Health Decision

PROTOCOL

Traditional Chinese medicine in treating corona virus disease 2019: A systematic review and cost-effectiveness analysis

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ABSTRACT

Background: Currently, corona virus disease 2019 (COVID-19) has affected 633,601,048 people worldwide according to World Health Organization, which leads to huge disease burden. A considerable number of trials of traditional Chinese medicine (TCM) have been carried out and have shown the efficacy of TCM in the treatment of COVID-19, but their cost-effectiveness has not been studied, especially in China. Therefore, we plan to perform a systematic review and cost-effectiveness analysis to explore the cost-effectiveness of using TCM in treating COVID-19.

Methods: A systematic review based on previously published secondary data from randomized controlled trials and observational studies which included TCM as one of the interventions for patients with COVID-19 will be performed. Patients with COVID-19 will be classified into five specific groups (patients without diagnosis; patients with mild, moderate, severe and critical symptoms). TCM versus western medicine on both effectiveness outcomes (cure rate and survival rate) and utility outcome (quality-adjusted life years [QALYs]) will be evaluated. A decision tree model will be established taking the perspective of Chinese health care system since the costs were paid by the Chinese government. Cumulative costs, QALYs, and incremental cost-effectiveness ratio will be selected as the outcome. Sensitivity analysis will also be conducted to evaluate the impact of parameter uncertainty on the base-case analyses. We will present results at various willingness-to-pay thresholds using a cost-effectiveness acceptability curve.

Discussion: We hope to demonstrate the cost-effectiveness of TCM, see an improvement in the patients' quality of life, achieve an improvement in the cure rate and survival rate of COVID-19. If TCM is cost-effectiveness, it could be applied to clinical practice.

Key words: traditional Chinese medicine, corona virus disease 2019, decision tree model, systematic review, cost-effectiveness analysis

INTRODUCTION

Till November 18, 2022, 633,601,048 people has been infected with syndrome coronavirus 2 (SARS-CoV-2) and diagnosed with corona virus disease 2019 (COVID-19),[1] which is the major public health burden in the world and has caused unprecedented social, economic and health systems disruptions. Millions of new cases are still increasing each week despite the rollout of vaccines in many countries and the recommended use of masks as well as other preventive measures to date. The direct economic cost of COVID-19 measures to reduce the spread of COVID-19 have been estimated at USD 7.7 trillion for the US alone[2] and have resulted in unprecedented increases in government debt in many countries.[3,4] According to a study based on US population,[5] a single symptomatic COVID-19 case would lead to a direct medical cost of $3045 during the course of the infection alone. Currently, paxlovid, remdesivir, and molnupiravir are recommended by several global

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guidelines to treat COVID-19.[6–8] However, several emerging variants have varying degrees of resistance to these drugs.[9] The prevalence of certain SARS-CoV-2 Omicron subvariants circulating has continued to rise in the past few weeks globally. The proportion of SARS-CoV-2 infections caused by subvariants that are likely to be resistant to tixagevimab plus cilgavimab is currently estimated to exceed 45% in all regions of the United States.[8]

After the outbreak of COVID-19, China always pursued the combination of traditional Chinese medicine (TCM) and western medicine (WM) to resist COVID-19,[7,10] including three prescriptions and three medicines (three medicines: Jinhua Qingxian Granules, Lianhua Qingxian Granules and Capsules, and Haibijing Injection; three prescriptions: Qingfei Paidu Decoction, Huashi Baidu Decoction, and Xuanfei Baidu Decoction).[11,12] Hu *et al.* conducted a randomized-controlled trial to show that Lianhua Qingxian Capsules could ameliorate clinical symptoms of COVID-19 considering safety and effectiveness.[13] Xiong *et al.* found that Xuanfei Baidu Decoction combined with conventional medicine might significantly improve patient's clinical symptoms, increase the number of white blood cells and lymphocytes to improve immunity.[14] Zhu *et al.* conducted a meta-analysis including 38 treatments and showed that TCMs were beneficial in treating mild or moderate COVID-19 patients.[15] Jiang *et al.* and Lei *et al.* provide evidence that treating COVID-19 with combined TCM and conventional WM was a potential treatment option for increasing clinical effective rate, improving the clinical symptoms, and preventing disease progression in COVID-19 patients.[12,16] Addition to listed evidence, many clinical trials, real world studies and meta-analyses have evaluated the safety and effectiveness of TCM in treating COVID-19 patients. However, whether the safety and effectiveness would be affected by variants and the cost-effectiveness of these therapies were still unknown.

In this study, we aim to explore the safety and effectiveness together with potential economic values of TCM monotherapy or combined therapy versus mainstream drugs in worldwide real-world practices.

METHODS

Protocol registration

This protocol has been reported under the guidance of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist[17] (see Supplementary Material 1) and will be reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement[18] and PRISMA.[19,20] The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number: CRD42021228887.

Meta-analysis

Inclusion criteria for study selection

Type of studies: We include randomized controlled trials (RCTs), cohort studies and other observational studies. Observational studies are considered for including in qualitative analysis since number of published RCTs might be limited. There will be no restrictions for blinding and follow-up. Language of the studies were limited to Chinese and English and there was no limitation on the publication time.

Type of participants: Participants diagnosed with COVID-19 in mainland China will be included in this study. This population will include people who were confirmed by nucleic acid testing, irregardless of whether they having COVID-19 infection like symptoms. According to the "New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 8)" and "Clinical Management of COVID-19"[21,22] we will classify all the patients into five specific population groups: (1) patients without diagnosis; and patients with (2) mild, (3) moderate, (4) severe, (5) critical symptoms. We particularly include patients without diagnosis because there might exist underreport of affection, so we also include this type of patients.

Type of interventions/comparators or control: Interventions including TCM, WM alone or combined are included. There is no strictly categorization of control group from the experiment group. There was no limitation on the number of herbs, administration methods, dosage, or duration of treatment for TCM.

All included studies may be within the following type of comparison: (1) Single-arm studies using TCM as intervention. (2) WM versus TCM. (3) WM+TCM versus WM. (4) Other possible comparisons (*e.g.* TCM versus Placebo). (WM: including Chloroquine, Hydroxychloroquine, Lopinavir/ritonavir, Remdesivir, Umifenovir, Favipiravir, Tocilizumab, Interferon-β-1α and so on. TCM: including Qingfei Paidu Decoction, Cold and Dampness Recipe, Xuanfei Baidu Recipe, Jinhua Qinggan Granules, Lotus Qingwen Capsules and other recipes and Chinese patent medicine.)

We exclude non-pharmacological interventions (including acupuncture, TaiChi, massage and so on) in this study because the number of publications may be very limited to be synthesized though they also belong to TCM.

Outcomes

Primary outcome: Our primary outcomes will be cure rate and survival rate. Time of cure will mainly be the duration of time from entering discharge given all patients would be admitted for compulsory treatment in mainland China.

Time of endpoint will be lengthened till complete follow-up for studies reporting re-admissions and deaths.

A patient is judged to be cured should meet the following criteria: (1) Body temperature returned to normal for more than 3 days; (2) respiratory tract symptoms improved significantly; (3) lung imaging showed significant improvement in acute exudative lesions; (4) two consecutive times consecutive respiratory tract specimens were tested negative for nucleic acid (at least 24 hours apart).[7]

Adverse reactions reported will also be included for safety and cost-effectiveness analysis.

Secondary outcome: Quality-adjusted life years (QALY) will be calculated if any research reports health utility.

Search strategy

The search will be conducted using the following databases or search platforms: PubMed, Embase, the Cochrane Library, ClinicalTrials.gov, medRxiv, Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database, SinoMed, and Wanfang database. Reference lists of relevant trials and reviews will also be searched. The detailed search strategy for PubMed will be shown in Table1. Similar strategies will be applied to the other databases (Examples for Embase and CNKI can be seen Supplementary Material 2 for detail).

Table 1: Search strategies for PubMed

No.	Search Items
#1	COVID-19 [Title/Abstract] OR novel coronavirus [Title/Abstract] OR 2019-nCoV [Title/Abstract] OR COVID 2019 pneumonia [Title/Abstract] OR SARS-CoV-2 [Title/Abstract] OR Corona Virus Disease 2019 [MeSH Terms]
#2	Randomized controlled trials [Title/Abstract] OR cohort study [Title/Abstract] OR observational study [Title/Abstract] OR cross-sectional study [Title/Abstract] OR randomized trials [Title/Abstract]
#3	Western medicine (including Chloroquine, Hydroxychloroquine, Lopinavir/ ritonavir and so on)
#4	traditional Chinese medicine (Qingfei Paidu Decoction, Jinhua Qinggan Granules, Lotus Qingwen Capsules and so on) OR Traditional Chinese Medicine [MeSH Terms]
#5	#3 AND #4
#6	(Influencing factors OR Mechanism) [Title]
#7	(Rat OR Pregnancy OR Mouse OR Animal OR Rabbit) [Title/Abstract]
#8	#6 AND #7
#9	#1 AND #2 AND #5 NOT #8

COVID-19: corona virus disease 2019; SARS-CoV-2: syndrome coronavirus 2.

Study collection

All retrieved papers will be imported into NoteExpress 3.2.0.7535 (AEGEAN, Beijing, China), and two reviewers will read the title and abstract of all identified studies, to select all candidate papers. All duplicates will be eliminated. After title and abstract screening, full text eligible papers will be obtained for further evaluation. If one reviewer is unsure of the eligibility of an article, the full paper will be reviewed again. In the case of differing opinions between the two reviewers, a third reviewer or other relevant authority will be consulted. All exclusions will be documented, along with the reasons for exclusion. The literature selection process will be illustrated in a flow diagram.

Data extraction

In order to extract accurate data, two investigators will independently perform the data extraction. We will extract data of basic study characteristics: first author, year of publication, trial information (duration of the trial, registration information, follow-up time), study design (*e.g.* randomized controlled trial, cohort study, observational study), population (*e.g.* sample size, age, sex, health status, inclusion and exclusion criteria), interventions (*e.g.* type and frequency of intervention, comparisons, dosage, type of health care), outcomes (primary and secondary outcomes specified and collected, time points reported), patient reported outcomes (the patient's expectations for the treatment results, the patient's understanding of the condition and so on), setting, and risks of bias. For RCTs, risks of bias were evaluated according to Cochrane Risk of Bias Tool,[23] which included sequence generation of the allocation; allocation concealment; blinding of participants, research personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. For observational studies, we will use the Newcastle-Ottawa (NOS) scale[24] to evaluate studies in terms of cohort/ population selection, comparability, exposure/outcome measures, and duration and completeness of follow-up. Any disagreement in the data extraction will be resolved through discussion between two investigators, with further disagreement decided by a third investigator or other relevant authority. (Example of a data extraction table can be found in Supplementary Material 2)

Data analysis

We will combine qualitative analysis on the basis of quantitative analysis to explore the adverse reactions in the treatment process of patients, the patient's expectations for the treatment results, the patient's understanding of the condition and so on. The results of qualitative analysis will refine our results and enhance the persuasion.

Statistical analysis will be conducted using the RevMan 5.3.5 (Cochrane Collaborations, London, UK). We will conduct analysis to provide effect estimates for continuous data and dichotomous data with 95% CI. Mean difference (MD) will be used for continuous data and risk ratios (RR) will be used for dichotomous data. The heterogeneity will be assessed by I^2 statistical test. If the I^2 is less than 50%, we will use the fixed-effect model. If the I^2 is more than 50%, the random-effects model will be used. What's more,

we will also find the possible reasons for high heterogeneity from both clinical and methodological perspectives and provide an explanation or conduct subgroup analysis (*e.g.* age, sex, region and variants).

Quality of evidence assessment

We will evaluate the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) evidence rating approach, which classifies the evidence as high, medium, low, and very low quality. According to the GRADE method,[25] we will measure the quality of evidence according to study limitations, imprecision, inconsistency, indirectness, and publication bias.

Dealing with missing data

If there are any unreported data, we will attempt to contact the authors to obtain the missing information. If the data are still unable to be retrieved, we will include the study in the descriptive analysis, and the impact of missing data will be described in the discussion section.

Health economic modeling and cost-effectiveness analysis

Model structure

Research perspective: A societal perspective will be applied, incorporating both direct and indirect costs.

A decision tree model will be established for the economic evaluation and an independent model constructed for each intervention.

Time horizon: The time horizon will be time till cure, death or recovery after readmission.

Model used: A decision tree model will be established for the economic evaluation as shown in Figure 1. We will establish an independent model for each specific group of patients.

Economic parameters

Effectiveness: Effectiveness will be estimated using primary and secondary outcomes. Both short-term efficacy (cure rate, less than one year), safety will be considered. Long-term effectiveness (more than one year) will be considered if data are enough. We will search for long-term effectiveness in published studies.

Prices: Prices of interventions reported in the literature will be entered into the model. If not reported in the literature, we will input weighted prices of drugs and medical services involved in the intervention by obtaining data from the Chinese public pricing systems (*e.g.* Menet, Yaozh).[26,27]

Utilities: Utilities will firstly be searched in included studies of the meta-analyses. If limited information are gained,

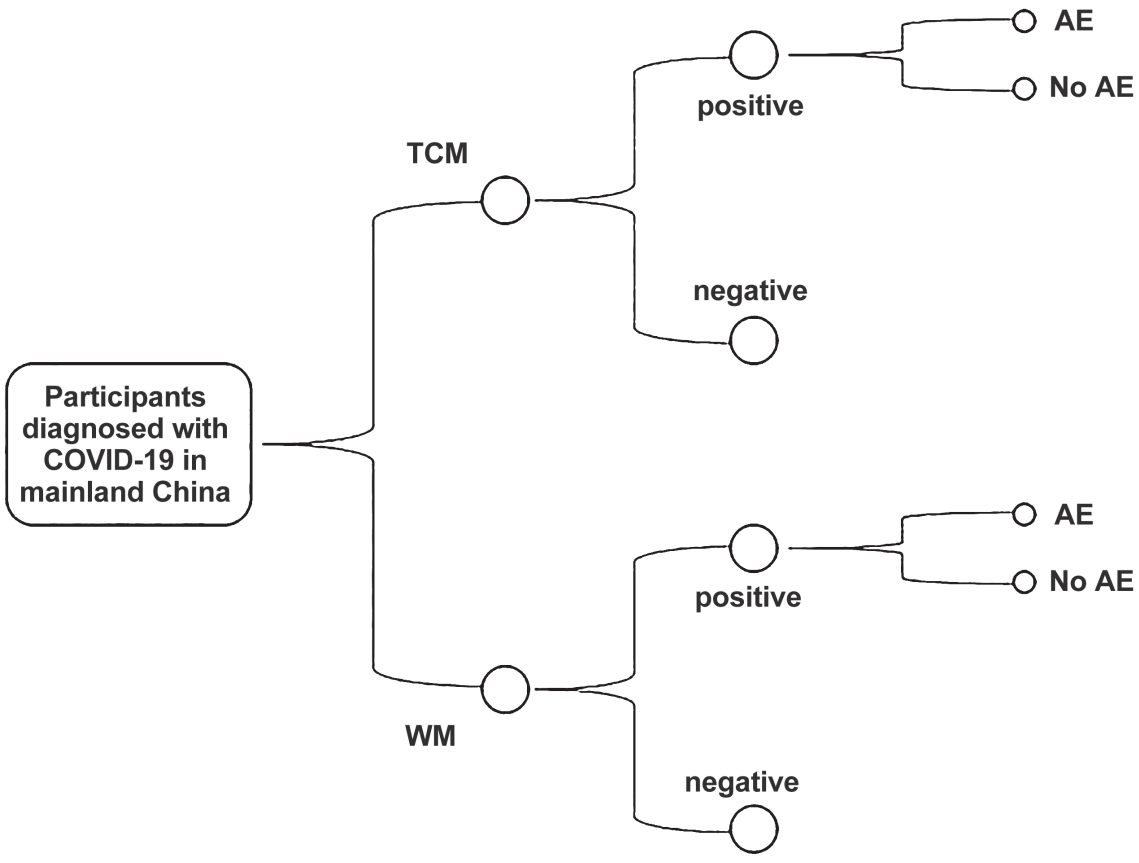

Figure 1. Decision tree model. TCM: traditional Chinese medicine; WM: western medicine; AE: adverse events; COVID-19: corona virus disease 2019.

we will search in other CEA studies which are related to COVID-19.

Discounting: For potential long-term effectiveness, a discount rate of 5% will be used. The rate we choose is in accordance with Chinese Guidelines for Pharmacoeconomics Evaluation 2020,[28] and is higher than typical discount rates basically due to a faster growing Gross Domestic Product (GDP) in China.

Incremental analysis

Decision indicator: The ICER is calculated using the following formula.

$$ICER \quad \frac{Cost\ of\ Intervention\ B\ than\ Intervention\ A}{Effect\ of\ Intervention\ B\ than\ Intervention\ A}$$

Incremental analysis process: (1) eliminate any option with absolute dominance; (2) sort the alternative intervention measures in ascending order of cost; (3) calculate the incremental cost-effectiveness ratio of the intervention with minimal cost versus zero-treatment and choose the one with cost-effectiveness (defined as ICER ≤ threshold of paying for one hypertensive patient effectively managed; (4) calculate the ICER of the second-smallest cost intervention with the remained option and run same decision; (5) make pairwise comparison in sequence until the final option is chosen.

Threshold: Since the willingness-to-pay for treating a COVID-19 patients is unknown an expert survey will be conducted to figure out the value.

Dealing with uncertainty

Model assumption: Usually, models of infectious diseases will include dynamic effectiveness for disease control, namely, if one patient had been cured, he/she could protect others from infection otherwise. In our study, we do not consider using dynamic models mainly because patients of COVID-19 are not allowed for discharge under rigid control. But we will include analysis counting for discharge-with-disease scenarios to estimate cost-effectiveness of treatments under usual disease control. In these scenario analysis, transmission dynamic models will be used to fully capture the impact of treatment.

Parameter sensitivity analysis: We will perform one-way sensitivity analysis as well as probabilistic sensitivity analysis (PSA) in the economic evaluation model. In one-way sensitivity analysis, we will use 95% CI of each single parameter as the interval; for unreported parameters, we assume they fluctuate by 20%–30% (allow for higher uncertainties). The results of the one-way sensitivity analysis will be presented in a tornado diagram. For PSA, we will use Monte Carlo simulation (10,000 iterations are expected). Prior distribution of the parameters will be applied, such as a beta distribution for, efficacy, safety, utility, mortality, and gamma distribution for costs. The PSA results will be presented with cost-effectiveness acceptability curve and incremental cost-effectiveness scatter plot.

DISCUSSION

Increasing evidences show that TCM has a good effect on the treatment of COVID-19,[12,15,16,29,30] but compared with western medicine, its clinical recognization is limited on a global scale.[6–8] In the treatment of COVID-19, some studies[12–16,29,30] have shown that Chinese medicine can reduce costs by shortening hospitalization days and reducing the number of concomitant medications when comparing with western medicine. At the same time, its efficacy and safety are not inferior. Therefore, some scholars believe that TCM may have advantages both clinically and economically.[12–16,29,30] Our study will explore the economic advantages of TCM compared with western medicine through cost-effectiveness analysis, aiming to provide economic evidence for clinicians to use TCM in treating COVID-19 as well as provide help for the rational allocation of clinical resources and the saving of medical costs.

However, this study has some limitations. First of all, we did not take into account that disease could spread among population when choosing the model given all patients were forced to stay in hospital until complete recovery since disease break out. Nonetheless, the results may still be biased. Second, adjustments will be needed in valuing interventions when estimating the costs. In addition, it's difficult to calculate the price of TCM since there are many kinds of TCM included in this study. Finally, the subjects included in the study are from mainland China, and due to limited source of patient-level data, there is difficulty in evidence extrapolation to other races. The results of this study may lead the way to promote global use of TCM. So that the evidence of clinical and economic value of TCM can be obtained in a wider range in the future.

DECLARATIONS

Author contributions

Xing Liao and Wenxi Tang: Conceptualization, Methodology, Software. Taihang Shao and Ke Wang: Data curation, Writing—Original draft preparation. Taihang Shao and Ke Wang: Visualization, Investigation. Wenxi Tang: Supervision. Taihang Shao and Ke Wang: Software, Validation. All authors: Writing- Reviewing and Editing.

Ethics approval

Ethics approval is not required for this systematic review and cost-effectiveness analysis. Because the data used

in this study is the secondary data from randomized controlled trials and observational studies. Our study started on Feb 2, 2021 and is supposed to be finished on Aug 2, 2023. Our study will explore the effectiveness and economic advantages of TCM compared with western medicine through systematic review and cost-effectiveness analysis. The results will be disseminated to the following groups for whom the results will be of interest: general public, clinicians, academics and policy makers. Findings from the study will be disseminated through peer-reviewed journals.

Source of funding
Not applicable.

Conflict of interest
Taihang Shao and Wenxi Tang are editors of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and his research group.

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