# Effect of Sitting and Lying Liuzijue exercise for pulmonary rehabilitation in AECOPD patients with noninvasive ventilation: Study Protocol for a Randomized Controlled Trial

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**Introduction** Chronic obstructive pulmonary disease (COPD) is a lung disease with the highest incidence and high mortality in the world. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) can significantly accelerate the progression of the disease. Pulmonary rehabilitation is one of the effective treatment methods in COPD patients, but few studies have focused on the effect of pulmonary rehabilitation in AECOPD patients. Liuzijue can improve the pulmonary function and relieve symptoms of COPD patients. However, due to the influence of disease and noninvasive ventilation, AECOPD patients have poor compliance with getting out of bed at the early stage. Sitting and lying Liuzijue is more suitable in AECOPD patients with NIV. Therefore, this study will evaluate the effect of sitting and lying Liuzijue for lung function, exercise endurance, and quality of life in AEOPD patients with NIV.

**Methods/design** A total of 80 AECOPD patients with noninvasive ventilation were randomly divided into the controlled group (CG)(n=40) and sitting and lying Liuzijue exercise group (LG)(n=40). The CG received AECOPD conventional treatment and nursing. The LG combined with sitting and lying Liuzijue therapy on the basis of this. Participants in the LG were required to take this training for 3 months, 30 minutes

once every morning and evening. In addition, lung function test, 6-minute walking test (6MWT), Modified Medical Research Council Dyspnea Scales (mMRC) and the St George's Respiratory Questionnaire (SGRQ) were conducted at the baseline and at the end of the intervention. Blood gas was measured before treatment, 3 days and 5 days after treatment. In addition, the length of hospital stay, the duration of noninvasive ventilation and the frequency of acute exacerbation within 6 months after the intervention were compared.

***Ethics and dissemination*** The study protocols were approved by the Ethics Committee of Hospital of Chengdu University of traditional Chinese medicine (2019KL-064). The research results will be disseminated through (open access) peer-reviewed publications and presentations at conferences.

**Trial registration number** ChiCTR2000034530.

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a kind of preventable and treatable lung disease. COPD is characterized by progressive and incompletely reversible airflow limitation[1]. It is often divided into stable stage and aggravating stage. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is mostly induced by infection[2]. It will lead to the aggravation of respiratory symptoms in COPD patients, accelerate the progression of the disease, and reduce the patient's quality of life. So that the patient's case fatality and disability rate will rise[3]. At the same time, AECOPD often requires additional therapy[4].

Pulmonary rehabilitation is recognized as an effective treatment for patients with COPD in addition to oxygen therapy and drug therapy[5]. Pulmonary rehabilitation mainly includes exercise, health guidance and so on. It can promote the change of their own behavior and long-term adherence. According to the guidelines of the European Respiratory Society / American Thoracic Society, early pulmonary rehabilitation exercise for AECOPD patients can combat skeletal muscle atrophy, improve exercise tolerance, improve lung function, reduce readmission rate and improve quality of life[6].

Traditional Chinese exercises (Tai Chi, Liuzijue and Yi Jin Jing) combine the advantages of breathing training and skeletal muscle training, which can significantly improve the function of respiratory and skeletal muscles, exercise ability, mental function and quality of life[7]. However, AECOPD patients mostly suffer from hypoxia with (or without) carbon dioxide retention, and then combined with respiratory failure. Patients need to stay in bed for long periods of time for noninvasive ventilation. Moreover, the compliance of early getting out of bed is poor[8]. Therefore, it is particularly urgent to explore an effective exercise method for AECOPD patients during the use of noninvasive ventilation.

Liuzijue is a method of breathing adjustment and limb movement guided by the theory of traditional Chinese medicine. It can adjust the body's qi and blood, yin and yang, promote the circulation of qi and blood, and restore the balance of yin and yang. According to the five zang-organs to the five tones, the exerciser produces six sounds (xu, he, hu, si, chui, and xi) by expiration to adjust the corresponding internal organ functions[9]. And Liuzijue has the characteristics of diaphragm breathing and shrinking lip breathing. It can make COPD patients breathe slowly and delay expiratory flow rate. Thus, it can prevent premature airway closure, and improve abnormal breathing patterns[10,11]. Previous studies have shown that Liuzijue, as a traditional exercise focusing on regulating respiration, can not only effectively slow down the progressive decline of lung function in patients with COPD[12,13], but also enhance the flexibility of limbs' nerves and muscles[14]. But standing posture training will make it difficult for the old and weak or those who can't stand for a long time. Therefore, Mr. Ma Li Tang specially compiled Liuzijue for sitting and lying. Sitting and lying Liuzijue is a kind of low intensity aerobic exercise based on standing Liuzijue, which is more suitable for AECOPD patients with long-term bedridden.

Previous studies mostly focused on the effect of Liuzijue on patients with stable COPD, but rarely used for AECOPD patients. Peijun Li's research[15] results show that Liuzijue combined with clinical guidance can effectively improve the lung function, exercise ability and quality of life of elderly patients with COPD at home for a long time. In addition, qigong (Wuqinxi, liuzijue, Baduanjin, etc.) has a good effect in

relieving dyspnea, enhancing the level of respiratory muscle strength, delaying the decline rate of lung function and anti infection ability[16]. Most previous studies used Qigong in stable COPD patients with easy mobility. However, the latest guidelines recommend that early pulmonary rehabilitation is particularly important for patients with AECOPD. Consequently, this study used sitting and lying Liuzijue to intervene AECOPD noninvasive ventilation patients.

The aim of this study was to investigate the effect of sitting and lying Liuzijue to provide a simple, implementable and effective new method for early rehabilitation of pulmonary function in patients with AECOPD noninvasive ventilation. This study hypothesized that sitting and lying Liuzijue can significantly improve lung function, exercise endurance, and quality of life in patients with AECOPD noninvasive ventilation. At the same time, it was hypothesized that the duration of noninvasive ventilation and the frequency of acute exacerbation could be reduced.

## 2. Methods

2.1. *Design.* A randomized controlled trial was conducted with concealed allocation and blinded outcome assessment. Patients who met the inclusion criteria were randomly divided into two groups: control group (CG), sitting and lying Liuzijue exercise group (LG). Randomisation was done by an independent person who generated random numbers using a computer before the start of the intervention. Then, the random number was sealed in opaque envelopes and the patients were allowed to draw the sealed number. Because of the characteristics of the intervention, it was difficult to blind the exercise instructor or participants to their allocation. But the outcome assessor was blinded. The study design was approved by the Ethics Committee of Hospital of Chengdu University of traditional Chinese medicine (Chengdu, China), and all patients signed an informed consent form before intervention. A brief flowchart of the entire study is shown in figure 1 and the schedule of events is provided in table 1.

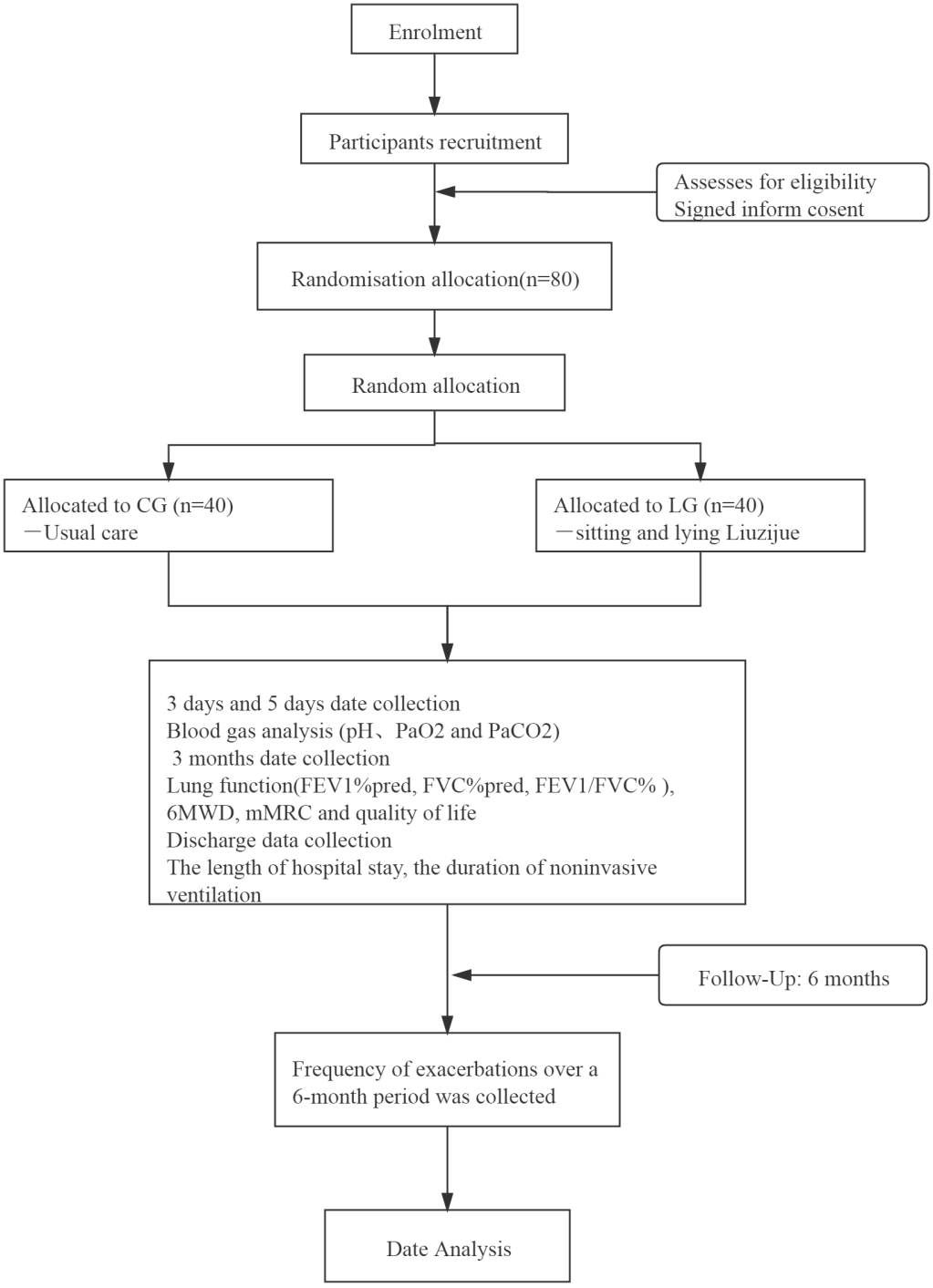


Figure 1 Flow diagram of study design. FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; %pred, percentage of predicted values; 6MWD, 6-min walking distend; mMRC, Modified Medical Research Council Dyspnea Scales; SGRQ, St. George's Respiratory Questionnaire.

Table 1 Outline and timelines of the assessments

| **Items** | **Phase Ⅰ: screening** | **Phase II: baseline** | **Phase III: 3days 5days** | **Phase IV: Discharge** | **Phase V: 3 months** | **Phase VI: 9 months** |
|---|---|---|---|---|---|---|
| Inclusion/exclusion criteria | × | | | | | |
| Inclusion/exclusion criteria | × | | | | | |
| Randomisation and allocation | × | | | | | |
| Safety index | × | × | × | × | × | |
| General clinical information | | × | | | | |
| Blood gas analysis (pH 、 $PaO_2$ and $PaCO_2$) | | × | × | | | |
| Lung function (FEV1%pred, FVC% pred, FEV1/FVC% ) | | × | | | × | |
| 6MWD | | × | | | × | |
| Quality of life | | × | | | × | |
| mMRC | | × | | | × | |
| The length of hospital stay | | | | × | | |
| The duration of noninvasive | | | | × | | |

| | | |
|---|---|---|
| ventilation | | |
| The frequency of acute exacerbations | × | × |
| Adherence | × | × |
| Adverse events | × | × |
| Summary at the end of the study | | × |

*2.2. Sample size.* The outcome indicators for evaluating lung function in this study were based on 6MWD, which is considered a simple and effective measure to reflect pulmonary rehabilitation. Based on the data used in previous studies[17], 54m was considered as the minimum significant difference between the group means, and the standard deviation (SD) of the measurement was 57m. Sample size was calculated by PASS 15.0 with $\alpha$=0.05 (two sides) and $\beta$=0.02 (power 80%). The results showed a minimum sample size of 19 patients in each group. Based on our team's upfront findings, it was estimated that 30% of patients could be lost, meaning there were at least 25 subjects in each group. To ensure that statistics were feasible, 80 patients were finally enrolled.

*2.3. Patients.* AECOPD patients were recruited from Hospital of Chengdu University of traditional Chinese medicine from June 2018 to June 2020. The inclusion criteria were the following: they were between 40 and 80 years; COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (forced expiratory volume in the first second [FEV1] / forced vital capacity [FVC] < 0.7), and was diagnosed as AECOPD (have acute worsening respiratory symptoms, including worsening dyspnea, worsening cough, increased sputum volume and/or purulent sputum)[5]; AECOPD patients treated with noninvasive ventilation; The patients did not take any regular exercise (at least twice a week) within 6 months before the intervention; They could complete the sitting and lying Liuzijue exercise under guidance; All patients signed an informed consent form. Patients were excluded if the: had severe cardiovascular, hepatorenal and haematopoietic diseases, psychosis or

participate in other clinical trials.

*2.4. Intervention.* All subjects continued to receive their prescribed medications and noninvasive ventilation. Patients in the CG received usual care according to the GOLD guidelines[5], including medication, smoking cessation, and life instructions. And they did not participate in any exercise intervention. On the basis of usual care, the patients in the LG chose the sitting and lying Liuzijue created by the martial arts master Mr. Ma Litang for exercise[18]. After the lung infection control window appeared[19], the sitting and lying Liuzijue exercise began. During the 3-month intervention, the LG exercised once a day in the morning and once in the evening for 30 minutes each time.

Before the start of sitting and lying Liuzijue exercise, the noninvasive ventilation mask was removed and a nasal cannula was used for low flow oxygen inhalation (2 ~ 4 L / min). During exercise, the exercise intensity goal was to achieve 60% ~ 80% of the maximum heart rate. Patients were closely monitored for changes in heart rate and fingertip oxygen saturation using pulse oximetry. Patient's feeling was questioned promptly.

The program of LG included the following: 1) warm-up: patients adopted abdominal breathing to adjust breathing and gently stretched the limbs for 5 minutes. 2) sitting and lying Liuzijue exercise: patients performed complete sitting and lying Liuzijue, including six different expiratory sounds (“Xu”,“He”,“Hu”,“Si”,“Cui”,“Xi”) and corresponding limb movements for 20 minutes. 3) cooling down: patients adjusted breathing and relaxed the body for 5 minutes.

During the period of hospitalization, each sitting and lying Liuzijue exercise was completed under the guidance of respiratory doctors. Patients in the LG were given sitting and lying Liuzijue exercise manual, video and intervention diary. Patients and their families were ensured to fully master the exercise methods before discharge. After leaving hospital, patients were guided and supervised by daily telephone and weekly family visit. Patients were asked to document their exercise program, including exercise duration, location, intensity, and so on.

*2.5. Outcome Measures.* Blood gas analysis (pH、$PaO_2$ and $PaCO_2$) was performed before treatment, 3 days and 5 days after intervention. Lung function, 6MWD, mMRC

and quality of life were determined at baseline and after 3 months of intervention. The length of hospital stay, the duration of noninvasive ventilation, and the frequency of acute exacerbations within 6 months after the intervention were also compared. Acute exacerbation was defined as an unplanned visit to any hospital due to exacerbation of respiratory symptoms. After the intervention, the patient's status was evaluated by monthly telephone call for 6 months.

*2.5.1 Pulmonary function tests.* Pulmonary function was measured using a respirator (Masterscreen-PFT, Jaeger, Germany) by doctors in the pulmonary function room of Hospital of Chengdu University of Traditional Chinese Medicine according to the guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS)[20]. Each patient was tested 3 times. The optimal value was used for the analysis.

*2.5.2 6-minute walking test (6MWT).* The 6MWT was tested in the corridor (30 meters long) specially designed by the respiratory department of our hospital. According to the guidelines of ATS, the respiratory doctors observed and recorded the discomfort and walking distance of patients, with an accuracy of 0.5 meters[21].

*2.5.3 Respiratory symptoms.* The symptoms of dyspnea were evaluated by the Modified Medical Research Council Dyspnea Scales (mMRC). The mMRC was originally proposed by experts in the field of chronic bronchitis and emphysema. After years of application and improvement, mMRC is now commonly used to assess the degree of dyspnea in patients with COPD[22]. It was divided into 0~4 levels, the higher the level, the more severe the breathing difficulties.

*2.5.4 Quality of life.* The quality of life was assessed by the St. George’s Respiratory Questionnaire (SGRQ). The questionnaire was divided into a total of 3 dimensions (symptoms, activity, and daily impact), which could well reflect the changes of exercise tolerance and quality of life in COPD patients[23].The total score of the questionnaire ranged from 0 to 100 points. The higher the score, the more severe the illness.

*2.6. Statistical Analysis.* All the data of this study were uniformly collated, summarized. Spss22.0 statistical software was used to analyze the data. Two sided test criteria were used in this study. A $P$-value < 0.05 was considered to indicate statistical significance.

Continuous variables were evaluated using normality and variance homogeneity tests. Continuous variables were described by mean and SD for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical variables were described as absolute numbers and percentages. The paired t-tests were used to perform analyses of within-group differences, and two independent samples t-test were used to analyze intergroup differences. Based on general linear models, the analysis of covariance models was used to analyze the differences between groups after intervention. For categorical data, the difference was analyzed by the chi-square test. Repeated measures ANOVA was used to examine daily changes of blood gas in to groups.

## 3. Discussion

COPD not only causes airway and pulmonary diseases, but also brings systemic secondary diseases. AECOPD will further accelerate the process of disease. GOLD (2020 Edition)[24] suggests that pulmonary rehabilitation with exercise as the main component should be recommended to patients with different levels of COPD. Because it can improve respiratory symptoms, quality of life, physical activity and participation in daily activities. And its safety has been confirmed. Liuzijue regulates zang-fu organs by regulating breathing, coordinating body movements and regulating emotions. So it plays an important role in pulmonary diseases. Previous studies[12] found that the Liuzijue was used in AECOPD patients for pulmonary rehabilitation, which can improve respiratory muscle fatigue, respiratory symptoms and exercise tolerance. It is difficult for patients with AECOPD to get out of bed early for pulmonary rehabilitation due to the need for disease treatment, physical and psychological factors. Therefore, this study adopted sitting and lying Liuzijue exercise, which is simple and easy to learn. The most important thing is that patients can complete the training in bed.

At present, the ways of pulmonary rehabilitation exercise generally include aerobic exercise, resistance exercise, aerobic combined with resistance exercise[25]. Training can only be done with instruments. This is not suitable for China’s national conditions. For the lung rehabilitation of stable COPD patients, Chinese traditional

exercise is mostly used in domestic research. Such as Baduanjin, Taijiquan, Wuqinxi, and Liuzijue[26]. However, there are few reports of traditional exercise intervention for AECOPD patients. There is no report of pulmonary rehabilitation intervention in AECOPD patients with noninvasive ventilation by using sitting and lying Liuzijue. Therefore, we designed this clinical randomized controlled trial to evaluate the effect of sitting and lying Liuzijue in AECOPD patients with noninvasive ventilation.

The main strength of this study is that an early pulmonary rehabilitation program in patients with AECOPD can be achieved. Sitting and lying Liuzijue is a low-intensity aerobic exercise that can be done in bed without special equipment. This makes sitting and lying Liuzijue feasible for noninvasive ventilation patients with AECOPD. After the intervention, the 6-month follow-up can observe the long-term effect. It is worth noting that this study also has some limitations. First, the sample size is relatively small. Second, patients come from the same hospital. Third, blind method cannot be achieved. Therefore, future studies with larger samples and multicenter are needed to further analyze the sitting and lying Liuzijue effects. Finally, because the sitting and lying Liuzijue movement is a meditative movement, its effect may be limited by the comprehending and acceptance of people from different cultural backgrounds.

## Author contributions

Conceptualization: Shunqi Liao, Qiao Lin, Feng Jian.

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Writing – review & editing: Fang Wang.

## Ethical Approval

The study protocols were approved by the Ethics Committee of Hospital of Chengdu University of traditional Chinese medicine (2019KL-064).

## Consent

Informed written consent was obtained from all participants.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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