVC (L)[b]	3.54±1.24	3.63±1.08	3.54±1.15	3.60±1.01	0.03 (−0.39 to 0.46)	0.025	0.875
FEV1/FVC(%)[b]	74.47±10.28	72.99±10.34	73.17±12.05	72.97±11.47	0.02 (−4.41 to 4.44)	0.000	0.994
FEV1%[b]	83.05±29.39	82.51±24.88	80.04±31.74	82.08±26.54	0.43 (−9.99 to 10.86)	0.007	0.934
PEF (L/s)[b]	7.13±2.61	6.75±2.36	7.16±2.75	6.99±2.38	−0.24 (−1.20 to 0.73)	0.237	0.628
DLCO (mL/mmHg/min)[b]	7.45±2.50	8.68±5.43	7.22±1.76	8.31±4.25	0.38 (−1.60 to 2.35)	0.143	0.706

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

Table 13 Secondary outcomes measures (pulmonary function) for the control and treatment groups (PP analysis)

Variable	Treatment group (*N*=43)		Control group (*N*=40)		95% CI for the difference	Statistics	*P*[a]
	Pre	Post	Pre	Post			
FEV1 (L)[b]	2.76±0.73	2.71±0.61	2.63±1.17	2.64±0.83	0.07 (−0.24 to 0.39)	0.206	0.651
FVC (L)[b]	3.59±0.91	3.66±0.73	3.57±1.25	3.65±1.10	0.10 (−0.40 to 0.41)	0.002	0.966
FEV1/FVC (%)[b]	76.45±8.07	74.22±8.45	73.15±13.18	72.47±12.17	1.76 (−2.79 to 6.30)	0.589	0.445
FEV1%[b]	86.74±21.49	85.29±17.11	81.18±33.92	83.48±27.92	1.81 (−8.23 to 11.84)	0.129	0.721
PEF (L/s)[b]	7.36±2.42	7.00±2.09	7.20±2.90	7.07±2.44	−0.07 (−1.06 to 0.92)	0.020	0.889
DLCO (mL/mmHg/min)[b]	7.75±2.20	9.13±5.46	7.35±1.73	8.66±4.51	0.47 (−1.72 to 2.67)	0.184	0.669

[a]*P* values are reported for between-group comparisons. [b]Repeated measures ANOVA.

major medical issue in China but also a social problem.

TCM plays an important role in the treatment of respiratory diseases, such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and asthma, which can delay the deterioration of lung function, improve the quality of life, and delay the progress of the disease [18–20]. TCM shows potential in the treatment of pneumoconiosis. Xuanfei Dichen decoction has been found to improve the clinical symptoms, pulmonary ventilation function, exercise endurance, and the quality of life of patients [21]. Syndrome differentiation and treatment is the traditional model of diagnosis in TCM and advantageous in treating diseases. TCM syndrome differentiation and treatment of pneumoconiosis can effectively improve the patient's condition and quality of life. In addition, acupuncture therapy has been proved to improve the cough, shortness of breath, and pulmonary functions in patients with pneumoconiosis [15,22,23]. However, most studies are of low quality [24]. Therefore, such study may have a large bias, and more original studies are needed to further verify the results.

This study adopted a multicenter, randomized, double-blind, and placebo-controlled trial design. The results suggested that the regimens in TCM syndrome differentiation and treatment had a good clinical effect in the treatment of pneumoconiosis. TCM syndrome differentiation and treatment could significantly improve the 6MWD of patients with pneumoconiosis. After treatment, the difference between the two groups was

91.61 m (47.25–135.97 m), which was greater than the minimum clinical difference of 24–45 m in the respiratory system [25]. The treatment of syndrome differentiated in TCM was not only statistically significant but also clinically significant in improving the exercise endurance of patients, which was better than the clinical effect of the compound frost mulberry leaf mixture combined with TCM physical intervention in the treatment of pneumoconiosis [26,27]. In terms of improving the patients' clinical symptoms, TCM syndrome differentiation and treatment could improve the patients' symptoms, such as dyspnea, expectoration, wheezing, shortness of breath, and fatigue. Such results were basically consistent with the clinical study of Bufei Huoxue capsule combined with the acupoint moxibustion in the treatment of phlegm-stasis silicosis and acupuncture combined with Shengmai Dihuang decoction in the treatment of coal worker's pneumoconiosis with lung and kidney qi deficiency [28,29]. In terms of improving the quality of life of patients, TCM syndrome differentiation and treatment can improve the patients' total SGRQ score and the dimensions' scores (symptoms, activity, and impacts), general health dimension score of SF-36, and CAT score. No statistical significance was found in the improvement in anxiety, depression, and pulmonary function. Studies have shown that most patients with pneumoconiosis have emotional disorders, and anxiety and depression are risk factors affecting the quality of life of patients with pneumoconiosis [30,31]. Therefore, the improvement of bad mood in patients with pneumoconiosis should still be used as an evaluation index of clinical research. Related research should be strengthened. This study is a pilot study and has some limitations. First, studies were limited by small sample sizes and lack of long-term follow-up. Second, although this study showed a favorable impact of TCM for pneumoconiosis, the sample size is not sufficiently powered to achieve statistical significance for outcomes, such as pulmonary function. Finally, the rate of loss to follow-up is 13.54%, the high rate of loss to follow-up affected the stability of the results, such as CAT score.

Conclusions

This pilot study provides preliminary evidence that TCM syndrome differentiation and treatment could be a promising treatment for pneumoconiosis. This method appears safe and highly effective to improve the exercise capacity, quality of life, and clinical symptoms of patients.

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Compliance with ethics guidelines

Jiansheng Li, Hulei Zhao, Yang Xie, Jieya Li, Qingwei Li, Xuexin Chen, and Weiyu Zhang declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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