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Comparative Efficacy and Safety of the Moxibustion for the Treatment of Coronavirus Disease 2019 (COVID-19): Protocol for a Systematic Review and Meta-analysis.

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Abstract

Background Coronavirus disease 2019 (COVID-19) has spread from its origins to the world and become a pandemic since late 2019. It predominantly damages the lungs and causes diffuse alveolar injury with edema, cellular fibroblasts and hyaline membrane formation, resulting in acute respiratory insufficiency, respiratory failure, sepsis, acute heart injury, heart failure and other severe complications. It is also reported that moxibustion can effectively modify the negative emotions and relieve the symptoms of chest distress and impaired appetite for the patient with COVID-19. The main objective of current research is to make an assessment for effectiveness and safety of the moxibustion as an important complementary and alternative therapeutic method for COVID-19.

Methods and analysis Articles for the systematic literature will be located at the MEDLINE, OVID, EMBASE, CNKI, CBM, NTR, Chi CTR databases. With no restriction about language, manual search will be conducted for potential eligible articles as supplements. Any randomized controlled trials (RCTs) with any moxibustion interventions issued by the therapeutic regimen on all patients diagnosed with COVID-19 will be included. We will include the published studies with no restriction about language. All study records of the title and abstract identified by the search strategies will be directly imported and assessed based on the eligibility criteria. Risk of individual studies for the methodological quality of eligible RCTs will be assessed with the tool from the Cochrane Collaboration's risk of bias tool.

Discussion The purpose of this study is to conduct a systematic review and meta-analysis of the efficacy and safety of moxibustion as a complementary and alternative treatment for COVID-19.

No studies have investigated whether moxibustion will relieve clinical symptoms and shorten the length of hospitalization time.To the best of our knowledge, this is the first systematic review and meta-analysis program designed to update the currently available evidence. Despite the fact of controversial views in using moxibustion, if this study confirms its efficacy and safety, it could provide a better guide for clinical practice around the world.

Systematic review registration

PROSPERO CRD42020176572.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also named coronavirus disease 2019 (COVID-19), has spread from its origins in Wuhan city of China to the world and become a pandemic since late 2019[1, 2]. As of November 8 ,2020, 219 countries are hit by the virus, with 49,- 242, -837 cases confirmed and 1,- 242,- 187 deaths registered worldwide[3].

The epidemiological characteristics of the coronaviruses show that it may originated from bats, but has undergone adaptive evolution in the intermediate host, such as pangolin, before transmitting to human[4,

5]. Compared with severe acute respiratory syndrome (SARS), although the COVID-19 shares about 82% of its genome, asymptomatic infection of coronaviruses is more difficult to investigate, with its high concealment and transmissibility features, the basic reproductive number in the early outbreak is much higher, resulting in a widespread infection[6–8]. The most common infectious model of the COVID-19 is the close contact (carrying virus with close touching) and face-to-face exposure (diffusing out the droplets via talking, coughing and sneezing)[9]. Aerosols that clusters of droplets with a continuum droplet size suspended in air is another model for transmission, but no sufficient and unequivocal evidence could support that[10, 11].

The COVID-19 causes respiratory, gastrointestinal, cardiovascular, immunological and neurological diseases. It predominantly damages the lungs and causes diffuse alveolar injury with edema, cellular fibroblasts and hyaline membrane formation[12, 13], resulting in acute respiratory insufficiency, respiratory failure, sepsis, acute heart injury, heart failure and other severe complications[14].SARS-CoV-2 could also compromise epithelial-endothelial barrier and endothelial cells, edema and interstitial mononuclear inflammatory infiltrates could display as the hallmarks bilateral and peripheral ground-glass and consolidative pulmonary opacities on imaging[13, 15].Current understanding of the SARS-CoV-2 induced host immune response, which could be associated with severe COVID-19 immunological misfiring and poor clinical outcome[16].

There is no effective treatment to date[17],the following categories of drugs are mainly adopted for the treatment at different stages of the disease: antiviral drugs, anti-inflammatory drugs, antibodies, targeted immunomodulatory therapies, anticoagulants and antifibrotic agents, using respiratory support when necessary[18, 19]. However, the detrimental effects on liver injury and abnormal liver function might be associated with certain medications used during hospitalization[20, 21].

As an ancient Chinese medical technique, moxibustion is defined to promote the heat of acupoints by burning herbal materials on the body surface. It has a history of thousands of years in treating large-scale epidemic diseases, and evidence has shown its efficacy in treating SARS in 2002–2003, including marked improvement of clinical symptoms, reduced dosage of conventional therapeutics, shortened length of hospitalization time, improved quality of life [22].Its possible mechanisms may be associated with temperature, smoke, smell, herbs effects factors[23]. It is also reported that moxibustion can effectively modify the negative emotions and relieve the symptoms of chest distress and impaired appetite for the patient with COVID-19[24].However, the clinical study has some shortcoming due to geographic limitation, only a few people are acquainted with this medical technique. As more and more widespread attention being paid, there are enough reasons to believe that it can improve COVID-19's remaining symptoms and be worthy of popularization and application in clinical treatment. Therefore, high-quality systematic evaluation and meta-analysis provide complementary and alternative therapy and for clinical treatment.

In this review, the main objective of current research is to make an assessment for effectiveness and safety of the moxibustion as an important complementary and alternative therapeutic method for COVID-

19. These data will provide the basis for other countries to respond to the current epidemic treatment.

Methods And Analysis

The protocol has been registered. It has been registered in the PROSPERO CRD42020176572 and will follow the PRISMA and Meta-analysis of observational studies in epidemiology to develop detailed search strategies and data analysis method[25, 26]. Our systematic research protocol will comply to the PRISMA-P checklist[27].

Criteria for studies

Study population and study design

Population: All patients diagnosed with COVID-19 with no limitation about age, race, sex differentiation.

Intervention: Any moxibustion interventions issued by the therapeutic regimen will be included, such as indirect moxibustion or direct moxibustion.

Outcomes: Only in those studies addressing definitions of the COVID-19-related will be included in this systematic review.

Study design: We will only include randomized controlled trials (RCTs) that associated with moxibustion. Moxibustion as a part of a complex (mixed but not add-on) intervention will not be included in our research. Observational studies, such as cohort, case–control, case-crossover and self-controlled cohort studies will be excluded. Placebo, usual or standard care, wait-list controls and other positive interventions will be taken as controls.

Definitions and outcome measures

Specifically, studies addressing time of disappearance clinical manifestation symptoms of COVID-19 are primary outcomes:

- Fever
- Fatigue
- Shortness of breath
- Dry cough disappearance rate
- Temperature recovery time
- Serum cytokine levels

Studies addressing test result of COVID-19 are secondary outcomes:

- Negative results rate for two consecutive times

- Addressing clinical accompanying symptoms disappear rate
- Radiographic improvement on chest computed tomographic imaging
- Average hospitalization time
- Occurrence rate of common type to severe form
- clinical cure rate and mortality

Search methods for identification of studies

The literature search was performed between May and July 2021. Two authors (JG and XJZ) conducted a systematic search of 5 English bibliographic databases including Medline, Ovid, Embase, the Cochrane Library, the Allied and Complementary Medicine Database (AMED), 3 Chinese bibliographic databases including Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), VIP Database and Wan fang Database. In addition, the unpublished data were quoted for ongoing trials such as Netherlands National Trial Register (NTR), the Chinese Clinical Trial Registry (Chi CTR), and ClinicalTrials.gov. With no restriction about language, manual search will be conducted for potential eligible articles as supplements. Included references are traced to expand the database. Firstly, the search strategy will be conducted in Pubmed and then adapt for use in the other databases by using the strategy described on the Additional file 1. The three search subjects ‘COVID-19’, ‘moxibustion’, ‘RCTs’ will make Mesh subject headings and free-text words.

Data collection and analysis

Study selection

Records and data from different sources will be managed using a data collection form with excel file. All study records of the title and abstract identified by the search strategies will be directly imported and assessed based on the eligibility criteria. Two independent methodological trained reviewers, (JG and XJZ) working in pairs, will screen against eligibility criteria first at the titles and abstracts level, then full text level. Any disagreement shall be resolved by consensus. A flow-chart of article inclusion and exclusion will be drawn in the systematic review to document the study selection, as PRISMA guidelines[25]. The process of the study selection will be illustrated using a flow-chart on the Additional file 2.

Data selection and management

Two independent methodological trained reviewers (JG and XJZ) will design and pilot data extraction form until they achieve convergence and agreement. Data extraction from study characteristics will include: first author and year, study design, country of publication, outcome, sample, intervention, type of measures, risk of bias assessment and findings. The selection of the extraction form will be cross-checked by the two authors. The further disagreements or conflicts between the reviewers will be

arbitrated by consulting a third review author (CGX). We will also request missing data from the original study author by email to provide additional detail information in the principle study. If there is no positive response from the corresponding authors (up to three contact attempts in one mouth by email).

Data synthesis and analysis

Relevant characteristics of the data for statistical analysis will be put into an excel file. To calculate the risk ratio, dichotomous data will be used with 95% CIs model. We plan to analyze the continuous outcomes by using standard mean difference (SMD) with 95% CIs or a weighted mean difference (WMD). The same scale or assessment instrument will be performed in the WMD; different assessment tools will be carried out in SMD. We will use frequentist framework of a network meta-analysis to operate the net-meta package in R software, to integrate direct and indirect evidences of included RCTs. We will perform a network plot to illustrate the results for primary outcomes if subsets of studies are sufficiently homogeneous. The assessment of statistical heterogeneity will be evaluated based on a standard χ^2 test. The random-effects model will be utilized when fixed-effect model is adopted if there is no significant heterogeneity .

Other sensitivity analyses will be clinically and statistically conducted the potential heterogeneity and inconsistency in special subgroup, such as age, gender and disease duration, trial blinding, evidence quality and so forth. We will adopt the meta-regression to quantify the inter-subgroup difference and explore statistical significance.

Quality assessments

The quality assessment for the methodological of eligible RCTs will be carried out applying the instrument: The Cochrane Collaboration's risk of bias tool and the modified Downs and Black instrument[28].The two tools focus risk bias on 6 aspects bias: selection bias, performance bias, detection bias, attrition bias, selective reporting bias and other bias[29] .According to the tool, we will judge the each domains as'low risk of bias' 'high risk of bias'or'uncertain risk of bias'.

Two independent methodological trained reviewers will access the quality of RCTs via these tools. Any Discrepancies between the pairs of reviewers will be solved by discussion and consulting a third review author (CGX). A funnel plot and Egger's test will be performed graphically for reporting bias assessment[30, 31].If the publication bias is considered to exist, another method such as the trim-and-fill method will be used to modify the bias.

Two reviewers/authors (GJ and LZY) will independently evaluate the quality of the included trials through assessing the risk of bias using the following tools, when appropriate.

Patient and public involvement

This study will use the existing database. Patients and the public will not participate in the design of this study. This article will evaluate the comparative efficacy and safety of moxibustion for the therapeutic method of COVID-19 patients. The insights provided in this study can be used in clinical practice to improve the prognosis, especially to provide an effective adjuvant treatment.

Discussion

Due to severely manspreading epidemic situation, it is necessary to update the current existing evidence on the efficacy of moxibustion, which can provide therapeutic ideas for clinical treatment. The purpose of this study is to conduct a systematic review and meta-analysis of the efficacy and safety of moxibustion as a complementary and alternative treatment for COVID-19.

No studies have investigated whether moxibustion will relieve clinical symptoms and shorten the length of hospitalization time.To the best of our knowledge, this is the first systematic review and meta-analysis program designed to update the currently available evidence. Despite the fact of controversial views in using moxibustion, if this study confirms its efficacy and safety, it could provide a better guide for clinical practice around the world.

Abbreviations

COVID-19
Coronavirus Disease 2019
SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus 2
SARS
Severe Acute Respiratory Syndrome
PRISMA-P
Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols
RCT
Randomized Controlled Trials
AMED
Allied and Complementary Medicine Database
CNKI
National Knowledge Infrastructure
CBM
Chinese Biomedical Literature Database
NTR
Netherlands National Trial Register
Chi CTR
the Chinese Clinical Trial Registry
SMD

Standard Mean Difference
WMD
Weighted Mean Difference

Declarations

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Availability of data and materials

Not applicable.

Author Contributions

JG, XJZ and CGX had the idea for the systematic review. HG and HYX contributed to the development and data curation and formal analysis. CGX led all authors conducted the standard methodology and investigation for systematic reviews in the series. XJZ, HG and XXF are in the charge of project administration and software conduction. The search strategy and sources management were developed by SHP and GPX. JG wrote the original manuscript of this protocol, which reviewed and edited the manuscript by XJZ and CGX. XJZ and CGX are the guarantors of the systematic reviews.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table1. Key terms for PubMed/MEDLINE search.

Search	Query
#1	“(COVID-19* OR 2019-nCoV* OR coronavirus disease 19* OR SARS CoV 2 Infection*)”
#2	“(moxabustion* OR moxibustion*)”
#3	“(random* OR randomly* OR placebo* OR single blind* OR double blind* OR clinical trials* OR randomized control trial* OR RCT* OR controlled clinical trials*)”
#4	#1 AND #2 AND #3 No limits

Figures

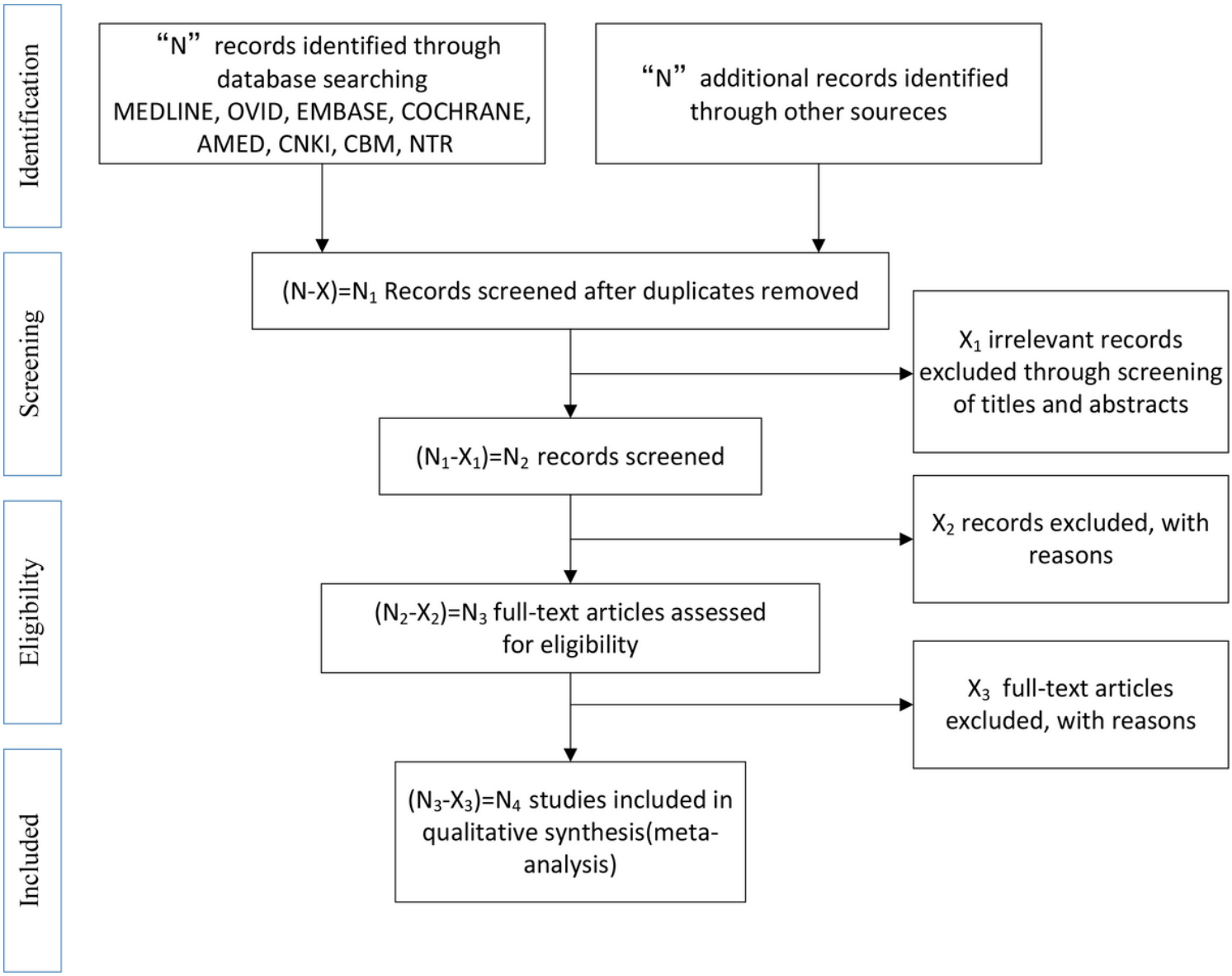

Figure 1

Flow Chart