Effect of traditional Chinese exercise on the treatment of "long-COVID" A protocol for systematic review and meta-analysis

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Study protocol

Keywords: coronavirus disease 2019, meta-analysis, systematic review, traditional Chinese exercise

Posted Date: September 14th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3272469/v1

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Abstract

Background

Since late 2019, there has been a widespread epidemic of coronavirus disease 2019 (COVID-19), and some patients infected with COVID-19 have developed symptoms of long COVID after acute infection control, severely affecting people's lives and work. Traditional Chinese exercise has a long history, with numerous studies proving its effectiveness in the prevention and treatment of COVID-19. Some previous studies only systematically reviewed the effect of TCE on acute covid infection, and there was not enough evidence to support the effect of TCE on persistent fatigue, dyspnea, and cognitive impairment in patients with long-term covid. The purpose of this study was to evaluate the efficacy of traditional Chinese exercise in patients with long COVID and to provide alternative therapy for long COVID.

METHODS

In this study, literature searches in the Cochrane Library, Embase, Web of Science, PubMed, the Chinese Biomedical Literature Database, the Chinese National Knowledge Infrastructure Database, the Chinese Science and Technology Journal Database, and the WanFang Database will be conducted to include literature related to randomized controlled trials of traditional Chinese exercise therapy for long COVID. Two researchers independently screened, extracted data, and assessed the methodological quality of each included trial using the Physiotherapy Evidence Database (PEDro) scale, followed by the Cochrane Collaboration organizational tool being used to assess the risk of bias for each study. The data captured in this study were statistically analyzed using comprehensive meta-analysis version 3.0 software.

PROSPERO registration number CRD42023402517

Strengths and limitations of this study

This review will assess the impact of TCE on long COVID and provide a new complementary therapy for long COVID treatment.

This review will use the Physiotherapy Evidence Database (PEDro) scale to evaluate the methodological quality of included studies.

It is not clear the course of disease and the severity of the disease of long COVID patients, which may increase the heterogeneity of the study.

There are many types of TCE, and different patient compliance and operating standards may also increase the bias of the results.

Introduction
COVID-19 is an acute, highly transmissible respiratory infectious disease. It has a wide range of clinical presentations and a potentially lethal clinical course from asymptomatic to critically ill. The clinical manifestations and complications, pathogenesis, diagnosis and prognosis of patients in the acute phase of COVID-19 have been systematically described. However, many COVID-19 patients continue to develop sequelae affecting multiple organ systems after the acute phase, which we have termed long COVID or acute sequelae of SARS-CoV-2 (PASC). Studies have shown that approximately 6.2%-79% of COVID-19 survivors may develop a long COVID\(^1\). Long COVID is a multi-system disorder characterized by persistent fatigue, dyspnea, cognitive deficits, anxiety, and depression\(^2\). Respiratory diseases are the common sequelae of Long COVID, followed by systemic symptoms and neurological symptoms with higher prevalence\(^3\), which seriously affect patients' daily life and study. As of June 28, 2023, the total number of confirmed COVID-19 cases worldwide is 767,518,723, including 947,192,26 deaths\(^4\). There are fewer Meta-analyses of long COVID treatments and there are no specific drugs available. Exercise not only improves pulmonary complications and cardiovascular health in COVID-19 sequelae\(^5\), but also reduces pro-inflammatory cytokines and improves the balance and function of impaired cellular pathways in the central nervous system in vivo (e.g., BDNF and glutamate), which positively affects neuropsychological symptoms in patients with COVID-19\(^6\)\(^7\).

Traditional Chinese Exercise (TCE), a form of exercise that combines movement with static, rigidity, and flexibility, includes Tai Chi, Qigong, Eight Brocades, Five-animal Boxing, and Yi Jinjing. TCE is now widely used in the prevention, treatment and rehabilitation of COVID-19 patients with significant efficacy. Studies have shown that TCE can effectively relieve respiratory symptoms, such as improving the 6-minute walk distance, BODE index, and FEV1/FVC ratio in patients with COPD\(^8\); it can also promote the absorption of lung lesions in patients with COVID-19, improve the negative mood of patients with anxiety and depression, and thus improve the quality of life\(^9\). However, some of the previous studies have only systematically reviewed the effects of TCEs on the acute COVID-19 infection period, and there is insufficient evidence to support the role of TCEs on persistent fatigue, dyspnea, and cognitive impairment in patients with long COVID. Therefore, we aimed to conduct a systematic review and meta-analysis to investigate the effects of TCEs on patients with long COVID and to provide methods and rationale for clinical treatment of long COVID.

Materials and Methods

This protocol is registered with PROSPERO under registration number CRD42023402517 and was produced following the reporting guidelines of the 2015 Preferred Reporting for Systematic Reviews and Meta-Analysis Protocols project (PRISMA-P).

Eligibility criteria

Types of studies
Only randomized controlled trials (RCT) of traditional Chinese exercise therapy for long COVID will be included, with no restrictions on language of publication. Relevant non-randomized controlled, case report and other types of studies will be excluded.

**Type of participants**

Participants were diagnosed positive for SARS-CoV-2 virus by polymerase chain reaction (PCR) testing, with continued persistent fatigue, cognitive impairment, dyspnea, cough, decreased sense of smell and taste, anxiety, and depression 4 to 12 weeks after diagnosis; symptoms persisted for at least two months.

**Type of interventions.**

The experimental group used the traditional Chinese exercise (e.g., tai chi, qigong, baduanjin, yijinjing, wuqinxi) as the intervention method, while the control group did not limit the intervention method. The control group interventions included: no treatment, placebo, and other treatments (e.g., traditional Chinese medicine, acupuncture, physical therapy).

**Types of outcome measures**

The primary outcome was the cure rate. The secondary outcomes included the disappearance time of major symptoms (including fatigue, dyspnea, cough disappearance rate, olfactory and taste disorders), quality of life score, fatigue scale score, anxiety and depression scale score, cognitive ability score, pulmonary function and adverse reactions.

**Information sources and search strategy**

Literature searches will be conducted in Cochrane Library, Embase, Web of Science, PubMed, China Biomedical Literature Database, China National Knowledge Infrastructure Database, China Science and Technology Journal Database, and Wanfang Database. The search terms are "Long COVID-19", "Traditional Chinese Exercise", and all the published RCTs on this subject will be included. From the database creation to March 2023, there are no language restrictions. The specific search strategies on PubMed are summarized in Table 1.

**Table 1** Search strategy for the PubMed database.
Table 1 Search strategy for the PubMed database.

<table>
<thead>
<tr>
<th>Number</th>
<th>Search items</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>&quot;Post-Acute COVID-19 Syndrome&quot;[Mesh]</td>
</tr>
<tr>
<td>#2</td>
<td>&quot;long-COVID&quot;[Title/Abstract] OR &quot;post acute covid syndrome&quot;[Title/Abstract] OR &quot;long-haul covid 19&quot;[Title/Abstract] OR &quot;post acute sequelae of sars cov 2 infection&quot;[Title/Abstract] OR &quot;post covid conditions&quot;[Title/Abstract] OR &quot;chronic covid syndrome&quot;[Title/Abstract]</td>
</tr>
<tr>
<td>#3</td>
<td>#1 OR #2</td>
</tr>
<tr>
<td>#4</td>
<td>&quot;Tai Ji&quot;[Mesh]</td>
</tr>
<tr>
<td>#6</td>
<td>#4 OR #5</td>
</tr>
<tr>
<td>#7</td>
<td>&quot;Randomized Controlled Trial&quot;[Publication Type]</td>
</tr>
<tr>
<td>#8</td>
<td>&quot;Randomized&quot;[Title/Abstract] OR &quot;Randomly&quot;[Title/Abstract] OR &quot;Placebo&quot;[Title/Abstract]</td>
</tr>
<tr>
<td>#9</td>
<td>#7 OR #8</td>
</tr>
<tr>
<td>#10</td>
<td>#3 AND #6 AND #9</td>
</tr>
</tbody>
</table>

Study selection and data extraction

All the relevant literature retrieved was imported into Endnote X9 software, and all the literature was managed. First, after the software automatically removed duplicate references, the two researchers conducted a preliminary screening of titles and abstracts and independently assessed the papers for eligibility.

If the content related to the abstract is considered unclear, the full article will be reviewed. When there is disagreement, a third researcher will be involved in the discussion and a consensus will be reached after evaluating the article. The process of research selection is illustrated in the flowchart of system review and meta-analysis.

Two researchers extracted data from the enrolled articles and independently generated a data extraction table with the following items: name of first author, year of publication, number of cases, duration of disease, symptoms, interventions, outcomes, and risk of bias assessment. Any disagreements will be resolved by inviting a third researcher to discuss or negotiate together. If the required data are lacking or the results are ambiguous, the author of the original article will be contacted to obtain relevant information; if data are still not available, the literature with missing data will be excluded.

Assessment of risk of bias.
The methodological quality of each included trial was assessed using the Physiotherapy Evidence Database (PEDro) scale (which consists of 11 entries to assess the quality of RCT studies). The "specified eligibility criteria" were excluded from the total score because they were related to external validity, and Pedro's total score was 10, with higher scores indicating better methodological quality and reporting. Secondly the use of the Cochrane Collaboration organizational tool was employed to assess the risk of bias for each study. The tool includes random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each study was assigned a risk rating of three levels: "low risk," "unclear risk," and "high risk".

**Data analysis and synthesis**

Statistical analyses of the collected data were performed using comprehensive meta-analysis version 3.0 software, and random-effects models with 95% confidence intervals (CI) were used to calculate in the total estimated effect sizes, as the included studies involved different centers, different populations, and different interventions. According to the Cochrane's Handbook, the Q statistic and $I^2$ index were used to assess heterogeneity of changes in true effect sizes in included studies; p values <0.1 and/or $I^2 \geq 50\%$ for the Q statistic indicated significant heterogeneity.

**Assessment of heterogeneity**

Subgroup and sensitivity analyses will be performed to search for sources of heterogeneity if there is significant heterogeneity in the included trials. Subgroup analysis is conducted on the basis of sex and age of the subject, duration of the disease, intervention cycle, and type of tai chi or qigong. To assess the robustness of the study results, sensitivity analyses were also performed on the included studies. Deletion of a study and determination of whether there was a significant proportion of the research that could explain the heterogeneity.

**Assessment of reporting biases**

If more than 10 studies are included, we assess publication bias using the symmetry of the funnel plot.

**Patient and public involvement**

Patients or members of the public were not involved in the design of this study.

**Ethics and dissemination**

This study will be based on the results of data from previous studies and therefore does not require ethical approval or consent. The results of the study will be submitted for publication in peer-reviewed journals.

**Discussions**
Long COVID has become an important public health issue and its long-term effects are worrisome, Han et al.\textsuperscript{10} conducted a pooled analysis of 8,591 Covid survivors from 18 studies, the most common symptoms were general symptoms such as fatigue and joint pain, with prevalence rates of 28% and 26%, respectively, followed by depression and anxiety, with prevalence rates of 23% and 22%, respectively, with 19% experiencing impaired memory, and 18% experiencing dyspnea; In Wuhan, China, 6 months after discharge of 1733 COVID-19 patients, 52% had fatigue, 26% had insomnia, and 23% were anxious and depressed\textsuperscript{11}. In Iran, 1680 patients developed at least one long COVID symptom 3 months after discharge from the hospital, and some of these young patients had prolonged brain fog symptoms and inability to concentrate, which severely affected their daily lives and school work\textsuperscript{12}. In long COVID patients, limb muscles, neuropsychiatric status, heart and respiration show varying degrees of impairment\textsuperscript{13}. Long COVID has a heterogeneous nature, and the specific pathogenesis is that the SARS-CoV-2 virus infests the host at different sites, and the body may produce different chronic inflammatory responses and involve different organ systems\textsuperscript{14}. Direct invasion of alveolar epithelial cells by the SARS-CoV-2 virus, for example, produces diffuse alveolar injury and an increase in proinflammatory cytokines, which cause aggregation of lymphocytes, macrophages, and neutrophils resulting in substantial lung damage such as pulmonary fibrosis\textsuperscript{15}. If the virus binds to ACE2 receptors on cardiomyocytes and enters macrophages, endothelial cells, and cardiomyocytes, it can lead to myocardial injury, myocarditis, and myocardial infarction\textsuperscript{16}. In addition, chronic neuroinflammation triggered by COVID-19 infection activates glial cells, which also affects the patient's cognitive ability, executive function, etc.\textsuperscript{17} There are no widely effective treatments for long COVID, but patient physical activity and exercise tolerance are modiers of the clinical presentation and prognosis of many chronic diseases, and adherence to physical activity exercise is strongly associated with a reduced risk of serious outcomes in adult patients with COVID-19\textsuperscript{5}.

TCE contributes to the physical and mental recovery of COVID-19 patients\textsuperscript{9}, TCE not only reduces the erythrocyte sedimentation rate (ESR) and inhibits the secretion of pro-inflammatory cytokines, such as IL-6, CRP, and TNF\textsubscript{α}, thus alleviating the inflammatory response of COVID-19\textsuperscript{18}. Castro et al.\textsuperscript{19} called for COVID-19 patients to be rehabilitated with Tai Chi to improve cognitive deficits, physical and mental health. A meta-analysis by Wang et al.\textsuperscript{20} found that TCE is beneficial to the improvement of physical fitness, balance and muscle strength of the elderly, and makes the alternating action between human muscle tissues more coordinated. TCE requires concentration during exercise, and the human body perspective shifts its gaze with the movement of the limbs, which in turn mobilizes the whole body organs for movement, improves the human body's reaction speed, and improves cognitive dysfunction\textsuperscript{21}. Previous Meta analyses have only discussed the efficacy of TCE on COVID-19 in the acute or rehabilitation phase, or the effect of one of the traditional feats in TCE on COVID-19, and have not investigated the effect of TCE on long COVID. Therefore, this study will identify the TCE modality that has the least adverse effects and is the most effective for patients with long COVID, and provide evidence-based medical support for TCE for long COVID through meta-analysis.
This study also has limitations, due to the varying severity of disease in patients with long COVID, the large number of TCE types, and the varying criteria for patient actions, which would increase study heterogeneity, and could also affect the final outcome of this study if there are not a sufficient number of high-quality randomized controlled trial studies.

**Abbreviations**


**Declarations**

**Contributors** PCW conceived the study; Wty and HC designed and wrote the first draft; Wty participates in the formulation of retrieval strategy, and WTX and HC participate in data extraction and inclusion; MMW will evaluate the quality of the final included study, and finally HC will synthesize the data; If there are differences, they can discuss and negotiate with PCW. The original is reviewed and finalized by PCW; All authors reviewed and approved the final version of the manuscript and allowed it to be published.

**Funding** This study was supported by the Heilongjiang Provincial Department of Science and Technology project (LH2021H091).

**Ethics and dissemination** This study will be based on the results of data from previous studies and therefore no ethical approval or consent is required. The results of the study will be disseminated for publication through peer-reviewed journals.

**References**


Figures

Figure 1

Flow chart of the study