**INTRODUCTION**

**Review question / Objective:** The effect of Traditional Chinese medicines on patients with Pulmonary Fibrosis Arising as a Sequelae during the recovery from COVID19?

**Rationale:** Severe acute respiratory syndrome coronavirus 2 (sars-cov-2) caused Coronavirus disease-2019.
(COVID-19) was discovered in December 2019, and the world broke out. The globe pandemic that has caused millions of deaths. With the preliminary understanding of the characteristics of COVID-19, include pathological changes, clinical manifestations, and specialist put forward the corresponding treatment measures. The corresponding treatment measures and vaccine development are being accelerated, and the mortality rate of patients with COVID-19 is extremely low. However, long-term sequelae of SARS-CoV-2 infection have become increasingly recognized and concerning. Up to now, there are no specific or effective drug treatments for COVID-19 patients. Some comprehensive treatment methods were used for the COVID-19 cases, including antivirals, antibiotics, hormones, oxygen therapy, nutritional support and so on. Although most of the patients with COVID-19 have been treated successfully, it has been reported that a small number of severe or critical patients with COVID-19 have some cardiopulmonary sequelae after rehabilitation. Pulmonary fibrosis is one of the sequelae of severe patients with COVID-19. Pulmonary fibrosis is characterized by a significant decline in lung function, leading to respiratory failure and death. The common clinical manifestations of pulmonary fibrosis are dyspnea and deterioration of pulmonary function. At present, the natural process of pulmonary fibrosis is irreversible, drugs such as pirfenidone and nintedanib can delay the decline of lung function in patients with pulmonary fibrosis. Therefore, lung transplantation is the only feasible treatment option known to improve prognosis. However, the drug treatment of modern medicine will cause that patients may experience some side effects, and affect the physical and mental function of patients, and reduce the quality of life. In China, Traditional Chinese medicine has been widely used to prevent fibrosis and improve lung function, for example Chinese patent drug Jinshuibao tablets, Shengmaiyin oral liquid, for example the Traditional Chinese granules will comprise extracts of adenophora tetraphylla, radix glehniae, liriope graminifolia, codonopsis pilosula, selfheal, meretricis, angelica sinensis, arrowhead mushroom, oysters, seaweed, peach kernel, the root of red-rooted salvia, curcuma aromatica, rhizome sparganii, radices zedoariae, and radix astragal. However, the systematic reviews examining the efficacy and safety of TCM in the treatment of patients with Pulmonary Fibrosis Arising as a Sequelae during the recovery from COVID-19 have never been systematically evaluated. Therefore, the purpose of this study is to explore the efficacy and safety of TCM in the treatment for patients with Pulmonary Fibrosis Arising as a Sequelae during the recovery from COVID-19 by pooling a large-sample, longstanding, double-blind RCT, in order to provide high-quality clinical evidence.

Condition being studied: Pulmonary Fibrosis Arising as a Sequelae during the recovery from COVID19.

METHODS

Participant or population: Patients with Pulmonary Fibrosis Arising as a Sequelae during the recovery from COVID19.

Intervention: Modern medicine (antifibrotic drugs) plus Traditional Chinese medicine.

Comparator: The control group will be administered modern medicine (antifibrotic drugs) plus TCM placebo or modern medicine (antifibrotic drugs) alone.

Study designs to be included: RCTs.

Eligibility criteria: 1)18-70 years old; 2) all patients met the diagnostic criteria of the COVID-19 recovery phase, the diagnostic criteria of the COVID-19 recovery phase were at least 72 h without fever, chest computed tomography (CT) showing substantial improvement in both lungs, clinical relief of respiratory symptoms, and two negative SARS-CoV-2 RNA pharynx tests obtained at least 24 h apart. 3)2LC4 weeks after discharge; 4)all patients should develop pulmonary fibrosis after rehabilitation. The diagnosis criteria of pulmonary fibrosis will be in accordance with the guidelines of evidence-based


Main outcome(s): Treatment effect: treatment effect were stratified into three groups: improvement, stabilization, and deterioration levels.

Additional outcome(s): Vital capacity (VC), total vital capacity (TLC), forced vital capacity (FVC), FVC%, diffusion capacity for carbon monoxide (DLCO), predicted diffusion capacity for carbon monoxide (DLCO%), Forced expiratory volume in 1 s (FEV1), residual volume (RV), maximum vital capacity (MVV), expiratory reserve volume (ERV), inspiratory reserve volume (IRV), peak expiratory flow (PEF), maximal middle expiratory flow (MMEF), tide volume (VT), inspiratory capacity (IC), 6-min walking distance test.

Data management: Based on the inclusion criteria and exclusion criteria, literature screening and date extraction were conducted by two investigators independently, and a third investigator ruled on the discrepancy. Data extraction contents include: 1) Basic characteristics of the ultimate eligible RCTs: title, author, publication date, publication journal, diagnostic criteria, inclusion criteria, exclusion criteria, sample size; 2) Baseline characteristics of patients: gender, age, time of recovery period, the severity of COVID-19, type of COVID-19 sequelae, clinical manifestations; 3) Intervention and control measures: Traditional Chinese medicine, frequency and course of treatment, basic treatment; 4) Outcome date and follow-up data; 5) Adverse events.

Quality assessment / Risk of bias analysis: Risk of bias for the included RCTs will be assessed by Review Manager 5.4. The items included: 1) selection bias: whether sequences generated are randomization process and whether allocation is hidden; 2) performance bias: whether participants and personnel are blinded; 3) detection bias: whether outcome assessment are blinded; 4) attrition bias: whether outcome data are incomplete; 5) reporting bias: whether reported result of the outcome is selective; 6) and other bias. Each item was evaluated 3 levels: (a) low risk of bias, (b) high risk of bias, or (c) unclear risk of bias. Two investigators will independently assess the quality of the included studies, and the divergence was judged by a third researcher.

Strategy of data synthesis: Review Manager 5.4 (RevMan 5.4, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration) software was used for aggregating the data and performing meta-analysis. For dichotomous outcomes, Odds ratio (OR) or relative risk (RR), 95% Confidence interval (CI) and P values were used. for continuous data, Mean difference (MD) or Std Mean difference (SMD) 95% Confidence interval (CI) and P values will used to estimate continuous data. The Q value test and I2 index was used to measure the statistical heterogeneity. Meta-analyses were performed using a random-effect model, Otherwise, a fixed effect model will be adopted.

Subgroup analysis: Subgroup analysis: 1) by age: patients were stratified into two groups: mean age >60 years and mean age ≤60 years. 2) by the severity of COVID-19: patients were stratified into four groups: Light, common, severe and critica.

Sensitivity analysis: Sensitivity analysis will be performed by excluding studies with high risk of bias and change the statistical model.

Country(ies) involved: China.
Keywords: COVID-19, Pulmonary fibrosis, Modern medicine, Traditional Chinese medicine, protocol, systematic review.

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