

STUDY PROTOCOL

Open Access



Efficacy of acupuncture as an adjunctive treatment to patients with stable COPD: a multicenter, randomized, sham-controlled trial protocol

Liuyang Huang^{1†}, Sha Yang^{1†}, Guixing Xu^{1†}, Qin Luo¹, Chunyan Yang¹, Hao Tian¹, Yilin Liu¹, Zhuo Zhou¹, Fengyuan Huang¹, Siyao Gong¹, Qian Li^{1,2}, Xin Yu¹, Ming Chen¹, Dan Huang¹, Yunyu Liu¹, Juan Tang¹, Ruixin Zhang³, Xin Sun⁴, Guangbing Lu⁵, Chunfang Zeng⁶, Shuangchun Ai⁷, Bin Li⁸, Jian qin Chen⁹, Quan Luo¹⁰, Chan Xiong¹¹, Zhi Zou¹², Qiang Hu¹³, Xiaochao Luo³, Ling Li³, Mingsheng Sun^{1*}, Fang Zeng^{1*} and Fanrong Liang^{1*}

Abstract

Background Chronic obstructive pulmonary disease (COPD) is a common respiratory disease and the third leading cause of death worldwide. Previous evidence has shown that acupuncture may be an effective complementary alternative therapy for stable COPD. However, large-sample, rigorously designed long-term follow-up studies still need to be completed. Notably, the relationship between the frequency of acupuncture and clinical efficacy in studies on acupuncture for stable COPD still needs further validation. This study aims to evaluate the efficacy and safety of acupuncture for stable COPD and further investigate the dose–effect relationship of acupuncture.

Methods/design This is a multicenter, randomized, controlled trial that uses central randomization to randomly allocate 550 participants in a 1:1:1:1:1 ratio to once a week acupuncture group, twice a week acupuncture group, three times a week acupuncture group, sham acupuncture group and waiting-list control group. The sham acupuncture group will receive placebo acupuncture treatments three times per week, and the waiting-list control group will not receive any form of acupuncture intervention. The study consists of a 2-week baseline, 12-week of treatment, and 52-week of follow-up. Patients with COPD between 40 to 80 years old who have received stable Western medication within the previous 3 months and have had at least 1 moderate or severe acute exacerbation within the past 1 year will be included in the study. Basic treatment will remain the same for all participants. The primary outcome is the proportion of responders at week 12. Secondary outcomes include the proportion of responders at week 64, change in the St. George's Respiratory Questionnaire (SGRQ) Scale, change in the Modified-Medical Research Council

[†]Liuyang Huang, Sha Yang and Guixing Xu contributed equally to this work.

*Correspondence:

Mingsheng Sun
sunmingsheng@163.com
Fang Zeng
telepathy-zf@126.com
Fanrong Liang
acuresearch@126.com

Full list of author information is available at the end of the article



(mMRC) Scale, change in the COPD Assessment Test (CAT) Scale, change in the Lung Function Screening Indicators (LFSI), change in the 6-min walk distance (6-MWD), change in Short-Form 36 Health Survey (SF-36) Scale, the number of moderate and severe acute exacerbations and adverse event rate during the follow-up period.

Discussion This study will provide robust evidence on whether acupuncture is safe and effective for treating stable COPD. Meanwhile, comparing the differences in efficacy between different acupuncture frequencies will further promote the optimization of acupuncture for stable COPD.

Trial registration This study was registered in the Chinese Clinical Trial Registry (ChiCTR2200058757), on April 16, 2022.

Keywords Acupuncture, COPD, Randomized controlled trial, Protocol

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by airflow limitation and persistent respiratory symptoms caused by a combination of small airway disease (obstructive bronchitis) and lung parenchymal destruction (emphysema), is the third most common cause of death [1, 2]. In 2019, 212.3 million prevalent cases of COPD were reported globally, including 3.3 million deaths and 74.4 million disability-adjusted life years [3, 4]. Continued exposure to COPD risk factors and an aging population have made COPD a global public health challenge [5]. Clinical treatment of stable COPD aims to reduce symptoms, decrease the frequency and severity of acute exacerbations, improve health status, and enhance exercise tolerance. Despite the importance of bronchodilators, glucocorticoids, mucolytics, and antibiotics as clinically indicated drugs in treating stable COPD, there are inevitable side effects [6]. For example, beta₂-agonists may cause hypokalemia and tardive dyskinesia [7, 8], antimuscarinic drugs cause dry mouth [9], glucocorticoids increase the incidence of pneumonia [10], and antibiotics cause bacterial resistance and tinnitus [11]. Moreover, some patients still have symptoms that cannot be effectively controlled based on conventional medications. Therefore, it is imperative to explore new treatment options that are safe and effective, with fewer side effects, to improve patient symptoms further, reduce acute exacerbations, and minimize the side effects of conventional drug therapy.

Acupuncture has been widely used worldwide as an essential complementary alternative therapy for preventing and treating many chronic diseases. Previous studies have shown that the Borg scale after the 6-min walk test (6-MWT) was significantly better in the acupuncture group than in the control group (treatment as usual). That 6-min walk distance (6-MWD), oxygen saturation, and lung function also improved compared to the control group [12, 13]. Compared with the placebo acupuncture group, the Borg scale score, 6-MWD, pulmonary ventilation function, and St George's Respiratory Questionnaire (SGRQ) were significantly improved in the acupuncture

group, and the body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity (BODE) index also experienced improvement [14–17]. The above studies have shown that acupuncture helps to reduce dyspnea, improve exercise capacity, and improve lung function and nutritional status in patients with stable COPD. Systematic reviews based on evidence-based medicine have also demonstrated acupuncture as an effective adjunctive non-pharmacological treatment to improve the quality of life and dyspnea in COPD medically treated patients. However, there still needs to be high-quality randomized controlled trials to validate it [18, 19].

Acupuncture dose affects the acupuncture effect and determines the treatment and prognosis of the disease [20]. Among these, the frequency of acupuncture is essential in influencing the outcome and determining the cost of medical care. However, the relationship between acupuncture frequency and efficacy remains largely unexplored. A recent systematic review found that 36 acupuncture treatments had the best clinical response in patients with major depression compared to 24 and 12 treatments [21]. Previous clinical studies on acupuncture for stable COPD had a treatment frequency of 1–3 times per week, with a treatment period of 2–12 weeks and a total number of sessions ranging from 6–24 [12, 14–17, 22–24]. No clinical studies comparing different frequencies of acupuncture for stable COPD are available; thus, it is not possible to determine the preferred frequency and intervention period for acupuncture for COPD.

Therefore, this study designed a multi-centered, large-sample randomized controlled trial with the aim of (1) evaluate the efficacy and safety of acupuncture for stable COPD and (2) exploring the frequency of acupuncture suitable for stable COPD.

Methods

Study design

This study outlines a protocol for a prospective, multi-center, randomized controlled trial in which participants will be assigned to 5 parallel groups. The protocol reporting follows the SPIRIT statement [25], and future trials

will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines [26], including an extension of the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [27].

550 participants with stable COPD who meet the diagnostic criteria will be enrolled in this study. All participants are coming from 11 tertiary hospitals in Sichuan Province, China: Hospital of Chengdu University of TCM, Sichuan Provincial People’s Hospital, Chengdu First People’s Hospital, Chengdu Second People’s Hospital, Chinese Traditional Medicine Hospital of Meishan, Mianyang Hospital of Traditional Chinese Medicine, Deyang People’s Hospital, Guangyuan Hospital of Traditional Chinese Medicine, Panzhihua Integrated TCM and Western Medicine Hospital, Meishan People’s Hospital, and Chengdu TCM Hospital of Pidu District. The entire

study period consists of 2 weeks of baseline, 12 weeks of treatment, and 52 weeks of follow-up. A flow chart of the trial design is shown in Fig. 1, and patient enrollment, intervention, and assessment times are shown in Table 1.

Randomization and blinding

The central randomization system is used to conduct dynamic block group randomization stratified by center, and participants are randomly assigned in a ratio of 1:1:1:1:1 to once a week acupuncture group, twice a week acupuncture group, three times a week acupuncture group, sham-acupuncture group, and waiting-list control group. Beijing Bioknow Information Technology Co. will perform randomization. An independent researcher from each center not involved in treatment and outcome assessment is responsible for logging on to the central

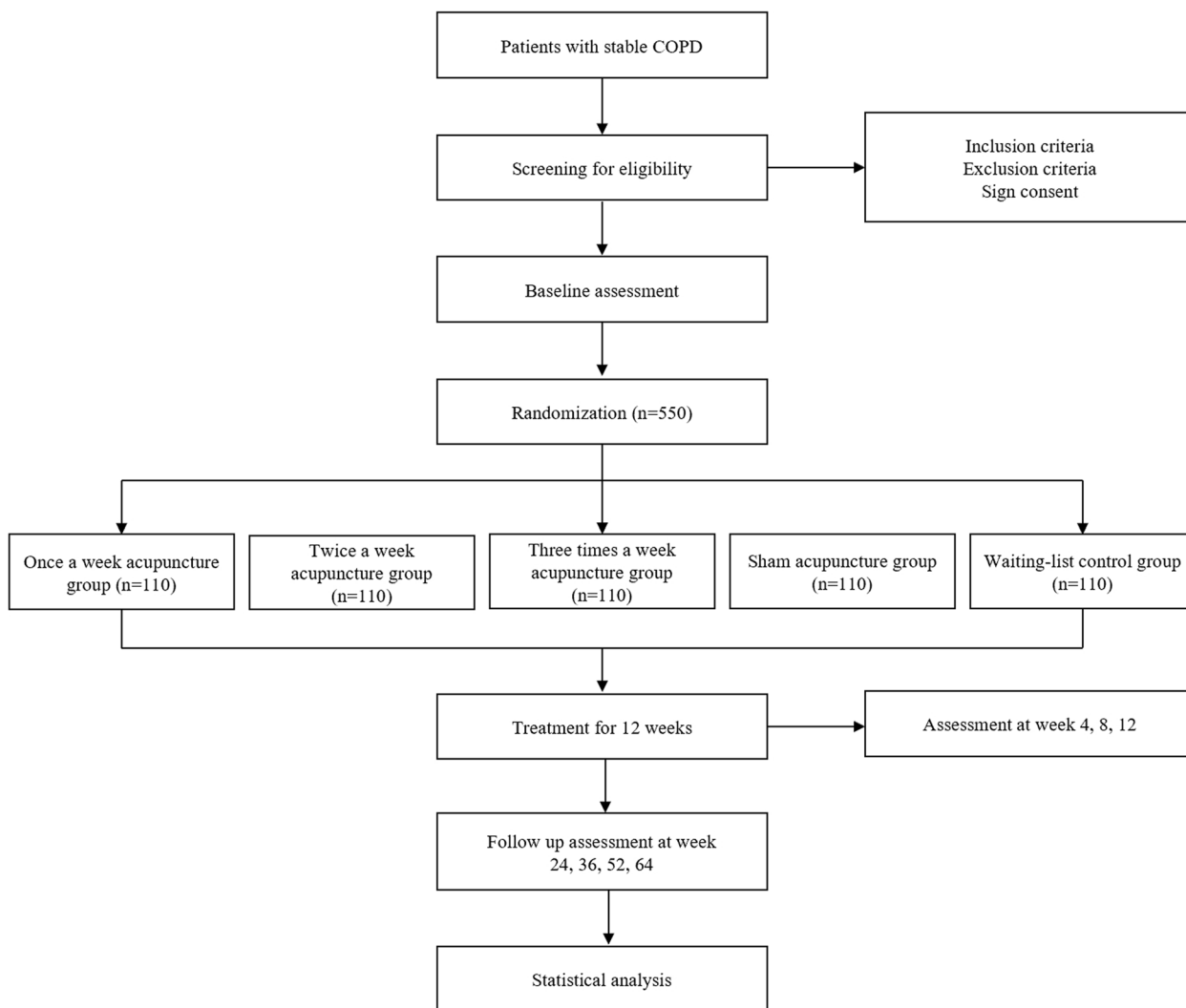


Fig. 1 Research flow chart

Table 1 Timepoint for recruitment, interventions and evaluation

Study period	Baseline	Allocation	Intervention period			Follow-up period			
Timepoint (week)	-2	0	4	8	12	25	38	51	62
Enrolment:									
Eligibility screen	x								
Informed consent	x								
Demographic characteristics	x								
Disease history of COPD	x								
COPD combination medication	x		x	x	x	x	x	x	x
Combined disease and medication history	x								
Randomization and allocation		x							
Interventions:									
Once a week acupuncture group			←————→						
Twice a week acupuncture group			←————→						
Three times a week acupuncture group			←————→						
Sham-acupuncture group			←————→						
Assessments:									
Acupuncture expectation assessment		x							
SGRQ		x	x	x	x	x	x	x	x
mMRC		x	x	x	x	x	x	x	x
CAT		x	x	x	x	x	x	x	x
6MWD		x			x		x		x
SF-36		x	x	x	x	x	x	x	x
Pulmonary Function Test		x			x				x
Needle sensation scale			x	x	x				
Number of acute exacerbations during the follow-up period			x	x	x	x	x	x	x
Patients' overall efficacy evaluation					x				
Adherence evaluation during treatment			x	x	x				
Blinding assessment					x				
Safety assessment			x	x	x	x	x	x	x

SGRQ St. George's Respiratory Questionnaire, mMRC Modified-Medical Research Council, CAT COPD Assessment Test, 6-MWD 6-min walk distance, SF-36 Short-Form 36 Health Survey

randomization system and entering randomization information (including the center number and the participant's name in *pinyin* initials). Randomization numbers and group assignments will be emailed to this independent assessor. Patients will be settled in separate treatment rooms to avoid communication with each other. Evaluators, statisticians, and participants will be blind to treatment allocations. The location of acupoints and the use of assistive devices will be the same for the acupuncture and sham acupuncture groups.

Participants

Inclusion criteria

Participants who meet the diagnostic criteria for COPD according to the Global Initiative for COPD and conform to all the following criteria will be included in the study [28]: 1) stable condition without acute exacerbation in the last 4 weeks; 2) age between 40 and 80 years, both sexes; 3) FEV₁pre between 25 and 80% after inhaled bronchodilators; 4) at least 1 moderate or severe acute exacerbation within the past year; 5) receiving stable Western medication within the previous 3 months; 6) willing to cooperate with the study and sign an informed consent form.

Exclusion criteria

Patients who meet any of the following conditions will be excluded: 1) combination of the severe cardiovascular, neurological, hematological, immune system, and malignant tumor diseases; 2) combined respiratory diseases that significantly impact the study (active tuberculosis, bronchial asthma, severe bronchiectasis, primary pulmonary hypertension, interstitial lung disease); 3) history of segmentectomy, wedge resection, lobectomy, total pneumonectomy, or lung volume reduction (including bronchoscopic lung volume reduction) for COPD; 4) continuous oxygen therapy is required according to long-term oxygen therapy (LTOT) criteria (oxygen therapy duration > 15 h/d) [29]; 5) unable to perform pulmonary function tests, unable to walk independently, unable to cooperate in completing questionnaires; 6) persistent breakage or infection of skin tissue at the needle site, coagulation dysfunction, skin allergy; 7) participated in another clinical trial or performed acupuncture for respiratory disease within the last 3 months; 8) pregnant and lactating women.

Patient recruitment

Recruitment strategies include poster recruitment, community recruitment, online recruitment, respiratory outpatients, and previous inpatients. Patients will be informed of study specifics, including study purpose, subgroup status, interventions, treatment period, benefits, and potential risks. A respiratory specialist will

diagnose patients who agree to participate in this study and must sign an informed consent form before randomization to the group. All patient information will be kept confidential. Patients may withdraw at any trial stage, and the reasons for patient withdrawal will be well documented.

Intervention and comparison

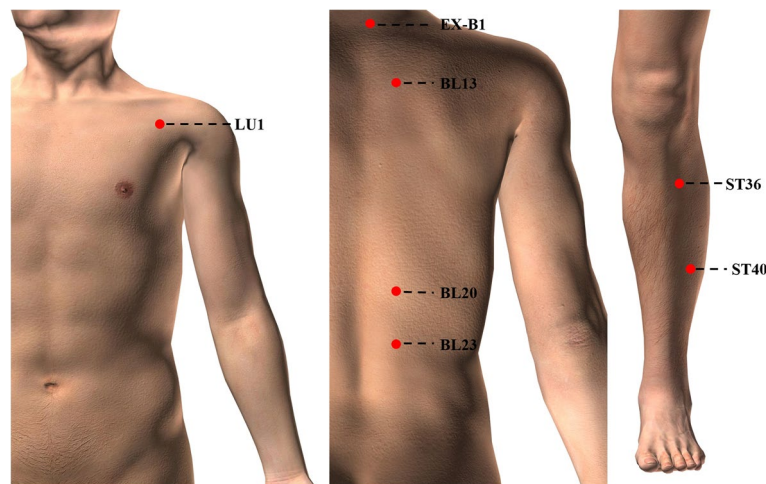
All patients will be given interventions based on conventional treatment. During the baseline period, all medications used by the subject to treat COPD and other underlying conditions will be recorded in detail on a case report form (CRF), including the name of the medication, the dose used, the frequency of use, the route of administration, and the start and end times. Any changes in the subject's medication throughout the study will also be recorded in detail. Medications used by patients to treat COPD will be categorized based on GOLD guideline criteria. A respiratory medicine specialist will assess the possibility of continuing acupuncture treatment during acute exacerbations. If a patient is hospitalized for an acute exacerbation, treatment will be continued 1 week after discharge, and the number of treatments delayed due to hospitalization will be replenished. During the study, we will discourage patients from using medications outside the guidelines to treat COPD, including herbal ones. However, if the patient has already used them, they must be documented accordingly.

The classification of basic therapeutic drugs is based on the 2023 GOLD guideline criteria: beta2 agonists (including fenoterol, levosalbutamol, formoterol, salmetero), anticholinergics (including ipratropium bromide, adiponium bromide), and short-acting beta2 agonists and anticholinergics in combination with inhalation devices (including fenoterol/ipratropium bromide, salbutamol/ipratropium bromide), long-acting beta2 agonists and anticholinergic combination inhalation devices (including formoterol/adiponium bromide, formoterol/glumonium bromid), methylxanthines (including aminophylline, theophylline), long-acting beta2 agonists in combination with hormonal inhalation devices (including formoterol/beclomethasone, formoterol/budesonid), and phosphodiesterase-4 inhibitors (including roflumilast).

The treatment protocol was developed based on the preliminary literature collation and a consensus meeting of acupuncture experts. 7 pairs of commonly used and effective acupoints for the treatment of COPD were selected, including bilateral Zhongfu (LU1), Dingchuan (EX-B1), Feishu (BL13), Pishu (BL20), Shenshu (BL23), Zusanli (ST36), and Fenglong (ST40). The acupuncture group and the sham acupuncture group used the same acupoints. Details of each acupoint are shown in Table 2 and Fig. 2. The acupuncturists are licensed and have at

Table 2 Locations of acupoints

Acupoints	Locations
Zhongfu (LU1)	On the upper lateral chest, 6 cun from the middle of the chest, level in the first intercostal space
Dingchuan (EX-B1)	0.5 cun lateral to DU14
Feishu (BL13)	1.5 cun lateral to the depression below the spinous process of the 3th thoracic vertebra
Pishu (BL20)	1.5 cun lateral to the depression below the spinous process of the 11th thoracic vertebra
Shenshu (BL23)	1.5 cun lateral to the depression below the spinous process of the 2th lumbar vertebra
Zusanli (ST36)	3 cun directly below ST35, and one finger-breadth lateral to the anterior border of the tibia
Fenglong (ST40)	One finger-breadth lateral to ST38, and at the midpoint of the line joining ST35 and the tip of the external malleolus

**Fig. 2** Locations of acupoints

least 3 years of clinical experience. All acupuncturists will receive training on acupoint positioning and manipulation before the trial. Each sub-center is assigned an acupuncturist responsible for treating all patients within that center. The acupuncture and sham-acupuncture groups will use a rubber base on the acupoints and perform needling (lifting, thrusting, twisting and rotating manipulation) at 10-min intervals to achieve a better blinding effect.

Manual acupuncture (MA) group

There are 3 acupuncture groups, which include once a week acupuncture group, twice a week acupuncture group and three times a week acupuncture group. The patient remains prone during acupuncture, and a soft pillow is placed on the front of the patient's chest to elevate the front of the chest to facilitate needling. The acupuncturist will sterilize the skin around the acupoint using 75% alcohol, then attach a rubber base to the acupoint and insert the needle through the rubber base into the acupoint. For LU1, a 1 cun needle (0.25×25 mm, Suzhou Hua Tuo, China) is used, and the needle is inserted in a lateral direction for

approximately 15–20 mm. The needle is angled at 45° toward the spine for the dorsal acupoints. BL13 is inserted with a 0.5 cun needle (0.25×13 mm, Suzhou Hua Tuo, China) for approximately 5–10 mm. EX-B1 and BL20 are inserted with a 1 cun needle (0.25×25 mm, Suzhou Hua Tuo, China) for approximately 15–20 mm. BL23, ST36, and ST40, using a 1.5-inch needle (0.25×40 mm, Suzhou Huatuo, China), are inserted for approximately 25–30 mm. After piercing the needle, gentle lifting, thrusting, swirling, and rotating movements are performed on the needle body to achieve *deqi* sensation (soreness, numbness, distension, or heaviness) [30]. The patient's degree of *deqi* sensation will be assessed immediately after the patient has *deqi* sensation [31]. The needles will be retained for 30 min each time, and *deqi* sensation operation will be performed every 10 min, about 15 s each time. When removing the needle, the acupuncturist uses a dry, sterilized cotton ball to gently press the needled area to avoid bleeding.

Once a week acupuncture group: needling once a week with 6-day intervals, 12 times for 12 weeks. Twice

Secondary outcomes

Secondary outcomes included the following eight items: 1) the proportion of responders at week 64; 2) change in the SGRQ Scale; 3) change in the mMRC Scale; 4) change in the CAT Scale; 5) change in the Lung Function Screening Indicators (including FEV1, FEV1%pre, FVC and FEV1/FVC); 6) change in the 6MWD; 7) change in SF-36 Scale; 8) the number of moderate and severe acute exacerbations during the follow-up period.

The mMRC consists of five grades (0 to 4) and contains statements that describe a range of physical limitations associated with dyspnea. It measures the degree to which a person has dyspnea during activities (such as "strenuous exercise") or limits a person's behavior (such as "too breathless to leave the house") [34]. The CAT consists of 8 items that involve breathing (cough, phlegm, chest tightness, and dyspnea) and other symptoms (low energy levels, sleep disturbances, limitations in daily activities, and confidence when leaving home). Item response values ranging from 0 to 5 (0 = no impairment). The total score was obtained by summing the response values for each item (ranging from 0 to 40). Higher scores indicate a greater impact of the disease on the patient's health and life [35]. Within the CAT, 0–9 is considered a low impact, 10–20 is considered a moderate impact, 21–30 is considered a high impact, and 31–40 is considered a very high impact [36]. Pulmonary function test will be evaluated at weeks 0, 12 and the end of follow-up. Pulmonary Function Test is the gold standard for COPD diagnosis and severity grading. The main indices to be collected include: forced expiratory volume in one second (FEV1), FEV1%pred, forced vital capacity (FVC) and FEV1/FV [37]. The 6-MWD will be evaluated at 12 weeks of enrollment and every 3 months during the follow-up period. The 6MWT is a test commonly used to objectively assess functional exercise capacity in patients with moderate-to-severe pulmonary disease. In the test, patients are asked to walk along a 30-m corridor for as far as possible for 6 minutes [38]. The SF-36 is used to measure self-reported health-related quality of life (HRQOL). SF-36 consists of 36 main questions covering 8 aspects (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). The total score is 0–100, with higher scores representing better quality of life [39]. An acute exacerbation of COPD is defined as an acute worsening of respiratory symptoms (increased dyspnea, cough and sputum purulence) that results in additional therapy [37, 40]. A mild exacerbation refers to patients treated with short-acting bronchodilators (SABDs) plus antibiotics and/

or oral glucocorticoids; a severe exacerbation refers to patients requiring hospitalization or emergency care. We will count the number of mild/severe acute exacerbations in the next year for all subjects after the end of treatment. The mMRC, CAT, SF-36 scales, and number of acute exacerbations will be evaluated at weeks 0, 4, 8, and 12 of enrollment and every 3 months during the follow-up period. Data will be collected on 6-MWD at weeks 0 and 12 of enrollment and every 6 months during follow-up. Pulmonary function tests will be performed at weeks 0 and 12 of enrollment and at the end of the 1-year follow-up.

Safety assessment

Theoretically, the most serious adverse reaction during needling is pneumothorax, so we have developed a strict procedure during the trial, including the selection of different lengths of needles, strict direction and depth of acupuncture. During acupuncture, patients may experience adverse reactions such as needle sickness, subcutaneous hemorrhage, hematoma, severe pain, infection, and needle breakage. Adverse events (AEs) that occur throughout the study will be recorded and reported, and patients will be treated promptly and reasonably. The occurrence, symptoms, duration, severity, treatment measures and disappearance time of AEs will be recorded in detail. When adverse reactions occur, clinicians judge whether to discontinue the trial based on the condition and report severe cases to the Project Management Office of Chengdu University of Traditional Chinese Medicine and the Ethics Committee within 24 h.

Sample size calculation

As reported in previous studies [15, 41], the mean improvement in SGRQ was -7.1 for patients in the three times a week acupuncture group, the mean change in SGRQ was -2 for patients in the SA group, the mean change in SGRQ was -0.8 for patients in the blank control group, with a standard deviation of 14.2. Using a two-tailed test with a category 1 error of 0.05 and a statistical efficacy of 80%, a sample size of 88 cases per group was calculated, with a maximum of 20% of subjects allowed to drop out or disengage for a required sample size of 110 cases per group. The once a week and twice a week acupuncture groups were set up with the same sample size as the three times a week acupuncture groups, and a total of 550 subjects were included.

Statistical analysis

Analyses will be performed according to the intention-to-treat (ITT) principle and will be statistically analyzed for all randomized participants. Missing data

will be filled in using the multiple imputation method. Statistical analysis will be performed by the Chinese Cochrane Center, West China Hospital, Sichuan University, China and SAS software will be used for statistical analysis. Quantitative indicators are described using mean, standard deviation, median, 25th percentile and 75th percentile. Categorical indicators are described using frequencies and percentages. The normality of the data will be verified by the Kolmogorov–Smirnov test (K-S test). Equality of variance between observed variables will be verified by Levene's Test. Baseline data will be analyzed using chi-square or Fisher's exact test for categorical indicators and ANOVA or the Kruskal–Wallis H test for quantitative indicators.

The primary outcome will be analyzed by generalized linear mixed effects model. Fixed effects included group, age, COPD sub-type, and years of smoking; random effects included sub-center, time, and time×group interaction. Secondary outcomes will be analyzed using linear mixed effects models, with fixed and mixed effects containing the same variables as the primary outcome indicators.

We will include participants who completed no less than 80% of their treatments in the per-protocol set (PPS). Several sensitivity analyses will be conducted to examine the robustness of the finding. First, we will exclude the participants with acute exacerbations during treatment period. Second, we will exclude the participants who have infected COVID-19 during treatment period. We will analyze each of the subgroups that may potentially influence the outcomes, including: 1) Age: <60 or >60; 2) Smoking history: yes or no; 3) FEV1%pre: ≤50 or >50; 4) Type of COPD: chronic bronchitis type or emphysema type. Statistical test will be a 2-sided test, with $P < 0.05$ considered statistically significant.

Treatment compliance

The number of expected and actual treatments for each patient will be counted to assess the patient's compliance. In patients whose treatment is discontinued due to an acute exacerbation, the patient will continue to complete the rest of the treatment after a week of stabilization. Patients who have been quarantined due to COVID-19 will continue to complete the rest of their treatment once they are unblocked. A patient will be regarded as compliant if receiving >80% of the expected treatments.

Quality control

The trial protocol was reviewed and revised by experts in acupuncture, respiratory medicine, methodology, and

statistics. Standard operating procedures (SOPs) will be developed in advance, and training sessions will be held before the start of the study to provide standardized training for investigators at each center and to ensure that each researcher is familiar with the research process and the specific implementation details. The participants in the trial should be fixed, and the recording methods and judgment criteria should be unified to ensure that the scale assessment, data management, and completion of the CRF are carried out under uniform standards. The data inspector will conduct quality control checks at each research center every 3 months to ensure that all elements of the study protocol have been strictly adhered to, as well as the correctness of the completed information, and to generate quality control analysis reports.

Data collection, management and monitoring

Data will be collected by telephone or on-site questioning by researchers not involved in the statistical analysis and treatment. The statistical company and the research team are jointly responsible for the data management of this project. The investigator fills out the clinical trial record requirements: timely, accurate, complete, standardized and truthful. The monitor verifies that the investigator follows the trial protocol during the experiment and regularly checks subjects' informed consent and inclusion at each sub-center. Data entry personnel will need to be trained to perform data entry. The CRF will be filled into the Electronic Data Capture (EDC) system by two independent data entry operators to ensure the accuracy of the data. Any changes to the data will be tracked in the EDC system.

Discussion

As the third leading cause of death worldwide, COPD affects patients' health and quality of life and imposes a substantial economic burden on society.

The GOLD guideline states that the primary goal of managing stable COPD is to relieve symptoms and reduce the risk of future acute exacerbations. The GOLD recognizes the SGRQ as the gold standard for evaluating COPD patients' symptoms. SGRQ is a comprehensive disease-specific quality-of-life health questionnaire used in clinical trials with high validity, sensitivity, and reliability. The SGRQ is systematic, rigorous, detailed, and comprehensive and consists of three main sections: mobility, respiratory symptoms, and impact on daily life. The severity of COPD patients is closely related to their quality of life, and it has been found that the effectiveness of treatments and interventions for COPD patients can be reflected in their quality of life. The SGRQ is generalizable, and its scores have been validated repeatedly for

different countries, races, ages, genders, and severities of respiratory diseases. The questionnaire covers the physical, emotional, and social aspects of the patient's life, correlates well with other clinical symptoms [42, 43], and is superior to other assessment scales [44, 45]. Pearson's analysis showed that the SGRQ, mMRC, and CAT had a good correlation ($P < 0.05$) and were consistent in the assessment of COPD, and all of them could be used to assess the degree of lung function impairment. The CAT scale is comprehensive, highly reliable, easy to understand, and time-consuming. The mMRC is also widely used in clinical practice because of its reproducibility, authenticity, and sensitivity. The 6-MWT is an objective sub-maximal exercise test. Because most of the daily activities of patients with COPD are at the sub-maximal level, the 6-MWT can reflect the functional compensatory capacity of patients to complete daily physical activities. The 6-MWT indicates the patient's functional compensatory capacity to perform daily physical activities. It can be used as an objective tool to assess the extrapulmonary effects of the disease on patients [38]. SF-36, as a universal measurement scale, can reflect the quality of life of patients with chronic diseases to a large extent. The pulmonary function test is a noninvasive tool for studying respiratory physiology, an objective indicator for determining airflow limitation with good reproducibility, and the gold standard for diagnosing COPD. It is vital for the diagnosis and differential diagnosis of COPD and evaluating severity, disease progression, prognosis, and response to treatment.

A clinically ideal placebo/sham acupuncture control should meet three basic principles: (1) placebo acupuncture has no or almost no specific therapeutic effect; (2) the needle is applied to a site that has no therapeutic effect; and (3) the subject cannot perceive the difference between placebo acupuncture and therapeutic acupuncture. However, due to the complexity of the acupuncture operation process, it is not easy to fully meet the above requirements. In most previous studies, non-acupoints or points on meridians not related to the treatment of disease were chosen as sham acupuncture points. One study found that acupoints have special efficacy in hand rheumatoid arthritis compared to non-acupoints. However, due to the nature of the disease and the size of the space of the acupoints, it is not possible to prove that the acupoints taken on the meridian side are non-acupoints [46]. Considering the above reasons, we will perform placebo acupuncture using flat-tipped needles at the same acupoints as the acupuncture group. In order to achieve a better blinding effect by convincing the patient, we will let the patient feel the pain of his/her stabbing but will

not pierce the patient's skin. When inserted, the blunt tips of these special placebo needles produce a mild sting on the skin's surface but do not puncture the skin. Moreover, the needle retention on the base after needle insertion simulates regular needle insertion, which, combined with the retention and exit of the needle after needling, the subject can perceive it as an actual needling for optimal blinding. Considering that the natural course and regression of COPD disease are unpredictable, we additionally set up a blank control group that was not given any interventions except for regular medication.

This study has strict nadir criteria, and respiratory diseases that impact pulmonary function tests (for example, bronchial asthma, bronchiectasis, lung cancer, and lung resection surgery) will be excluded. Any additional use of Western medicine will be recorded in detail. Acupoint selection is a critical factor in acupuncture treatment. The acupoints selected for this study were based on data mining of modern acupuncture prescriptions for COPD. The most commonly used safe and effective acupoints were selected with consultation with clinical acupuncturists. The patient's prone position was also considered for easy manipulation [14, 47]. At the time of signing the informed consent form, subjects in the waiting-list group control group, the SA group, will be promised that compensatory treatment will be given at the end of the study. In this way, potential problems caused by patient disappointment will be overcome.

Inevitably, this study also has some limitations. First, due to the acupuncture operation's nature, it is impossible to blind the acupuncturist, which may also lead to bias. Second, the blunt-tipped needle touching the skin may have some stimulating effect on the acupoints, therefore it is necessary for us to set up a waiting-list control group.

Conclusion

In conclusion, this study is a multicenter, randomized controlled trial to objectively evaluate the effectiveness and safety of acupuncture for stable COPD. It is the first RCT to investigate different acupuncture frequencies for stable COPD. It is proposed to explore the quantitative effect pattern of acupuncture from the perspective of acupuncture frequency influencing the acupuncture effect and to provide a reference for optimizing clinical decisions of acupuncture for chronic diseases.

Trial status

The recruitment process began on April 17, 2022, and is anticipated to end on December 31, 2023.

Abbreviations

COPD	Chronic obstructive pulmonary disease
CAT	COPD assessment test
CRF	Case report form
EDC	Electronic data capture
LFSI	Lung function screening indicator
MCID	Minimal clinically important difference
mMRC	Modified-medical research council
PPS	Per-protocol set
PFT	Pulmonary function test
RA	Research assistant
MA	Manual acupuncture
SF-36	Medical outcomes study short form-36
SGRQ	St. George's respiratory questionnaire
SA	Sham acupuncture
6-MWT	Six-minute walk test
6-MWD	Six-minute walk distance

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12906-024-04412-6>.

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*.

Acknowledgements

First, we thank the sub-center hospitals for their trust, support and help in subject recruitment and management. Secondly, we thank the Chinese Evidence-based Medicine Center and Cochrane China Center, West China Hospital, Sichuan University, for their collaboration and technical assistance in center randomization and statistical analysis. Finally, we would like to express our gratitude to all the researchers who have participated and will participate in this study.

Authors' contributions

LF, FZ and MS conceived the study and initiated the study design. All authors were involved in the design and writing of the study protocol from different focuses. LY, SY and GX are responsible for writing the study protocol, RX, GB, CF, SC, BL, ZZ, QL, CX, and QH will be responsible for subject consent and recruitment, QL, CY, HT, YL, ZZ, FY, SY and JT will be responsible for subject treatment, QL, XY, MC, DH and YY will be responsible for subject scale assessment and data collection, and XS, XC and LL will be responsible for statistical analysis of the data. All authors have read and approved the final draft.

Funding

This study was supported by the Innovation Team and Talents Cultivation Program of the National Administration of Traditional Chinese Medicine supported this study. (No: ZYYCXTD-D-202003). The funding agency was not involved in the study design, data collection, data analysis, data interpretation, report writing, or submission of the report as an article for publication.

Availability of data and materials

Not applicable; no data have yet been generated.

Declarations

Ethics approval and consent to participate

This trial will be conducted under the requirements of the Declaration of Helsinki. The entire project has been approved by the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (ID: 2022KL-021) and registered in the Chinese Clinical Trials Registry (No. ChiCTR2200058757). Before randomization, patients are required to sign an informed consent form. Subjects' personal information is confidential, and participation in the study is entirely voluntary, with the right to withdraw at any time during any study phase.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, No. 37, Shi'er Qiao Road, Jinniu District, Chengdu 610075, Sichuan, China. ²School of Health and Wellness, Panzhihua University, No. 10, North Section of Sanxian Avenue, East District, Panzhihua 617000, Sichuan, China. ³Department of Acupuncture and Tuina Medicine, Guangyuan Hospital of Traditional Chinese Medicine, No.133 Jianshe Road, Lizhou District, Guangyuan 628099, Sichuan, China. ⁴Chinese Evidence-Based Medicine Center and Cochrane China Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China. ⁵Department of Respiratory Medicine, Chinese Traditional Medicine Hospital of Meishan, No. 9, North Section of Mindong Avenue, Dongpo District, Meishan 620010, Sichuan, China. ⁶Department of Respiratory Medicine, Deyang People's Hospital, No.173, Section 1, Taishan North Road, Jingyang District, Deyang 618009, Sichuan, China. ⁷Department of Acupuncture and Tuina Medicine, Mianyang Hospital of TCM, No.14, Fucheng Road, Fucheng District, Mianyang 621053, Sichuan, China. ⁸Department of Respiratory Medicine, Guangyuan Hospital of Traditional Chinese Medicine, No.133 Jianshe Road, Lizhou District, Guangyuan 628099, Sichuan, China. ⁹Department of Respiratory Medicine, Hospital of Chengdu University of TCM, No. 39, Shi'er Qiao Road, Jinniu District, Chengdu 610075, Sichuan, China. ¹⁰Department of Traditional Chinese Medicine, Chengdu Second People's Hospital, No.10 Qingyun South Street, Jinjiang District, Chengdu 610021, Sichuan, China. ¹¹Department of Respiratory Medicine, Chengdu TCM Hospital of Pidu District, No.169, Sec.1, Zhongxin Avenue, Pidu District, Chengdu 611730, Sichuan, China. ¹²Department of Respiratory Medicine, Meishan People's Hospital, No. 288, South Section 4Dongpo Avenue, Dongpo District, Meishan 620020, Sichuan, China. ¹³Department of Respiratory Medicine, Panzhihua Integrated TCM and Western Medicine Hospital, No. 27, Taoyuan Street, Bingcaogang, East District, Panzhihua 617099, Sichuan, China.

Received: 10 October 2023 Accepted: 27 February 2024

Published online: 07 March 2024

References

- Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med.* 2022;206(11):1317–25.
- Venkatesan P. GOLD COPD report: 2023 update. *Lancet Respir Med.* 2023;11(1):18.
- Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. *BMJ (Clinical research ed).* 2022;378: e069679.
- Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England).* 2020;396(10258):1204–1222.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3(11): e442.
- Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. *Lancet (London, England).* 2022;399(10342):2227–42.
- Wang MT, Lai JH, Tsai CL, Liou JT. Risk of adverse cardiovascular events with use of inhaled long-acting bronchodilators in management of chronic obstructive pulmonary disease. *J Food Drug Anal.* 2019;27(3):657–70.
- Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and Therapeutics of Bronchodilators Revisited. *Pharmacol Rev.* 2020;72(1):218–52.
- Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol.* 2015;8(4):479–501.
- Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;2012(7):Cd002991.
- Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med.* 2011;365(8):689–98.
- Li Y, Xiong C, Zeng Y, et al. Acupuncture treatment of lung-spleen Qi deficiency in stable chronic obstructive pulmonary disease: a randomized, open-label, controlled trial. *J Trad Chin Med.* 2019;39(6):885–891.

13. Suzuki M, Namura K, Ohno Y, et al. The effect of acupuncture in the treatment of chronic obstructive pulmonary disease. *J Altern Complement Med (New York, NY)*. 2008;14(9):1097–105.
14. Suzuki M, Muro S, Fukui M, et al. Effects of acupuncture on nutritional state of patients with stable chronic obstructive pulmonary disease (COPD): re-analysis of COPD acupuncture trial, a randomized controlled trial. *BMC Complement Altern Med*. 2018;18(1):287.
15. Suzuki M, Muro S, Ando Y, et al. A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-acupuncture trial (CAT). *Arch Intern Med*. 2012;172(11):878–86.
16. Tong J, Guo YM, He Y, Li GY, Chen F, Yao H. [Regulatory effects of acupuncture on exercise tolerance in patients with chronic obstructive pulmonary disease at stable phase: a randomized controlled trial]. *Zhongguo Zhen Jiu*. 2014;34(9):846–850.
17. Feng J, Wang X, Li X, Zhao D, Xu J. Acupuncture for chronic obstructive pulmonary disease (COPD): A multicenter, randomized, sham-controlled trial. *Medicine*. 2016;95(40):e4879.
18. Hsieh PC, Yang MC, Wu YK, et al. Acupuncture therapy improves health-related quality of life in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2019;35:208–18.
19. Coyle ME, Shergis JL, Huang ET, et al. Acupuncture therapies for chronic obstructive pulmonary disease: a systematic review of randomized, controlled trials. *Altern Ther Health Med*. 2014;20(6):10–23.
20. Fei YT, Cao HJ, Xia RY, et al. Methodological challenges in design and conduct of randomised controlled trials in acupuncture. *BMJ (Clinical research ed)*. 2022;376:e064345.
21. Xu G, Lei H, Huang L, et al. The dose-effect association between acupuncture sessions and its effects on major depressive disorder: A meta-regression of randomized controlled trials. *J Affect Disord*. 2022;310:318–27.
22. Maekura T, Miki K, Miki M, Kitada S, Maekura R. Clinical effects of acupuncture on the pathophysiological mechanism of chronic obstructive pulmonary disease during exercise. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2787–98.
23. Ge Y, Yao H, Tong J, He Y, Li G, Kong X. [Effects of acupuncture on peripheral skeletal muscle exercise ability in patients with chronic obstructive pulmonary disease at stable phase]. *Zhongguo Zhen Jiu*. 2017;37(4):366–371.
24. Gao J, Ouyang BS, Sun G, Fan C, Wu YJ, Ji LL. [Comparative research on effect of warm needling therapy on pulmonary function and life quality of patients with COPD in the stable phase]. *Zhongguo Zhen Jiu*. 2011;31(10):893–897.
25. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)*. 2013;346:e7586.
26. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)*. 2010;340:c332.
27. MacPherson H, Altman DG, Hammerschlag R, et al. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT statement. *J Evid Based Med*. 2010;3(3):140–55.
28. Global strategy for prevention, diagnosis and management of COPD: 2023 Report. <https://goldcopd.org/2023-gold-report-2/>. Accessed.
29. Castellano M, Pereira LFF, Feitosa PHR, et al. 2022 Brazilian Thoracic Association recommendations for long-term home oxygen therapy. *J Bras Pneumol*. 2022;48(5):e20220179.
30. Park JE, Ryu YH, Liu Y, et al. A literature review of de qi in clinical studies. *Acupunct Med*. 2013;31(2):132–42.
31. Yu DT, Jones AY, Pang MY. Development and validation of the Chinese version of the massachusetts general hospital acupuncture sensation scale: an exploratory and methodological study. *Acupunct Med*. 2012;30(3):214–21.
32. Celli B, Locantore N, Yates JC, et al. Markers of disease activity in COPD: an 8-year mortality study in the ECLIPSE cohort. *Eur Respir J*. 2021;57(3).
33. Meguro M, Barley EA, Spencer S, Jones PW. Development and Validation of an Improved, COPD-Specific Version of the St. George Respir Question Chest. 2007;132(2):456–63.
34. Yorke J, Khan N, Garrow A, et al. Evaluation of the Individual Activity Descriptors of the mMRC Breathlessness Scale: A Mixed Method Study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2289–99.
35. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline LN. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–54.
36. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. *BMC Pulm Med*. 2011;11:42.
37. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948–68.
38. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–117.
39. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care*. 1992;30(6):473–483.
40. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196–204.
41. Deering BM, Fullen B, Egan C, et al. Acupuncture as an adjunct to pulmonary rehabilitation. *J Cardiopulm Rehabil Prev*. 2011;31(6):392–9.
42. Engström CP, Persson LO, Larsson S, Sullivan M. Reliability and validity of a Swedish version of the St George's Respiratory Questionnaire. *Eur Respir J*. 1998;11(1):61–6.
43. Güell R, Casan P, Sangesis M, Morante F, Belda J, Guyatt GH. Quality of life in patients with chronic respiratory disease: the Spanish version of the Chronic Respiratory Questionnaire (CRQ). *Eur Respir J*. 1998;11(1):55–60.
44. Engström CP, Persson LO, Larsson S, Sullivan M. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *Eur Respir J*. 2001;18(1):69–76.
45. Wijnhoven HA, Kriegsman DM, Hesselink AE, Penninx BW, de Haan M. Determinants of different dimensions of disease severity in asthma and COPD: pulmonary function and health-related quality of life. *Chest*. 2001;119(4):1034–42.
46. Seca S, Patrício M, Kirch S, Franconi G, Cabrita AS, Greten HJ. Effectiveness of acupuncture on pain, functional disability, and quality of life in rheumatoid arthritis of the hand: results of a double-blind randomized clinical trial. *J Altern Complement Med (New York, NY)*. 2019;25(1):86–97.
47. Xie F, Wu YP, Liu L, Ren JG, Zhang BD. [Warm acupuncture on chronic obstructive pulmonary disease with phlegm-turbid obstructing of the lung: a randomized controlled trial]. *Zhongguo Zhen Jiu*. 2019;39(9):918–922.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.