Efficacy and safety of acupuncture therapy for COVID-19
A protocol for systematic review and meta-analysis

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Abstract
Background: The study aims to evaluate the effectiveness and safety of acupuncture therapy for coronavirus disease 2019.
Methods: The following electronic databases will be searched from December 2019 to December 2020: Medline, PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure, Wan-fang database, Chinese Scientific Journal Database, Chinese Biomedical Literature Databases, and other databases. All published randomized controlled trials about this topic will be included. Two independent researchers will operate article retrieval, duplication removing, screening, quality evaluation, and data analyses by Review Manager (V.5.3.5). Meta-analyses, subgroup analysis, and/or descriptive analysis will be performed based on the included data conditions.
Results: High-quality synthesis and/or descriptive analysis of current evidence will be provided from mortality rate, cure rate, the time of negative nucleic acid detection for 2 consecutive times (not on the same day), improvement of chest CT scans, disappearance time of fever and cough, and side effects.
Conclusion: This study will provide the evidence of whether acupuncture is an effective and safe intervention for coronavirus disease 2019.

PROSPERO registration number: CRD42020179298.

Abbreviations: COVID-19 = coronavirus disease 2019, RCT = randomized controlled trial.
Keywords: acupuncture, coronavirus disease 2019, protocol, systematic review and meta-analysis.

1. Introduction
1.1. Description of the condition
Coronavirus disease 2019 (COVID-19) is a newly discovered highly contagious respiratory disease, with outbreaks in late December 2019 in Wuhan, China. COVID-19 has strong infectivity and pathogenicity, and it has affected 2,344,983 people in 210 countries worldwide and caused 161,191 deaths by April 19, 2020. The main clinical characteristics of COVID-19 are fever, dry cough, fatigue and ground-glass opacities on computed tomography. The COVID-19 pandemic represents the greatest global public health crisis of this generation, and no proven effective therapies for this virus currently exist.

1.2. Description and function of intervention
Acupuncture is an important part of complementary therapy guide by the theory of traditional Chinese medicine. It treats diseases through the conduction of meridians and acupoints adding certain operations. Acupuncture therapies include many different treatments, such as acupuncture, moxibustion, electro-acupuncture, fire needle, acupoint injection, auricular point therapy, etc. Acupuncture has been proved effective in some diseases. During the period of COVID-19, the China Association of Acupuncture-Moxibustion recommends acupuncture therapy for the treatment of COVID-19. And some hospitals in China have used acupuncture therapy to prevent and treat COVID-19.

1.3. Why the review is important
According to the published research, there is a lack of high-quality evidence on acupuncture in the treatment of COVID-19.
Therefore, this systematic review aims to assess the effectiveness and safety of acupuncture therapy for COVID-19.

2. Methods

This systematic review protocol has been registered in the PROSPERO network (No. CRD 42020179298). All steps of this systematic review will be performed according to the Cochrane Handbook (5.2.0).

2.1. Selection criteria

2.1.1. Types of studies. Randomized controlled trials (RCTs) of acupuncture therapy for COVID-19 without any limitation of blinding or publication language will be included. RCTs that involve at least 1 acupuncture-related treatment to COVID-19, and 1 control treatment (or blank treatment) will be included. The studies of animal experiment, review, case report, meta-analysis, and duplicate publications will be excluded.

2.1.2. Types of patients. Patients who were diagnosed as COVID-19 will be included, without limits on gender, age, race, nationality, and disease classification.

2.1.3. Types of interventions and comparisons. Interventions can be any type of acupuncture therapy: acupuncture, moxibustion, electroacupuncture, fire needle, acupoint injection, auricular point therapy. Multiple control interventions will be included: no treatment, placebo, and other interventions (e.g., standard care, drugs, Chinese medicine). Comparisons contain acupuncture and its relation will be excluded. Interventions of acupuncture combined with other therapies will also be included, only if the other therapies were used as comparisons.

2.1.4. Types of outcomes. Primary outcomes will include mortality rate, cure rate, the time of negative nucleic acid detection for 2 consecutive times (not on the same day), and improvement of chest CT scans. Secondary outcomes will include disappearance time of fever and cough, serum level of TNF-α and IL-6, and side effects of acupuncture.

2.2. Search methods for identification of studies

2.2.1. Electronic searches. The following electronic databases will be searched from December 2019 to December 2020: Medline, PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure, Wan-fang database, Chinese Scientific Journal Database, Chinese Biomedical Literature Databases, and other databases. All published RCTs about this topic will be included. Exemplary search strategy of Medline is listed in Table 1. According to the difference of databases, keywords may combine with free words and comprehensive search will be performed.

2.3. Data collection and analysis

2.3.1. Selection of studies. Two reviewers (SLH and SYW) will independently select the studies. They will check the results with each other. When disagreements occur, a third reviewer (JL) will make the final decision. They will read the full texts of all included studies if necessary. Screening operation will flow the diagram of Figure 1. If the full literatures are unable to obtain or related data is incomplete, we will contact the corresponding author.

Table 1

| Medline search strategy | 
|-------------------------|
| #1 MeSH major topic: COVID-19 |
| #2 MeSH major topic: Coronavirus disease 2019 |
| #3 MeSH major topic: 2019 novel coronavirus |
| #4 MeSH major topic: new coronavirus |
| #5 MeSH major topic: novel coronavirus |
| #6 MeSH major topic: acupuncture |
| #7 MeSH major topic: moxibustion |
| #8 MeSH major topic: electroacupuncture |
| #9 MeSH major topic: fire needle |
| #10 MeSH major topic: acupoint injection |
| #11 MeSH major topic: auricular point |
| #12 MeSH major topic: needle warming moxibustion |
| #13 MeSH major topic: infants |
| #14 MeSH major topic: children |
| #15 MeSH major topic: pediatric |
| #16 MeSH major topic: adult |
| #17 MeSH major topic: elderly |
| #18 MeSH major topic: acupoint injection |
| #19 MeSH major topic: agingness |
| #20 MeSH major topic: gerontism |
| #21 #1 or #2 or #3 or #4 or #5 or #6 |
| #22 #7 or #8 or #9 or #10 or #11 or #12 or #13 |
| #23 #14 or #15 or #16 or #17 or #18 or #19 or #20 |
| #24 #21 and #22 and #23 |

MeSH = medical subject heading

2.3.2. Assessment and quality of included studies. Two reviewers (MMW and JR) will evaluate quality of included articles and assess the risk of bias based on Cochrane Handbook (5.2.0). Quality assessment of included studies contains randomized method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective reporting. Divergence of evaluation will also consult a third reviewer (JL).

2.3.3. Data extraction. Two independent reviewers (SLH and WJY) will extract data after selection and quality assessment, they will extract the data using a standardized data extraction form and any differences of opinion between them will be resolved through discussion, if failed, they will discuss with the third reviewer (JL). Data will be recorded onto an electronic form, including the basic information of the article (the title of article, first author, year, and language), inclusion and exclusion criteria, the baseline of the study (the sample size, sex ratio, age, and disease classification), interventions in the observation group and the control group, and outcome measures.

2.3.4. Measures of treatment effect. Two reviewers (SLH and SYW) will perform analysis independently and then cross-check treatment effect with Review Manager 5.3.5. Risk ratio with 95% confidence intervals will be adopted when dichotomous data existence. Continuous data will be presented by mean difference or standard mean difference with 95% confidence interval. Risk ratio form will be changed to analyze when binary data existence.

2.3.5. Dealing with missing data. Due to the possibility of data loss in the literature, we will contact the corresponding author by email or other means. If the missing data is not available, we will analyze the existing data assumed to be lost at random.
2.3.6. Assessment of heterogeneity. The heterogeneity of studies will be evaluated by $Q$ test and $I^2$ statistic with RevMan5.3.5. The heterogeneity will be deemed as low ($I^2 < 50\%$), moderate ($50 – 75\%$), and high ($I^2 > 75\%$).

2.3.7. Assessment of reporting bias. Publication bias and other reporting bias will be assessed by creating funnel plots. A symmetrical funnel plot indicates a low risk of bias, while an asymmetric funnel plot indicates a high risk of bias.

2.3.8. Data synthesis. Meta-analysis or descriptive analysis will be conducted according to the intervention method, measurement method, and heterogeneity level. If clinical and methodological heterogeneity are low, the fixed-effect model with merger analysis will be used. When heterogeneity is at medium level, the random-effects model with merger analysis will be used. However, if the heterogeneity is significantly high, subgroup analysis or descriptive analysis will be performed.

2.3.9. Subgroup analysis. Subgroup analysis will be performed based on the results of data synthesis, and if heterogeneity is found to be caused by the specific characteristics of the included study (e.g., age, disease classification, the intervention methods and the measurement methods used in the clinical trials), subgroup analysis will be conducted relevant to these categories.

3. Discussion

COVID-19 is a respiratory disease with wide infectivity and strong pathogenicity. It poses great threat to public health and affects social production and life seriously. Acupuncture is an important traditional Chinese medicine treatment with simple operation and low cost. Some Chinese hospitals are using acupuncture therapy to prevent and treat COVID-19. If the evidence could prove acupuncture is useful for COVID-19, it might save much cost and be beneficial to worldwide people. However, no systematic reviews on this topic have been published. In order to give compelling evidence and better guide in clinic practice, all actions of this review will be performed according to Cochrane Handbook 5.2.0.

Author contributions

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