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Effect of acupuncture on patients with chronic obstructive pulmonary disease: A multicenter randomized controlled trial

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a common and frequently occurring disease that seriously endangers health, causing a heavy economic burden on patients and society. Acupuncture has been reported to have a therapeutic effect on patients with chronic obstructive pulmonary disease (COPD). However, compared with medications, it is difficult to identify a superior therapy. Therefore, the aim of this study was to evaluate the efficacy and safety of acupuncture, conventional drug and acupuncture plus conventional drug in the treatment of COPD.

Methods: This was a multicenter, open-label randomized controlled trial (RCT) through a central randomization system. A total of 150 COPD patients were randomly assigned at a 1:1:1 ratio to the acupuncture group, conventional drug group or acupuncture plus conventional drug group for 12 weeks of treatment, followed by 12 weeks of untreated follow-up. The primary outcomes included the six-minute walk distance (6MWD) and St. George's Respiratory Questionnaire (SGRQ), and the secondary outcomes included the modified Medical Research Council dyspnea scale (mMRC), acute exacerbation, lung function, and quality of life (COPD assessment test). Statistical analysis was conducted via SPSS software (version 26.0).

Results: A total of 150 patients were included in the study, and 143 patients completed the trial. There were time effects, group effects and interaction effects in the three groups ($P < 0.05$). Compared with that in the conventional drug group, the 6MWD in the acupuncture plus conventional drug group increased significantly at 4, 8, and 12 weeks of treatment and at 12 weeks of follow-up. The difference was statistically significant ($P < 0.05$). The symptom scores, motor scores, impact scores and total SGRQ scores at different time points in the three

Abbreviations: COPD, Chronic obstructive pulmonary disease; RCT, Randomized clinical trial; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWD, Six-minute walk distance; SGRQ, St. George's Respiratory Questionnaire; MMRC, Modified Medical Research Council dyspnea scale; FEV1, Forced Expiratory Volume in One Second; FVC, Forced Vital Capcacity; PEF, Peak Expiratory Flow.

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groups tended to change with time, with a time effect ($P < 0.05$), and there was no group or interaction effect ($P > 0.05$). Among the secondary outcomes, there were time effects on the number of acute exacerbations, forced expiratory volume in one second (FEV1) and forced expiratory volume in one second/forced vital capacity (FEV1/FVC) at different time points in the three groups ($P < 0.05$). mMRC had time and group effects ($P < 0.05$). CAT had time effects, group effects and interaction effects ($P < 0.05$).

Conclusions: Compared with the acupuncture group and the conventional drug group, the acupuncture plus conventional drug group was better at improving exercise ability, improving quality of life, and reducing dyspnea. It is safe and effective for the treatment of chronic obstructive pulmonary disease in the stable period, which can provide a reference for further related research.

Trial registration:

ClinicalTrials.gov, NCT03169504. Registered on 30 May 2017.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major chronic noncommunicable disease that seriously endangers human health. It is usually caused by significant exposure to toxic particles or gases characterized by persistent airflow limitation and corresponding respiratory symptoms. The prevalence, disability, and mortality rates are high worldwide and continue to rise, placing a heavy medical burden on families and society.[1–3] COPD has become the third leading cause of death globally and is one of the major challenges to global public health. The prevention and control situation is extremely severe.[4,5] Patients with COPD generally experience dyspnea, limited exercise, decreased lung function and overall health impairment. Therefore, effective measures should be taken to improve the symptoms of patients, increase their exercise capacity, reduce the number of acute attacks and improve their quality of life.[6] Although appropriate medications and interventions have been proven to significantly improve the symptoms of COPD patients, many gaps remain.[6] For example, disease phenotypes cannot be fully covered, and the cost and adverse reactions of drug treatment cannot be ignored.[7]

Acupuncture, an important part of traditional Chinese medicine, has been practiced for thousands of years in the fight against diseases in China. It has been widely used around the world. In recent years, basic research and clinical research on the use of acupuncture for treating chronic respiratory diseases through various mechanisms, which may have some beneficial effects, have been reported.[8–10] In addition, previous clinical studies have shown that acupuncture treatment may lead to important clinical improvements in quality of life, dyspnea, functional performance, and lung function in patients with COPD.[11–13] However, there are still problems such as the lack of unified standards for the course, frequency and duration of treatment, which is not conducive to evaluating the efficacy of acupuncture in treating COPD.[14] There is a lack of evidence to directly compare the efficacy and safety of the three therapies (acupuncture, conventional drugs, and acupuncture combined with conventional drugs), and it is difficult to determine the most appropriate treatment.[1,6] Therefore, further research on acupuncture with a rigorous design, a reasonable control setting, appropriate index selection, a standardized operation process and good quality control, which can provide a reference for the clinical application of acupuncture for the treatment of COPD, is important.

This project combined previous literature research and expert consensus to determine the treatment plan of COPD acupuncture and carried out a multicenter, open, randomized, controlled trial. The innovation point of this study is to directly compare the three therapies, evaluate the efficacy and safety of different treatment plans, and then determine the most appropriate treatment plan, so as to provide scientific basis for clinicians, patients and health policy makers.

2. Methods

2.1. Study design and setting

This multicenter, open-label, randomized controlled trial was coordinated by Henan University of Chinese Medicine and conducted in the Department of Acupuncture and Moxibustion or Departments of Respiratory Diseases in 5 Grade III hospitals in China: a from November 2017 to September 2019: Hebei Provincial Hospital of Traditional Chinese Medicine, The Third Affiliated Hospital of Henan University of Chinese Medicine, The Second Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shanxi Hospital of Integrated Traditional and Western Medicine and Henan Province Chinese Medicine Research Institute. All the subjects signed written informed consent before randomization. All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional Research Committees and with the 1964 Helsinki Declaration and its later amendments. The trial protocol and amendments were approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Chinese Medicine (2017HL-018–01) and registered at https://www.clinicaltrials.gov (NCT03169504). This study followed the Consolidated Standards of Reporting Trials (CONSORT 2010) Guidelines and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) for reporting results.[15,16] The study protocol is detailed in the Appendix.

2.2. Participants

This study mainly recruited research subjects by posting recruitment advertisements from the outpatient setting of the Department of Acupuncture or the Department of Respiratory Diseases.The inclusion criteria were as follows: (1) a diagnosis of COPD with a classification of airflow limitation severity from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 to GOLD 3 according to GOLD 2017[17]; (2) The patient is in the stable phase of COPD; (3) syndrome differentiation that meets the criteria of Qi deficiency of the lung ZHENG, Qi deficiency of the lung and spleen ZHENG, Qi deficiency of the lung and kidney ZHENG, or Qi and Yin deficiency of the lung and kidney ZHENG[18];(4) age ranging from 40 years to 80 years. The exclusion criteria were as follows: (1) pregnant or lactating women; (2) patients with severe cardiovascular or cerebrovascular diseases; (3) patients with severe liver or kidney diseases; (4) patients with bronchiectasis, active pulmonary tuberculosis, pulmonary embolism or other severe respiratory diseases; (5) patients with tumors after resection, radiotherapy or chemotherapy in the past 5 years; (6) patients with severe neuromuscular disorders; (7) patients with severe arthritis; (8) patients with severe peripheral vascular diseases; (9) patients with severe cognitive or psychiatric disorders; (10) patients who had participated in other clinical studies in the past 4 weeks; (11) patients who had experienced one or more acute exacerbations in the past 4 weeks; and (12) patients who were unwilling to sign informed consent. **(Appendix** Fig. 1**)**

2.3. Randomisation and blinding

A total of 150 COPD patients were randomly assigned to the acupuncture group, the conventional drug group, or the acupuncture plus conventional drug group at a ratio of 1:1:1, and signed a written

informed consent before randomization. The randomization sequence was generated via the 'proc plan' procedure of SAS software (version 9.2) according to stratified block randomization with a block size of 6, and the random number and group assignment were obtained from a central randomization system provided by Jiangsu Famous Medical Technology Co., Ltd, ensuring that an equal number of patients were allocated to different study groups within each group. This study is an open-label trial, and due to the characteristics of acupuncture operation and drug use, no blinding design was used. Nevertheless, this study complied with the CONSORT 2010) guidelines and the STRICTA to ensure the scientific integrity and transparency of the study.[15,16]

2.4. Interventions

2.4.1. Acupuncture group

Patients in this group received acupuncture 3 times weekly for 12 weeks. The acupoints were selected on the basis of literature analysis and expert consensus. The acupoints for each ZHENG are described in **Appendix** Table 1. The acupoint location, depth of insertion and manipulation methods were selected according to the WHO standards and textbooks in China.[19,20] Hwato Sterile Acupuncture Needles for Single Use (Hwato®, Suzhou Hua Tuo Medical Instruments Co., Ltd., Suzhou, China) with sizes of 0.30*25 mm, 0.30*40 mm or 0.30*50 mm were adopted in this study. The needling sensations called Deqi were achieved by manipulating the needles. The needle retention time for each treatment session was up to 30 minutes, during which the needles were manually stimulated every 10 minutes. The acupuncture operators employed all the qualification certificates of Chinese medical practitioners, had been involved in the clinical practice of acupuncture and moxibustion for more than 5 years in Grade III hospitals, and mastered the standardized operating procedures of this study. To ensure that patients in this group received only acupuncture, we took the following measures: 1. A standardized treatment protocol was developed to ensure that all patients in this group received only acupuncture. 2. Patient education was used to increase patients' willingness to adhere to the treatment plan and reduce their tendency to request other treatments. 3. A strict monitoring and follow-up protocol was established to monitor the patient's treatment process and results to ensure that the patient did not use other treatment methods on his own. 4. Jointly supervise and guide the patient's treatment process through teamwork to ensure that the treatment plan is unified and implemented.

Table 1
Syndrome differentiation and selected acupoints.

Acupoints	Qi deficiency of the lung ZHENG	Qi deficiency of the lung and spleen ZHENG	Qi deficiency of the lung and kidney ZHENG	Qi and Yin deficiency of the lung and kidney ZHENG
Feishu (BL13)	×	×	×	×
Dazhui (DU14)*	×	×	×	×
Fengmen (BL12)	×	×	×	×
Taiyuan (LU9)	×	×	×	
Zusanli (ST36)	×	×	×	
Pishu (BL20)		×		
Shenshu (BL23)			×	×
Gaohuang (BL43)				×
Taixi (KI3)				×
Guanyuan (RN4)*				×
Acupoints for specific symptoms	When necessary	When necessary	When necessary	When necessary

Note:
* The needles are inserted unilaterally.

2.4.2. Conventional drug group

Patients in this group were individually divided into Group A, Group B, Group C and Group D according to the comprehensive COPD assessment described in GOLD 2017.[17] The drugs and their administration methods are described in detail in **Appendix** Table 2.

2.4.3. Acupuncture plus conventional drug group

Patients in this group received both acupuncture and conventional drugs described above.

2.4.4. Criteria for discontinuing allocated intervention

The allocated intervention was discontinued for several reasons, such as poor tolerance to the treatment, adverse events, participant requests, and worsening disease.

2.4.5. Concomitant treatments

Participants were not permitted to undertake any additional interventions for COPD beyond our research scheme. Once any disallowed intervention has already been used, relevant information should be recorded in detail. Complications such as coronary heart disease, diabetes mellitus and hypertension should be treated according to the corresponding guidelines. To ensure that no additional interventions were carried out besides research interventions, we had the following measures: 1. Prior to the implementation, the clinical researchers participating in this project were specially trained, including research protocols, working manuals, standard operating procedures, and the consistency was checked; 2. The research units strictly followed the standard operating procedures of the "Working Manual" formulated by the project, and the laboratory test results should be traceable; 3. Project monitors and inspectors monitored Sops during the implementation of the project, and monitored data recording and reporting for accuracy and accuracy to ensure that there were no additional interventions beyond the study intervention; 4. Strict inclusion and exclusion criteria, fully explaining the purpose, methods, benefits and risks of the study to the participants, enhanced their compliance and willingness to cooperate.

2.5. Outcomes

The primary outcomes included exercise capacity measured by the

Table 2
Drugs used and methods of drug administration.

Grouping	Drugs	Specifications	Administration methods
Group A	Salbutamol Sulphate Inhalation Aerosol (Ventolin®, GlaxoSmithKline Australia Pty Ltd)	100 μg/press, 200 press	100 μg each time (when needed), no more than 8 press daily for 12 weeks
Group B	Tiotropium Bromide Powder for Inhalation (Spiriva®, Boehringer Ingelheim International GmbH)	18 μg/capsule, 10 capsules	18 μg each time, once daily for 12 weeks
Group C	Tiotropium Bromide Powder for Inhalation (Spiriva®, Boehringer Ingelheim International GmbH)	18 μg/capsule, 10 capsules	18 μg each time, once daily for 12 weeks
Group D	Fluticasone Propionate Powder for Inhalation (Seretide®, Laboratoire GlaxoSmithKline)	50 μg/250 μg/ inhalation, 60 inhalations	50 μg/250 μg each time, twice daily for 12 weeks.

six-minute walk distance (6MWD)[21] and quality of life measured by St. George's Respiratory Questionnaire (SGRQ).[22] The secondary outcomes included lung function (FEV1, FVC, FEV_1%, FEV_1/FVC and peak expiratory flow (PEF)), acute exacerbation, severity of dyspnea measured by the modified Medical Research Council dyspnea scale (mMRC),[23] Chronic Obstructive Pulmonary Disease Assessment Test (CAT).[24] Safety was assessed via adverse events and medical examination indices,blood routine examination, routine urine test, stool routine examination, electrocardiogram, liver and kidney function test were recorded once before and 12 weeks of treatment, and chest imaging was recorded once before treatment. Adverse events are observed and recorded at any time during the treatment and follow-up periods. **(Appendix** Fig. 2**)**

2.6. Data collection and management

The project responsible unit strictly followed the Standard Operating Procedure (SOP) for operation, and the needle punching operator strictly filled in the needle punching operation. Data were collected via standardized paper case report forms, and recorded various types of information such as disease symptoms and treatment processes in a clear and unified format. The normal reference values of each unit were submitted to the data analysis personnel to ensure the accuracy of the data and the traceability of the test results. Double data entry, data coding and data checking were performed via a special platform provided by Jiangsu Famous Medical Technology Co., Ltd. Project supervisors and inspectors monitor the implementation of SOP in the process of project implementation, and monitored the authenticity, accuracy and completeness of test data records and reports. Participant files were securely stored in numerical order at the central site with restricted access for at least 3 years after completion of the trial.

2.7. Sample size

The sample size calculation was based on the primary outcomes of the 6MWD and SGRQ. According to our previous results,[25] the 6MWD improved by 20.0 ± 61.2 m after 12 weeks of conventional drug treatment. In comparison, the 6MWD increased 63.5 ± 49.9 m after 12 weeks of treatment with acupuncture plus conventional drugs, according to the published literature.[26] Owing to the lack of reliable RCTs reporting the effect of acupuncture alone, we assumed that the 6MWD could also increase by 63.5 ± 49.9 m after 12 weeks of acupuncture alone. Thus, the sample size for each group was approximately 30 according to the calculation method described elsewhere.[27] Assuming a maximal attrition rate of 20 %, a total of 114 patients (38 patients for each group) should be recruited. Similarly, a total of 150 patients (50 patients in each group) were recruited according to the SGRQ. Therefore, the sample size was ultimately determined to be 150.

2.8. Statistical analysis

SPSS software (version 26.0) was used for statistical analysis. The measurement data were expressed as the means (± standard deviations) or medians (interquartile ranges). Repeated measurement data were analyzed by repeated measures analysis of variance, the Bonferroni method was used for pairwise comparisons, one-way analysis of variance was used for comparisons of means among multiple groups, the LSD-t method was used for comparisons of pairwise differences between groups, and Tamhane's T2 method was used for comparisons of unequal variance. Count data were presented as frequencies and proportions and were compared via the chi-square test or Fisher's exact test. The level of significance was set at $\alpha < 0.05$ with a two-tailed test, and the study detected the treatment effect with 90 % power.

2.9. Monitoring

Given the short duration of this study, interim analysis was also not planned. Any adverse events during the trial were recorded. Serious adverse events were reported to the institution review board in a timely manner. The sponsor regularly assigned specialized personnel to monitor the research quality of each center.

3. Results

3.1. Participant flow

The study was conducted between November 2017 and September 2019, and 150 subjects were randomly assigned to the acupuncture group (n = 50), conventional drug group (n = 50), or acupuncture plus conventional drug group (n = 50). After 3 months of treatment and 3 months of follow-up, 7 patients dropped out: there were 4 cases in the acupuncture group, of which 2 subjects were unable to participate in the continuous 3-month treatment and subsequent 3-month follow-up on time due to conflicts between the treatment cycle and personal life and work arrangements, resulting in withdrawal midway. 1 subject chose to withdraw from this study because their symptoms did not improve as expected during the treatment process, and 1 subject used other interventions outside the protocol during the treatment period, which violated the experimental protocol and withdrew. One subject in the conventional drug group was unable to continue participating in the study due to personal reasons, as the specific reason was not specified. There were 2 subjects in the acupuncture plus conventional drug group, of which 1 subject did not follow the treatment frequency required by this study and did not meet the study standards, resulting in withdrawal. One subject had poor compliance and was unable to receive acupuncture treatment on time, affecting the integrity of the study data and resulting in withdrawal. A total of 143 patients completed the study.

3.2. Baseline characteristics

There were no significant differences in gender, age, disease course, education level, occupational distribution, smoking history, body mass index (BMI), lung function classification, comprehensive assessment group, number of acute exacerbations or number of hospitalizations among the three groups ($P > 0.05$), as shown in **Appendix** Table 3.

3.3. Primary outcomes

3.3.1. Effects of three treatments on the 6MWD in patients with stable COPD

The 6MWD at different time points in the three groups tended to change with time and group, and there were time, group and interaction effects ($P = 0.000$, $P = 0.039$, $P = 0.000$). Compared with that before treatment, the 6MWD of the acupuncture plus conventional drug group was significantly greater at 4, 8, and 12 weeks of treatment and 12 weeks of follow-up ($P < 0.001$), the 6MWD of the acupuncture group was significantly greater at 12 weeks of treatment and 12 weeks of follow-up, and the difference was statistically significant ($P < 0.001$, $P = 0.003$). The conventional drug group showed an increasing trend at 8, 12, and 12 weeks of follow-up, with no significant difference ($P > 0.05$). Compared with those in the conventional drug group, the 6MWD of patients in the acupuncture plus conventional drug group increased significantly at 8 weeks, 12 weeks of treatment, and 12 weeks of follow-up ($P = 0.008$, $P = 0.002$, $P = 0.001$). Compared with the acupuncture group, there was no statistically significant difference in the 6MWD between the conventional drug group and the acupuncture plus conventional drug group at any time point ($P > 0.05$), as shown in **Appendix** Table 4 and Fig. 3.

3.3.2. Effects of three treatments on SGRQ in patients with stable COPD

The symptom scores, exercise scores, lifestyle impact scores and total scores of the three groups of patients at different time points tended to change over time, with time effects ($P < 0.001$, $P < 0.001$, $P < 0.001$,

Table 3
Baseline characteristics.

Variables of interest	Intervention			χ^2/F	P
	Acupuncture group (n = 46)	conventional drug group (n = 49)	acupuncture plus conventional drug group (n = 48)		
Gender				2.475	0.290
male	28	37	34		
female	18	12	14		
Age(years)	63.43 ± 8.609	63.51 ± 9.136	61.33 ± 8.104	0.981	0.377
Course of disease(months)	116.43 ± 91.856	104.80 ± 101.581	78.85 ± 86.930	1.992	0.140
Degree of education				2.644	0.331
Illiteracy or Semi literate	2	1	2		
Primary school education	6	5	3		
Junior high school education	13	15	14		
High school or technical secondary school education	12	15	15		
Junior college degree	8	9	10		
Bachelor's degree	5	4	4		
Occupations				14.743	0.459*
workers	4	2	11		
Farmer	7	9	21		
The intellectual	3	1	9		
Personnel in charge	2	0	4		
Service personnel	1	1	3		
retirees	28	30	84		
Unemployed persons	1	2	7		
Laid-off persons	0	2	2		
Smoking				1.107	0.180*
Yes	25	28	31		
No	21	21	17		
Duration of smoking(months)	365.56 ± 150.184	396.93 ± 153.668	360.55 ± 153.668	0.511	0.602
Number of cigarettes(days)	20.00 ± 7.439	22.43 ± 8.561	21.55 ± 11.177	0.455	0.636
Passive smoking				0.127	0.470*
Yes	21	23	21		
No	25	26	27		
BMI	24.26 ± 2.82	24.04 ± 2.95	24.26 ± 2.75	0.099	0.906
Pulmonary function classification				2.647	0.248*
Level 1	4	2	6		
Level 2	26	32	28		
Level 3	16	15	14		
Comprehensive assessment grouping				1.274	0.219*
Group A	8	9	11		
Group A	15	16	17		
Group A	14	16	12		
Group A	9	8	8		
Number of acute exacerbations	1.28 ± 1.205	1.29 ± 1.225	1.29 ± 1.166	0.001	0.999
Number of hospitalizations	0.85 ± 1.010	0.84 ± 1.087	0.88 ± 1.024	0.017	0.983

$P < 0.001$) but no group or interaction effects ($P > 0.05$). Compared with those before treatment, the total scores of the three groups of patients decreased at 12 weeks of follow-up, but only the acupuncture group showed significant differences ($P = 0.001$), and there was no significant difference among the three groups ($P > 0.05$). Compared with those before treatment, the symptom scores of the three groups of patients decreased at 12 weeks of treatment and follow-up. Except for the acupuncture plus conventional drug group at 12 weeks of treatment, there were statistically significant differences ($P < 0.05$), but there was no statistically significant difference among the three groups ($P > 0.05$). At the 12-week follow-up, the lifestyle impact scores of the three groups of patients tended to decrease compared with those before treatment, with a statistically significant difference between the acupuncture group and the acupuncture plus conventional drug group ($P < 0.001$, $P = 0.037$). There was no statistically significant difference ($P > 0.05$) in the exercise scores of the three groups of patients at 12 weeks of treatment and 12 weeks of follow-up compared with before treatment, as shown in **Appendix** Table 4 and Figs. 4–5.

3.4. Secondary outcomes

3.4.1. Effects of three treatments on lung function in patients with stable COPD

FEV1 and FEV1/FVC tended to change with time at different time points in the three groups of patients, with time effects ($P = 0.020$, $P < 0.001$) but no group or interaction effects ($P > 0.05$). FVC, FEV1 %, and PEF had no time, group, or interaction effects ($P > 0.05$). Compared with that before treatment, the FEV1/FVC of the acupuncture plus conventional drug group significantly increased at 12 weeks of treatment and follow-up ($P < 0.001$, $P = 0.001$), but there was no statistically significant difference among the three groups ($P > 0.05$). The FEV1 of the three groups of patients tended to increase at 12 weeks of treatment and follow-up, but the difference was not significant ($P > 0.05$), as shown in **Appendix** Table 5 and Figs. 6–8.

3.4.2. Effects of three treatments on the number of acute exacerbations in patients with stable COPD

There was a time effect ($P < 0.001$) on the number of acute exacerbations in the three groups of patients at different time points but no group or interaction effect ($P = 0.832$, $P = 0.972$). Compared with that before treatment, the number of acute exacerbations in the three groups of patients decreased significantly at 4, 8, and 12 weeks of treatment and at 12 weeks of follow-up ($P < 0.05$). The number of acute exacerbations in the acupuncture plus conventional drug group was the lowest among the three groups of patients at all treatment and follow-up time points, but there was no statistically significant difference between the groups at any time point ($P > 0.05$), as shown in **Appendix** Table 5 and Fig. 9.

Table 4
Primary outcomes.

index	time		acupuncture group (n = 46)	conventional drug group (n = 49)	acupuncture plus conventional drug group (n = 48)	F	P
6MWD	Before treatment		387.8370 ± 55.0893	384.8286 ± 106.2567	388.1187 ± 81.6218	0.023	0.978
	Treatment for 4 weeks		397.20 ± 55.779	384.49 ± 96.143	420.28 ± 79.401a	2.533	0.083
	Treatment for 8 weeks		403.7326 ± 59.4369	384.7327 ± 92.2253	434.0854 ± 80.6804abB	4.808	0.010
	Treatment for 12 weeks		416.33 ± 60.457abc	393.27 ± 89.396	446.93 ± 78.041abcB	5.889	0.004
	Follow-up for 12 weeks		414.2391 ± 57.9595ab	387.4571 ± 87.2431	444.8750 ± 82.8077abcB	6.678	0.002
	F		6.935	1.949	23.358		
	P		0.000	0.106	0.000		
	Time effects (F,P)		(22.595,0.000)				
	Group effects(F,P)		(3.330,0.039)				
	interaction effects(F,P)		(4.398,0.000)				
SGRQ	Total	Before treatment	43.5813 ± 17.2770	36.9197 ± 16.0378	37.9917 ± 16.7992	2.153	0.120
		Treatment for 12 weeks	43.3391 ± 14.9287	41.1111 ± 13.8206a	40.9634 ± 16.6062	0.361	0.698
		Follow-up for 12 weeks	37.6333 ± 13.7550ad	36.3554 ± 13.7138d	34.4604 ± 14.3299d	0.618	0.540
		F	12.194	7.776	13.138		
		P	0.000	0.001	0.000		
		Time effects (F,P)	(29.819,0.000)				
		Group effects(F, P)	(0.992,0.373)				
		interaction effects (F,P)	(1.684,0.154)				
	Symptoms	Before treatment	61.7030 ± 26.3635	54.4130 ± 22.3409	50.5514 ± 22.0818	2.690	0.071
		Treatment for 12 weeks	49.8482 ± 25.7228a	46.7913 ± 17.8280a	44.7738 ± 24.3080	0.588	0.557
		Follow-up for 12 weeks	48.2345 ± 25.5245a	47.9645 ± 20.6563a	40.4955 ± 21.0575a	1.827	0.165
		F	13.728	4.546	7.705		
		P	0.000	0.012	0.001		
		Time effects (F,P)	(22.950,0.000)				
		Group effects(F, P)	(1.741,0.179)				
		interaction effects (F,P)	(1.680,0.155)				
	Exercise	Before treatment	50.3150 ± 17.9169	46.2856 ± 20.8622	47.0045 ± 20.7443	0.546	0.580
		Treatment for 12 weeks	46.1698 ± 17.8719	43.9738 ± 19.8727	42.7598 ± 21.4616	0.356	0.701
		Follow-up for 12 weeks	50.5691 ± 13.1926d	50.2445 ± 17.2906d	48.3262 ± 16.7055d	0.277	0.758
		F	3.638	7.050	5.500		
		P	0.029	0.001	0.005		
		Time effects (F,P)	(13.314,0.000)				
		Group effects(F, P)	(0.382,0.684)				
		interaction effects (F,P)	(0.561,0.691)				
	lifestyle impact	Before treatment	34.8356 ± 18.0809	26.8412 ± 16.0115	29.4490 ± 17.7787	2.620	0.076
		Treatment for 12 weeks	39.9624 ± 14.1408a	37.9403 ± 13.3628a	38.9071 ± 15.4344a	0.236	0.790
		Follow-up for 12 weeks	27.3807 ± 14.3126ad	25.2860 ± 14.0060d	24.9118 ± 15.3793ad	0.390	0.678
		F	37.582	45.943	50.232		
		P	0.000	0.000	0.000		
		Time effects (F,P)	(129.710,0.000)				
		Group effects(F, P)	(1.055,0.351)				
		interaction effects (F,P)	(1.825,0.124)				

a indicates comparison with before treatment, $P < 0.05$; b indicates comparison with treatment for 4 weeks, $P < 0.05$; c indicates comparison with treatment for 8 weeks, $P < 0.05$; d indicates comparison with treatment for 12 weeks, $P < 0.05$; A indicates comparison with the acupuncture group, $P < 0.05$; B indicates comparison with the conventional drug group, $P < 0.05$.

3.4.3. Effects of three treatments on the mMRC in patients with stable COPD

The mMRC scores of the three groups of patients at different time points tended to change with time and grouping, with time and group effects ($P < 0.001$, $P = 0.016$) and no interaction effect ($P = 0.077$). Compared with those before treatment, the mMRC scores of the acupuncture plus conventional drug group were significantly lower at 4, 8, and 12 weeks of treatment and at 12 weeks of follow-up ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.005$), the conventional drug group had significantly lower mMRC scores after 8 and 12 weeks of treatment ($P = 0.010$, $P < 0.001$), and the acupuncture group had lower mMRC scores after 12 weeks of treatment ($P < 0.05$). Compared with those at 12 weeks of treatment, the mMRC scores of all three groups of patients increased at 12 weeks of follow-up ($P = 0.039$). Compared with the conventional drug group and acupuncture group, the acupuncture plus conventional drug group showed a significant decrease ($P < 0.05$) at 4

Table 5
Primary outcomes.

index	time		acupuncture group (n = 46)	conventional drug group (n = 49)	Acupuncture plus conventional drug group (n = 48)	F	P
mMRC	Before treatment		1.48 ± 0.863	1.57 ± 0.816	1.65 ± 0.812	0.480	0.620
	Treatment for 4 weeks		1.46 ± 0.585	1.29 ± 0.540	1.02 ± 0.252aAB	9.821	0.000
	Treatment for 8 weeks		1.26 ± 0.575	1.14 ± 0.500a	0.85 ± 0.357aAB	8.831	0.000
	Treatment for 12 weeks		1.13 ± 0.499ab	1.04 ± 0.351a	0.94 ± 0.598a	1.808	0.025
	Follow-up for 12 weeks		1.46 ± 0.622d	1,31 ± 0.548d	1.21 ± 0.504acd	2.345	0.032
	F		5.480	6.419	12.175		
	P		0.000	0.000	0.000		
	Time effects (F,P)		(20.230,0.000)				
	Group effects(F,P)		(4.265,0.016)				
	interaction effects(F,P)		(1.800,0.077)				
acute exacerbations	Before treatment		1.28 ± 1.205	1.29 ± 1.225	1.29 ± 1.166	0.001	0.999
	Treatment for 4 weeks		0.04 ± 0.206a	0.06 ± 0.242a	0.02 ± 0.144a	0.487	0.616
	Treatment for 8 weeks		0.04 ± 0.206a	0.10 ± 0.306a	0.02 ± 0.144a	1.616	0.202
	Treatment for 12 weeks		0.07 ± 0.250a	0.08 ± 0.277a	0.04 ± 0.202a	0.326	0.722
	Follow-up for 12 weeks		0.04 ± 0.206a	0.04 ± 0.200a	0.02 ± 0.144a	0.212	0.809
	F		12.323	13.421	13.547		
	P		0.000	0.000	0.000		
	Time effects (F,P)		(38.699,0.000)				
	Group effects(F,P)		(0.184,0.832)				
	interaction effects(F,P)		(0.280,0.972)				
Lung function	FEV1	Before treatment	1.3098 ± 0.51692	1.4292 ± 0.49518	1.4552 ± 0.61726	0.944	0.392
		Treatment for 12 weeks	1.4033 ± 0.61876	1.4912 ± 0.58856	1.5625 ± 0.57430	0.847	0.431
		Follow-up for 12 weeks	1.3933 ± 0.56336	1.4486 ± 0.63574	1.5198 ± 0.58825	0.531	0.589
		F	1.636	0.649	1.838		
		P	0.199	0.524	0.163		
		Time effects (F,P)	(3.989,0.020)				
		Group effects(F,P)	(0.851,0.429)				
		interaction effects (F,P)	(0.224,0.925)				
	FVC	Before treatment	2.4302 ± 0.81852	2.5669 ± 0.69885	2.6360 ± 0.86173	0.813	0.446
		Treatment for 12 weeks	2.4335 ± 0.87908	2.6094 ± 0.77117	2.6765 ± 0.77943	1.123	0.328
		Follow-up for 12 weeks	2.4293 ± 0.80806	2.4439 ± 0.74099	2.6196 ± 0.81875	0.858	0.426
		F	0.002	3.119	0.307		
		P	0.998	0.047	0.736		
		Time effects (F,P)	(1.488,0.228)				
		Group effects(F,P)	(0.979,0.378)				
		interaction effects (F,P)	(0.669,0.614)				
	FEV1/ FVC	Before treatment	54.2567 ± 11.3243	55.2720 ± 10.1525	53.8825 ± 11.7468	0.204	0.816
		Treatment for 12 weeks	56.9972 ± 10.8909	56.8949 ± 9.6521	58.4473 ± 11.7375a	0.311	0.733
		Follow-up for 12 weeks	57.5820 ± 10.3937a	56.9061 ± 10.0745	58.0038 ± 10.4005a	0.141	0.869
		F	4.407	1.231	8.535		
		P	0.014	0.295	0.000		
		Time effects (F,P)	(12.224,0.000)				
		Group effects(F,P)	(0.035,0.966)				
		interaction effects (F,P)	(1.016,0.400)				
	FEV1 %	Before treatment	52.1970 ± 19.6297	53.8224 ± 16.6011	54.5721 ± 17.8131	0.212	0.809
		Treatment for 12 weeks	53.4217 ± 21.9607	54.1837 ± 19.4328	56.0552 ± 19.4114	0.211	0.810
		Follow-up for 12 weeks	55.8900 ± 21.7828	53.7551 ± 16.6114	57.2292 ± 19.3429	0.400	0.671
		F	2.001	0.025	0.998		
		P	0.139	0.975	0.371		
		Time effects (F,P)	(1.615,0.201)				
		Group effects(F,P)	(0.225,0.799)				
		interaction effects (F,P)	(0.511,0.728)				
	PEF	Before treatment	3.3363 ± 1.7171	3.7606 ± 1.2677	3.8329 ± 1.8062	1.298	0.276
		Treatment for 12 weeks	3.4135 ± 1.8034	4.0020 ± 1.8550	3.7490 ± 1.7336	1.276	0.282
		Follow-up for 12 weeks	3.3765 ± 1.7095	3.8680 ± 1.9657	3.7767 ± 1.7889	0.961	0.385
		F	0.080	0.892	0.091		
		P	0.923	0.412	0.913		
		Time effects (F,P)	(0.290,0.749)				

(*continued on next page*)

Table 5 (*continued*)

index	time		acupuncture group (n = 46)	conventional drug group (n = 49)	Acupuncture plus conventional drug group (n = 48)	F	P
		Group effects(F,P)	(1.328,0.268)				
		interaction effects (F,P)	(0.383,0.821)				
CAT		**Before treatment**	18.80 ± 3.532	18.69 ± 3.280	18.63 ± 4.276	0.028	0.266
		Treatment for 12 weeks	15.59 ± 2.517a	16.18 ± 2.421a	13.81 ± 3.140aAB	9972	0.143
		Follow-up for 12 weeks	16.78 ± 2.270ad	16.73 ± 3.161a	15.54 ± 2.324ad	3.425	0.035
		F	24.310	16.376	56.780		
		P	0.000	0.000	0.000		
		Time effects (F,P)	(100,960,0.000)				
		Group effects(F,P)	(3.311,0.039)				
		interaction effects (F,P)	(3.791,0.005)				

a indicates comparison with before treatment, $P < 0.05$; b indicates comparison with treatment for 4 weeks, $P < 0.05$; c indicates comparison with treatment for 8 weeks, $P < 0.05$; d indicates comparison with treatment for 12 weeks, $P < 0.05$; A indicates comparison with the acupuncture group, $P < 0.05$; B indicates comparison with the conventional drug group, $P < 0.05$.

and 8 weeks of treatment, as shown in **Appendix** Table 5 and Fig. 10.

3.4.4. Effects of three treatments on CAT in patients with stable COPD

The CAT scores of the three groups of patients at different time points revealed time, group, and interaction effects ($P < 0.001$, $P = 0.039$, $P = 0.005$). Compared with those before treatment, the CAT scores of all three groups of patients decreased at 12 weeks of treatment and 12 weeks of follow-up ($P < 0.05$). Compared with those at 12 weeks of treatment, the CAT scores of all three groups of patients increased at 12 weeks of follow-up, with a significant increase in the acupuncture group and the acupuncture plus conventional drug group ($P = 0.011$, $P < 0.001$). Compared with the acupuncture group and conventional drug group, the acupuncture plus conventional drug group had the lowest CAT score at 12 weeks of treatment, and the difference was statistically significant ($P = 0.006$, $P < 0.001$). At 12 weeks of follow-up, the acupuncture plus conventional drug group had the lowest CAT score among the three groups, but there was no intergroup difference ($P > 0.05$), as shown in **Appendix** Table 5 and Fig. 11.

3.5. Adverse events

There were no significant differences in blood routine examination, routine urine test, stool routine examination, electrocardiogram and liver and kidney function test among the three groups before and after treatment. During the treatment period, all three groups of patients did not experience adverse events such as needle retention, bending, needle breakage, bleeding, hematoma, pneumothorax, etc.

4. Discussion

This trial revealed that acupuncture, conventional drugs, and acupuncture plus conventional drugs all have certain value in the treatment of stable COPD. Among them, the acupuncture plus conventional drug group was superior to the acupuncture group and conventional drug group in improving the exercise endurance and quality of life of COPD patients and improving the severity of respiratory distress but had no effect on the lung function of stable COPD patients. These findings indicate that combined acupuncture can improve the conventional treatment efficacy for COPD patients in the stable phase, encouraging the use of acupuncture as an adjuvant therapy combined with conventional drugs to become a better choice for COPD in stable phase plans and providing a reference for further related research.

Meta-analysis revealed that most studies currently compare acupuncture combined with other treatments (such as Western medicine or traditional Chinese medicine) with the use of other treatments alone or in combination with sham acupuncture to analyze the effectiveness of acupuncture as an adjuvant therapy.[28] In our study, patients were divided into three main groups to clarify the efficacy and safety of acupuncture and conventional drugs alone and in combination for the treatment of stable COPD and to provide stronger evidence-based medicine for acupuncture. This study screened the most acupoints for acupuncture in COPD patients on the basis of previous literature evaluation and expert consensus research results. These acupoints are mainly concentrated in the waist, back, chest, and abdomen, which is roughly consistent with Shi's research results.[10] Our experimental process lasted for a total of 24 weeks, including 12 weeks of treatment, which is roughly consistent with the basic design cycle of multiple clinical trials of acupuncture treatment for COPD.[29,30] Moreover, we designed a 12-week follow-up period to ensure a more comprehensive evaluation of whether acupuncture has a lasting effect on the symptoms and quality of life of patients with COPD, a chronic disease. In addition, LUO reported that intermediate-frequency needling for more than 60 days (2–3 times per week) may lead to the greatest improvement in FEV1 in stable COPD patients, whereas our trial protocol involved needling 3 times per week at a moderate frequency, which is consistent with the best needling frequency reported in similar studies.[12] As far as our research is concerned, the design of the experimental protocol is scientific and reasonable, and the results are clear and meaningful for the long-term treatment of stable COPD. Therefore, the acupuncture regimen proposed in this study can serve as an adjuvant therapy to improve exercise endurance and quality of life in stable COPD patients.

Appropriate outcome measures for evaluating the efficacy of intervention measures are crucial, and in our study, the 6MWD and SGRQ were used as the primary outcome measures. A previous study revealed that, compared with the use of conventional drugs alone, the combination of acupuncture significantly improved the 6MWD of stable COPD patients after 12 weeks of treatment and follow-up. Suzuki M's study also reported similar results, which is consistent with our study.[31] However, there is currently a lack of direct scientific research evidence to clarify its mechanism. Some studies have suggested that the effect of acupuncture on the exercise ability of COPD patients is mediated mainly by improvements in respiratory distress and leg fatigue. Our research revealed that acupuncture combined with conventional drugs can improve the severity of respiratory distress in stable COPD patients and is superior to the use of acupuncture or conventional drugs alone, which can serve as evidence for the mechanism of the impact of acupuncture on exercise ability in COPD patients.[31,32] In addition, we found that after acupuncture, conventional drugs, and acupuncture plus conventional drugs, the symptom scores and lifestyle impact scores improved, but there was no significant difference among the three groups, indicating

that acupuncture can improve the quality of life of stable COPD patients, which is consistent with the research results of Feng J.[33] However, some scholars have suggested that there is significant heterogeneity among studies that use SGRQ scores to evaluate the quality of life of COPD patients, and the source of this heterogeneity cannot be determined. This may be related to the lack of placebo injections as controls and the absence of blinding of participants during the randomization process.[28]

A previous study revealed that acupuncture did not significantly improve lung function, and our study yielded similar results.[34] However, a recent study showed that acupuncture-assisted treatment for stable COPD patients can improve the FEV1 % and delay the decline in lung function, which is inconsistent with our research results.[11] We believe that this may be related to differences in baseline levels of lung function. In the study by Xu,[11] the baseline FEV1 and FEV1 % were 1.16 and 49.12, respectively, whereas in our study, they were 1.46 and 54.57, respectively. Patients had higher baseline levels of lung function, so although there was improvement after treatment, the space for improvement was relatively small. In addition, the irreversibility of airway damage in COPD patients can lead to less significant improvement in lung function than early treatment, which is also the main reason for the differences in research. In our study, after 12 weeks of treatment and 12 weeks of follow-up, the FEV1/FVC of the acupuncture plus conventional drug group increased, indicating that acupuncture as an adjuvant therapy can improve lung ventilation function in stable COPD patients to some extent. Currently, most studies suggest that acupuncture is beneficial for improving lung function in COPD patients.[35] The mMRC has been widely used for the assessment of respiratory distress symptoms in COPD patients.[36] As a safe and effective adjuvant therapy, acupuncture has been reported to improve the severity of respiratory distress in COPD patients. Our study revealed that acupuncture plus conventional drugs had the greatest effect on improving respiratory distress, which is consistent with previous research.[37] In chronic obstructive pulmonary disease, reducing the frequency of acute exacerbations is an important aspect of management. Our research revealed that all three interventions can reduce the frequency of acute exacerbations in COPD patients. Among them, the acupuncture plus conventional drug group had fewer acute exacerbations than did the conventional drug group and acupuncture group at 12 weeks of treatment and follow-up, but the difference was not statistically significant. At present, there is a lack of attention and reporting on the number of acute exacerbations during the treatment process in the clinical studies of acupuncture treatment for COPD that have been published.[11,38] The reporting of acute exacerbation indicators in this study can provide some reference for future clinical research on acupuncture diagnosis and treatment of COPD. CAT can be used to evaluate and quantify the health status of stable COPD patients. Our study revealed that all three treatment and follow-up regimens significantly improved the CAT score, with the acupuncture plus conventional drug group showing the best effect, which is consistent with the findings of a previous study.[39]

Notably, in this study, compared with those in the 12-week treatment group, the 6MWD, mMRC, FEV1, and CAT scores at the 12-week follow-up all worsened. Although the perception of dyspnea improved after acupuncture, it only had short-term efficacy, which is similar to our results.[40,41] Some analyses suggest that this may be related to acupuncture techniques, acupoints, needle retention time, and patient cooperation. The precision of these key elements has a significant impact on clinical outcomes, but there is currently a lack of precise and standardized acupuncture clinical treatment plans and a large amount of basic research support, which should be further explored in future research.[42] In addition, all stable COPD patients described here had good tolerance to acupuncture, and there were no adverse events related to acupuncture, such as needle breakage, bleeding, hematoma, or pneumothorax, indicating that acupuncture treatment for COPD has good safety.

In our study, patients showed very good compliance, which may be related to the following reasons: first, the high-level skills of the acupuncture operators were widely recognized by the subjects during the research process; second, chronic disease patients had high expectations for the efficacy of acupuncture therapy; and finally, our treatment plan was simplified and optimized. These factors work together to improve patient compliance. However, this study also has several limitations. Although the experimental design minimized bias to the greatest extent possible, the small sample size and potential participant bias limited our ability to draw definitive conclusions. Multicenter trials were not conducive to controlling the quality of the studies and had a negative impact on the generalizability of the results.

5. Conclusion

The results of this study are in line with our expectations; that is, in the treatment of stable COPD, acupuncture plus conventional drug is superior to simple acupuncture and conventional drug in improving exercise ability, improving quality of life, and reducing dyspnea, and is an acceptable and safe auxiliary treatment measure. Our results promote further research on this promising strategy.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional Research Committees and with the 1964 Helsinki Declaration and its later amendments (all participants read and signed a dedicated consent form). The trial protocol and amendments were approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Chinese Medicine (2017HL-018–01) and registered at https://www.clinicaltrials.gov (NCT03169504).

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Author Statement

We declare that this manuscript is original, has not been published before and is notcurrently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Wu Lei: Investigation. **Wang Yanjun:** Investigation. **Bai Li:** Investigation. **Yu Xuefeng:** Investigation. **Zhou Miao:** Investigation. **Shao Suju:** Investigation. **Zhang Mingli:** Investigation. **Han Weihong:** Data curation. **Yu Xueqing:** Investigation. **Xie Yang:** Writing – original draft. **Li Xuanlin:** Data curation. **Li Jiansheng:** Writing – review & editing, Writing – original draft.

Author Contributions

Jian-sheng Li contributed to the conception and design, critical revision, and should be the corresponding author. Yang Xie contributed to the design of trial, the data collection, data analysis and draft manuscript writing. Jian-sheng Li and Yang Xie jointly completed the writing and proofreading of the paper, so they are co-first authors. Yanjun Wang, Lei Wu, Suju Shaoao, Miao Zhou, Xuefeng Yu, Li Bai, Mingli Zhang, Xueqing Yu contributed to the enrollment and visit of participants. Weihong Han, Xuanlin Li contributed to the data collection. Tao Chen contributed to the methodological and statistical support. All the authors have read and approved the final manuscript.'

Consent for publication

Not applicable.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix

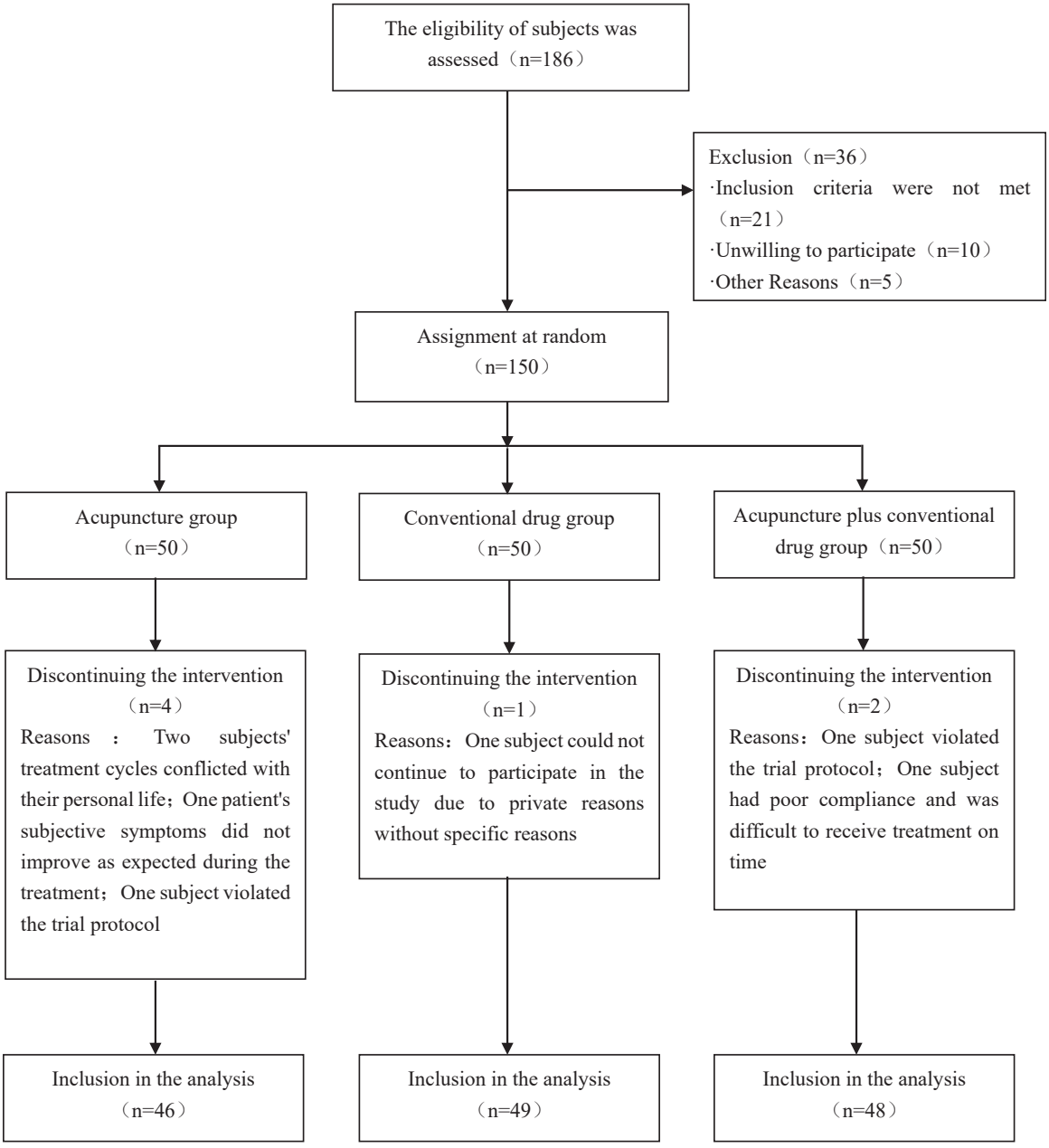

Fig.1. Study flow diagram

Measure	Enrollment	Baseline	Treatment phase			Follow-up phase
			Week 4	Week 8	Week 12	Week 24
Eligibility screen	×					
Informed consent	×					
Demographic data	×					
Medical history	×					
Physical examination	×					
Lung function examination	×				×	×
Six-minute walk distance		×	×	×	×	×
St. George's Respiratory Questionnaire		×			×	×
Modified Medical Research Council dyspnea scale		×	×	×	×	×
Frequency of acute exacerbation		×	×	×	×	×
COPD assessment test		×			×	×
Clinical Symptom Assessment Questionnaire		×			×	×
COPD Patient-reported Outcome Scale		×			×	×
EuroQol-5 Dimensions		×			×	×
Economic evaluation		×	×	×	×	×
Concomitant treatments		×	×	×	×	×
Adverse events			×	×	×	×
Blood/urine/stool test	×				×	
Liver and kidney function test	×				×	
Electrocardiography examination	×				×	
Chest imaging examination	×					

Fig.2. SPIRIT diagram

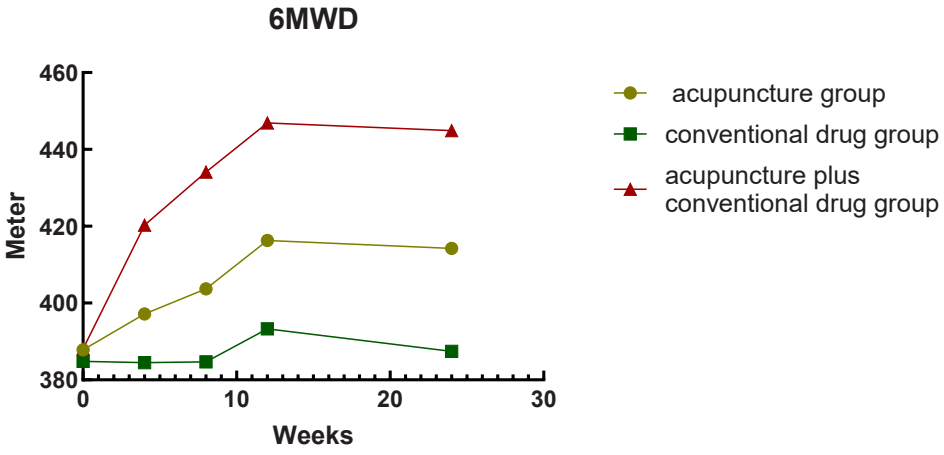

Fig.3. Comparison of difference between groups on score of 6MWD

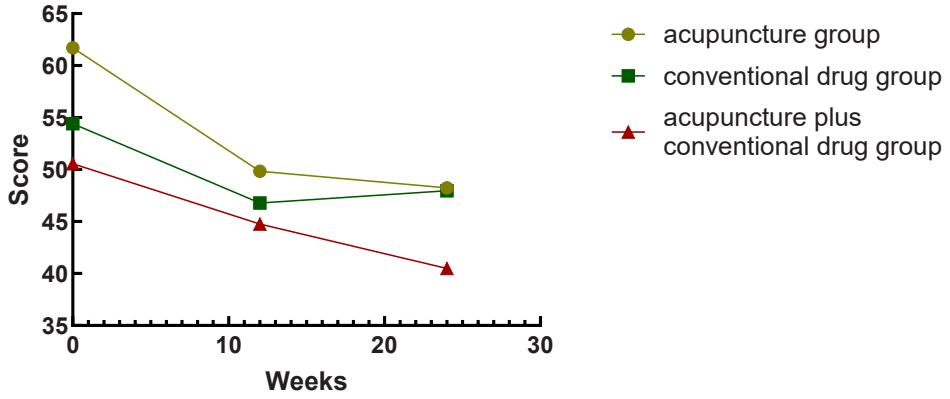

Fig. 4. Comparison of difference between groups on symptom score of SGRQ

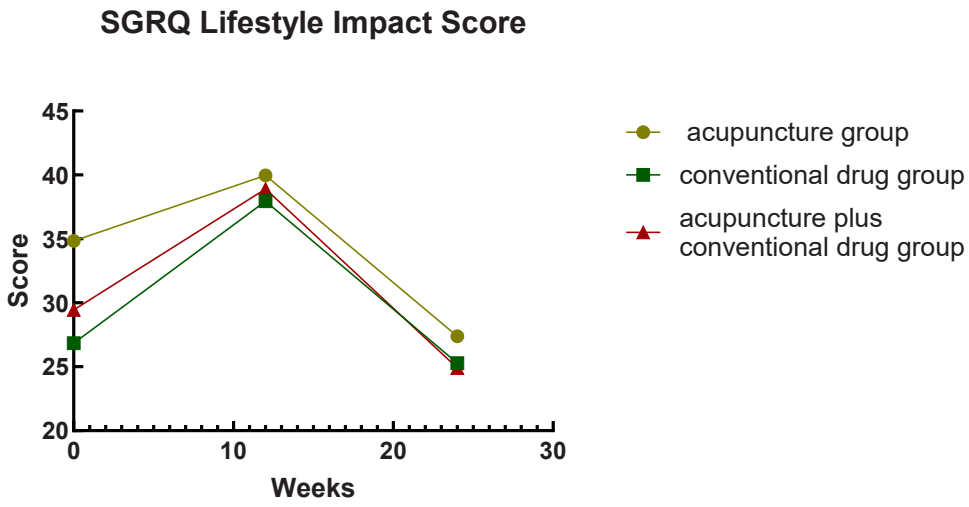

Fig.5. Comparison of difference between groups on lifestyle impact score of SGRQ

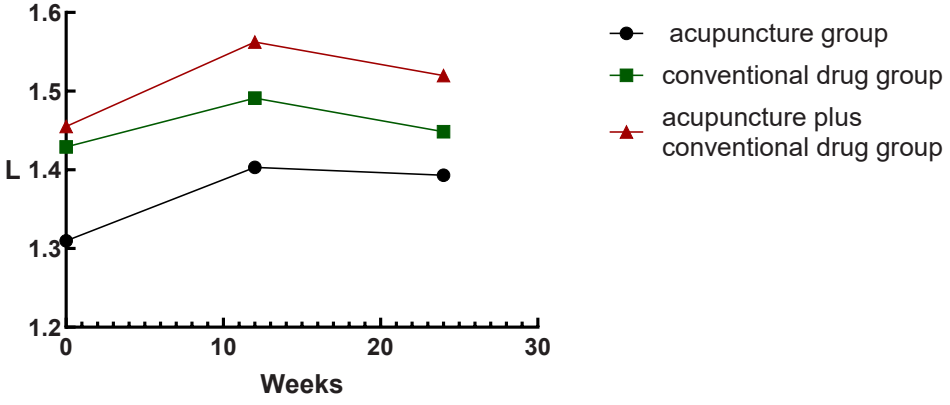

Fig.6. Comparison of difference between groups on FEV1 score of lung function

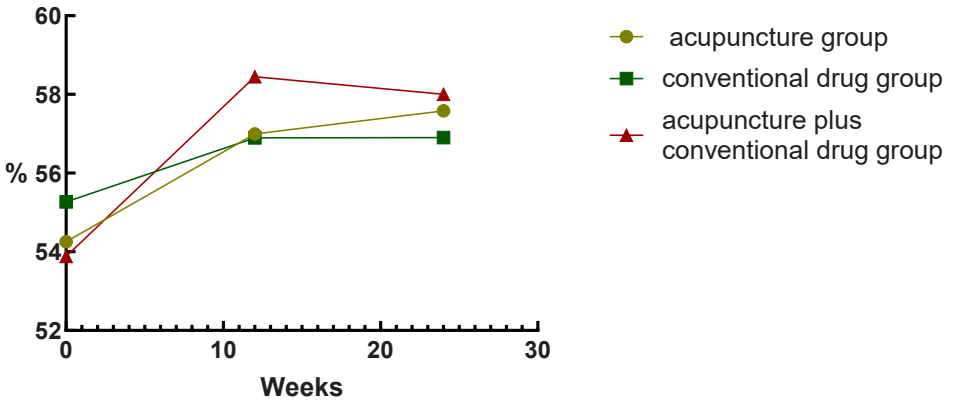

Fig.7. Comparison of difference between groups on FEV1/FVC score of lung function

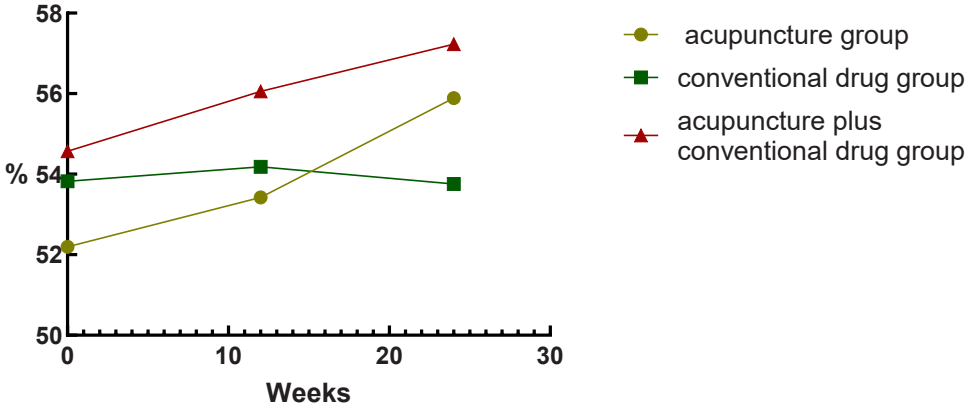

Fig.8. Comparison of difference between groups on FEV1 Pred (%) score of lung function

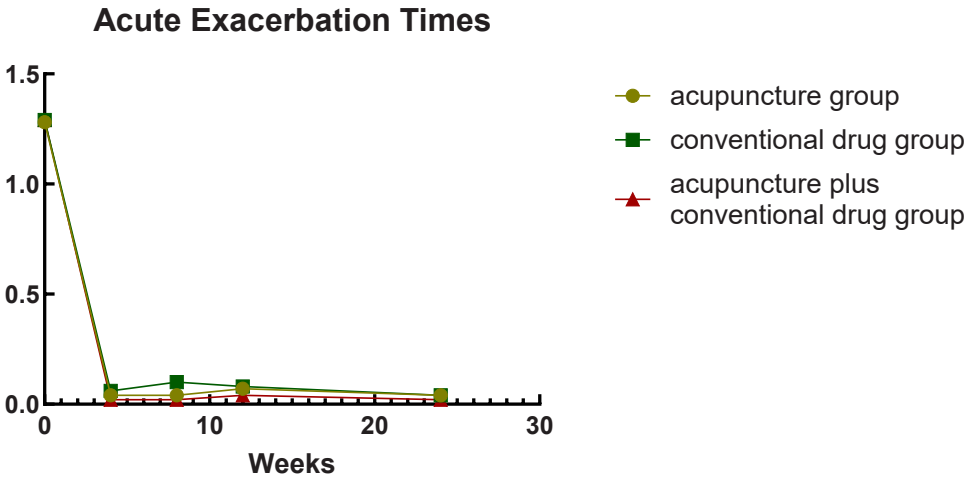

Fig.9. Comparison of difference between groups on acute exacerbation times score

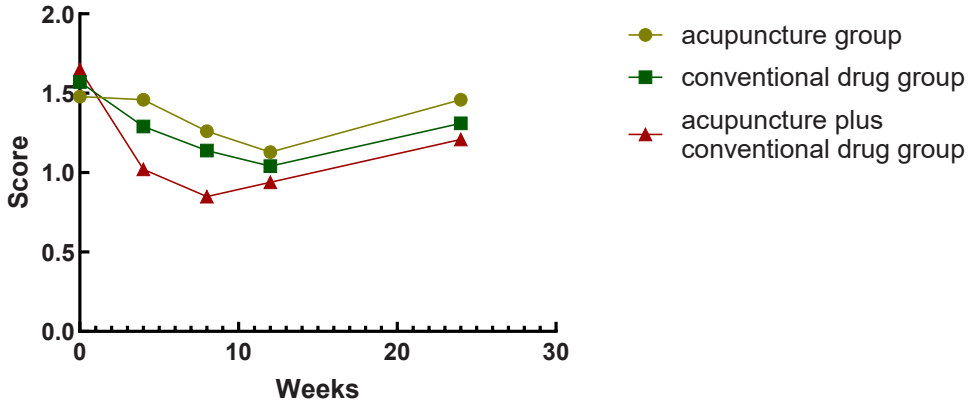

Fig.10. Comparison of difference between groups on mMRC score

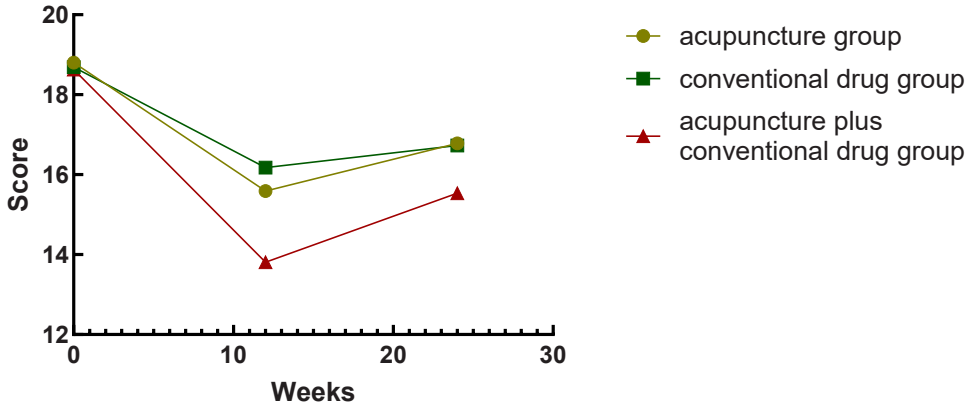

Fig.11. Comparison of difference between groups on CAT score

Data availability

The data supporting the results of this study are available from the correspondi-ng author on reasonable request.

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