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Review Article

PROSPERO's systematic review protocols of traditional Chinese medicine for COVID-19: An overview

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ABSTRACT

Background: A large number of protocols for Systematic Reviews (SR) of Traditional Chinese Medicine (TCM) for coronavirus disease 2019 (COVID-19) have been registered in the International Prospective Register of Systematic Reviews (PROSPERO). This study aimed to analyze the innovativeness and rigorousness of the SR protocols and make recommendations for the design and implementation of future SRs on TCM for COVID-19. This effort is likely to enhance the value of the produced information and prevent the futility of the research.

Methods: PROSPERO was searched comprehensively for identifying SRs of TCM for COVID-19 from the inception of the database to August 2020. Two researchers independently screened the literature, extracted the data, and cross-checked the retrieved information for consistency. The following details were recorded: database, registration time, organizations, types of research included, participants, interventions, and outcome measures. All extracted data were analyzed by an overview. The "P - participants, I - interventions, C - controls, and O - outcomes (PICO)" included in the protocols were compared for similarity. The outcomes of the included SR protocols were compared with the newly published Core Outcome Sets (COSs).

Results: A total of 80 protocols of SR related to TCM for COVID-19 were obtained after a primary search, and finally 71 protocols were included. The majority of the protocols were from China. Thirty-two organizations participated in the protocol registrations, including 11 hospitals and 21 universities/colleges. However, some protocols were not innovative or rigorous enough, as the PICO of some protocols were similar and non-specific, and the searched literature was incomprehensive. In addition, COS is not commonly adopted.

Conclusions: Registering a protocol of SR is an effective way to ensure the usefulness of the produced information, and to avoid the duplication of research and the wastage of resources. In future SR protocols, it is important to focus on and solve the methodological problems such as non-specific PICO, incomprehensive literature retrieval, and improper outcome measures.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, resulted in a large-scale outbreak worldwide.[1] The global impact of the disease has been much higher than could have been foreseen.[2] Until 13th June 2021, COVID-19 has caused 3,792,777 deaths all over the world (https://covid19.who.int/). As an emerging disease, the diagnosis, treatment, and prognosis of COVID-19 need deep research.[1] To quickly control the spread of the epidemic and restore normalcy, researchers from all over the world have indulged in studies on COVID-19.

Traditional Chinese Medicine (TCM) has played an important role in the treatment of COVID-19 in China. Extensive studies have been carried out to evaluate the effectiveness of TCM for COVID-19.[3] Original studies need to be systematic reviewed to provide reliable evidence for clinical practice and decision-making.[4] Publishing a SR protocol with a robust methodological design before the conduct of the SR is the first step[5,6] that can guard against

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selective reporting and arbitrary decision making, facilitate transparency, and ensure reproducibility and usability of the SRs. [7,8]

The PROSPERO accepts any SR with a health-related outcome, and the new protocols for Cochrane have been added to it since November 2013.[7] Research has shown that until October 10, 2017, 26,535 SRs were registered in PROSPERO and that the monthly submission rates were up to 800.[7,9,10]

Since the outbreak of the epidemic, there was a significant increase of protocols in COVID-19.[2,11,12] A large number of SRs of TCM for COVID-19 have been registered in PROSPERO. However, whether these protocols are innovative and methodology are rigorous have not been evaluated.

This study analyzed the protocols of SRs on TCM for COVID-19 registered in PROSPERO to assess their innovativeness as well as rigorousness and make recommendations for the design and implementation of future SRs.

2. Methods

2.1. Eligibility criteria

2.1.1. Inclusion

(1) SR protocols on TCM for COVID-19 (referred to as "protocol") were included.
(2) All types of interventions in TCM were included. TCM includes Chinese herbal medicine, Chinese patent medicine, acupuncture, moxibustion, and traditional exercises.[13,14]
(3) All control measures and outcomes were eligible for inclusion in this overview.
(4) There was no language restriction.

2.1.2. Exclusion

(1) Non-SR protocols were excluded.
(2) All non-COVID-19 SR protocols, as well as protocols for COVID-19 combined with other diseases, were excluded.
(3) SR protocols focusing on non-TCM therapy were excluded.

2.2. Data sources and search strategy

PROSPERO was searched for SR protocols on TCM for COVID-19 from the date of inception to August 2020. All SRs in the Chinese medicine category of the PROSPERO COVID-19 filter were retrieved.

2.3. Literature selection and data extraction

Two researchers independently conducted literature screening according to the established inclusion and exclusion criteria. Literature that did not meet the inclusion criteria was excluded. Two researchers extracted the data and cross-checked for consistency; disagreements were resolved by discussion with a third researcher. The following details were recorded: registration ID, title, database, types of the study included, participants, interventions, outcomes, organizations, funding, and time of registration.

2.4. Statistical analysis

All extracted data were analyzed by an overview. The "P - participants, I - interventions, C - controls, and O - outcomes" included in the protocols were compared for similarity. "P" was sorted by similarity using Excel to distinguish between the different protocols. According to the above method, "I," "C," and "O" in the protocols were compared. Protocols that met the following conditions simultaneously were considered to be similar: 1) identical participants; 2) identical interventions or at least one of the interventions is the same; 3) identical controls or at least one of the controls is the same; 4) identical outcomes or at least one of the outcomes is the same.

The outcomes of the included protocols were compared with the newly published Core Outcome Sets (COSs). There were three COVID-19 COSs published.

The first COS—*Core Outcome Set for Clinical Trials on Coronavirus Disease 2019(COS-COVID)*[15]—was published by the Chinese Clinical Trials Core Outcome Set Research Center on March 18, 2020. The COS can be used for mild, ordinary, severe, critical, and rehabilitation period patient assessment, and consists of eight outcomes, such as, time to 2019-nCoV reverse transcription-polymerase chain reaction (RT-PCR) negativity, length of hospital stay, composite events, the score of clinical symptoms, arterial oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2), duration of mechanical ventilation, all-cause mortality, pulmonary function.

The Clinical Characterisation and Management Working Group of the WHO Research and Development Blueprint program, the International Forum for Acute Care Trialists, and the International Severe Acute Respiratory and Emerging Infections Consortium developed a *Minimal Common Outcome Measure Set for COVID-19 Clinical Research*.[16] This set was published on June 14, 2020, and includes three elements: a measure of viral burden (quantitative PCR or cycle threshold), a measure of patient survival (mortality at hospital discharge or 60 days), and a measure of patient progression through the healthcare system by use of the WHO Clinical Progression Scale.

Core Outcomes Set for Trials in People with COVID-19[17] was published by the University of Sydney on August 14, 2020, which informed the researchers that mortality, respiratory failure, multiple organ failure, shortness of breath, and recovery are the critically important outcomes to be consistently reported in COVID-19 trials.

3. Results

3.1. Selection of included protocol

Eighty protocols of SRs related to TCM for COVID-19 were obtained after a primary search. Nine protocols were excluded after full-text reading, including five protocols[18-22] for non-COVID-19, two protocols[23,24] for COVID-19 combined with other diseases, one protocol[25] for COVID-19 guidelines, and one protocol[26] for nature therapy. Finally, 71 protocols[27-97] were eligible for inclusion in this study. Information pertaining to the included protocols is shown in Supplement 1 and Supplement 2.

3.2. Distribution of countries and organizations

Among these protocols, 66 were from China, 1 from Australia,[89] 1 from Singapore,[92] and 1 from Canada.[61] "China & Australia"[59] and "China & England"[39] comprised one protocol each. Thirty-two organizations participated in these protocol registrations, including 11 hospitals and 21 universities/colleges. The Chengdu University of TCM participated in 16 protocol registrations (Figure 1).[28,31,38,41-43,57,66,71,72,74,76,82,88,96,97]

3.3. Innovativeness of the protocols

Among the protocols registered by different organizations, some protocols had similar "P-participants, I - interventions, C-control, and O-outcomes,"(PICO). For example, the PICO of two protocols were similar (n = 22);[40,45,47,48,50,52,56,57,60,62,63,71,72,76,81,82,86,87,89,92-94] the PICO of three protocols were similar (n = 12);[27,36,53,59,65-68,74,78,80,95] and even as many as 7 protocols[28,31,32,44,51,55,70] had similar PICO (n = 7). These protocols add up to 41, more than half of the

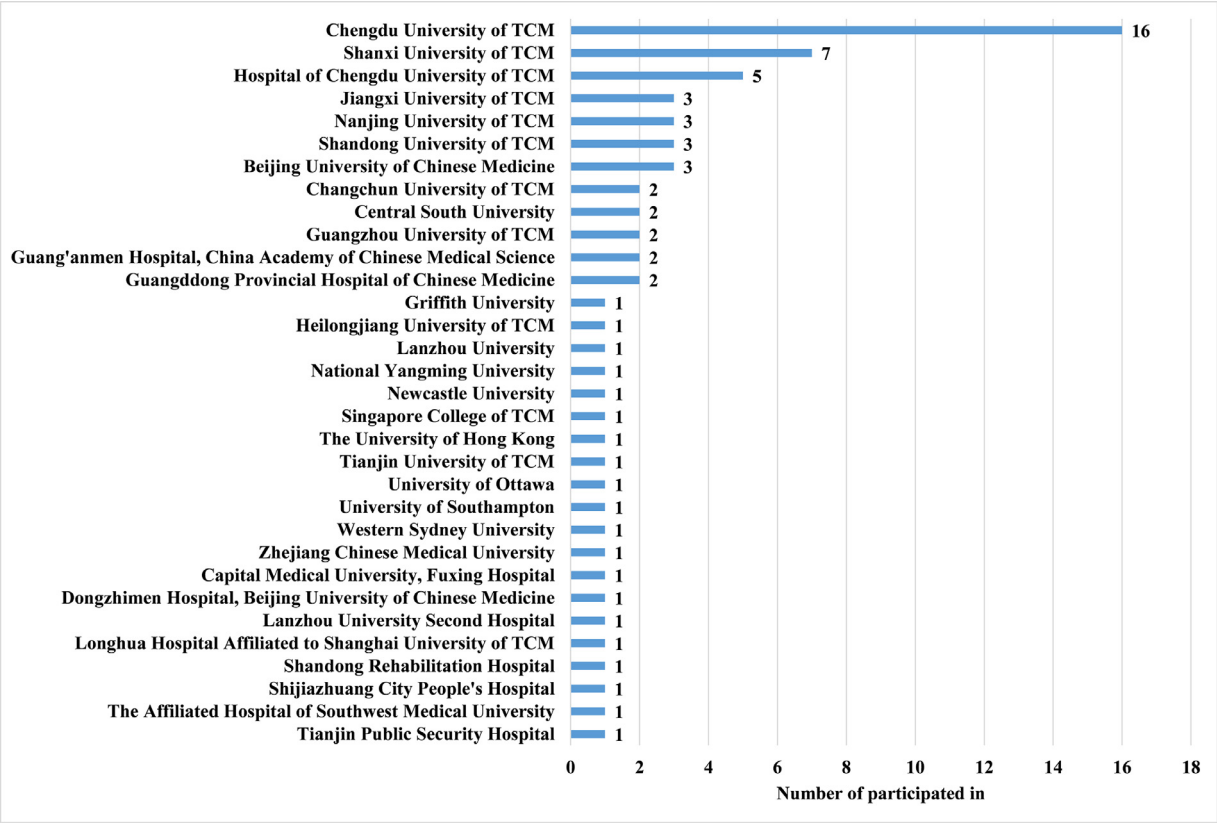

Figure 1. The distribution of organizations

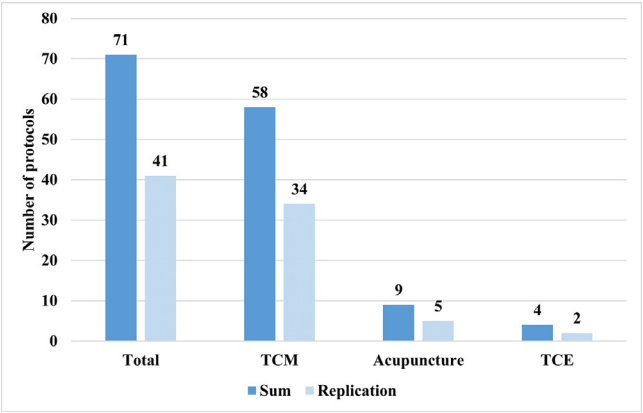

Figure 2. The similarity level of the protocols

included protocols. Among the 41 protocols, 34 were about Chinese medicine (patent medicine, injection, and decoction),[28,31,32,40,44,47,48,50-53,55,57,59,60,62,63,66-68,70,71,74,76,78,80,81,86,87,89,92-95] 5 were about acupuncture,[27,36,65,72,82] and 2 were related to traditional exercises.[45,56] These protocols were related to the effectiveness or safety of TCM for COVID-19 (Figure 2).

3.4. Databases included for literature search

Seventy protocols reported to include Chinese databases for literature search, of which 45[27-32,35,37,38,41,42,45,47-49,51-53,56-58,63-67,69,74,76,77,79,80,83-88,90,91,93-97] included 4 databases (CNKI, CBM, VIP, and Wanfang) for their search. The CNKI was the most frequently included database. A total of 142 English databases were included among all 71 protocols. and one of them[70] included 6 English databases. Ten protocols[27,38,45,47,55,56,76,83,84,88] included 5 English databases for search. Approximately 50% of the protocols included more than 3 English databases. Embase was the most frequently included database as it was included in 68 studies.[27-32,34-85,87,88,90-97] Thirty protocols[27-34,45-47,50,53,55-58,64,68,70,77,79,80,82-84,87,88,92,97] supplementarily included clinical trial protocol platforms, including eight such platforms. The Chinese Clinical Trial Registry and ClinicalTrials.gov were the most frequently included platforms (Figure. 3).

3.5. Types of included studies

Randomized controlled trial (RCT) was the most included type, followed by observational studies and controlled trials. Two protocols[29,89] reported including all trials but did not describe the specific type of trials. Two protocols[94,95] did not state the types of studies included.

3.6. Participants

Among the 71 protocols, the inclusion criteria for participants were not rigorous in 4 protocols.[29,33,39,43] Among the other 67 protocols, only 18 protocols[34,35,37,41,42,49,54,57,58,69,73,75,84,85,88,89,96,97] defined the specific types of participants, including disease severity, patient age, symptoms, and population. The remaining 49 protocols[27,28,30-32,36,38,40,44-48,50-53,55,56,59-68,70-72,74,76-83,86,87,90-95] only reported confirmation of the participants as COVID-19 positive without any other restrictions.

In addition, only four protocols[40,48,49,70] reported reference guidelines for the diagnosis of COVID-19, three[48,49,70] of which referred to WHO's Diagnostic Criteria of Confirmed or Suspected

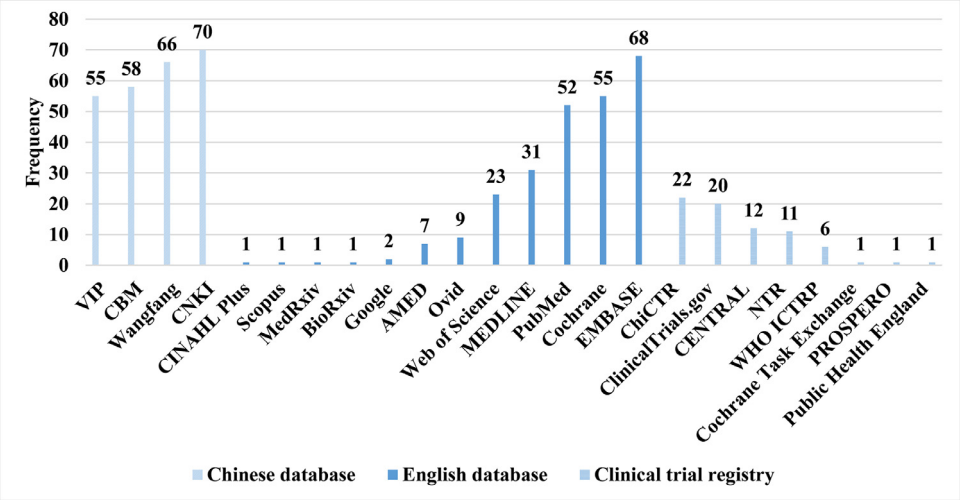

Figure 3. The frequency of databases included for literature search.

COVID-19 and one[40] referred to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Version 7) issued by the National Health Commission of China.

3.7. Interventions

The intervention categories of the 71 protocols included Chinese medicine, acupuncture, moxibustion, traditional exercises, etc. Only 28 protocols[29-31,33-35,37,39,40,47,63,66-68,74,75,77,78,80,83,85-87,90-92,94,95] reported specific interventions, as follows: Lianhua-Qingwen capsules/granules (n = 13),[29,30,33,35,37,47,66,68,75,77,78,80,92] Jinhua-Qinggan capsules/granules (n = 7),[33,47,68,77,83,85,92] Shufeng-Jiedu capsules/granules (n = 4),[39,40,68,94] Tanreqing capsule (n = 1),[77] Xuanfei-Baidu granules (n = 1),[33] and Huoxiang-Zhengqi capsules/granules (n = 1);[68] Xuebijing injection(n = 8)[33,34,67,74,77,87,92,95], Xiyanping injection(n = 2),[77,87] Tanreqing injection(n = 1),[87] Reduning injection(n = 1),[87] Xingnaojing injection(n = 1),[87] Shenfu injection(n = 1),[87] Shengmai injection(n = 1),[87] and Shenmai injection (n = 1);[87] Qingfei-Paidu decoction (n = 5),[33,47,63,86,92] Maxing-Shigan decoction (n = 2),[31,47] Huashi-Baidu decoction (n = 2),[33,92] Yupingfeng powder (n = 1),[47] Xuanfei-Baidu decoction (n = 1),[92] and Pingwei powder (n = 1).[31]

3.8. Outcomes

Seventy-one protocols reported the outcomes. The number of outcomes adopted in the protocols ranged from 1 to 15. Totally, 76 kinds of outcomes were present, and 3 of them were reported for more than 35 times, were adverse event (n = 42),[27,28,30-32,35-37,39,40,42,45-49,54-58,60,62,65,67,71-73,75-81,85,87,88,92,95-97] time of disappearance of main symptoms (n = 39),[27-33,35,39-41,44-47,51,54-57,63,65-67,70-72,78,79,82,86,88-93,97] and mortality (n = 36), respectively.[27,28,31,32,36,38,40,43-47,51,54-57,60,62,63,65,71-73,75-78,82,85-89,95,96] Fifty-one of them were reported for less than five times. The reported frequencies of the outcomes are listed in Table 1.

3.8.1. Analysis of outcomes with COSs

No protocol completely reported all core outcomes of the published COSs. Different protocols covered different outcomes from COSs.

3.8.1.1. COS for Clinical Trials on Coronavirus Disease 2019 (COS-COVID). Eight outcomes of *COS for Clinical Trials on Coronavirus*

Table 1
The reported frequency of outcomes

Outcomes	Frequency
Adverse events	42
Time of disappearance of main symptoms	39
Mortality	36
Length of hospital stay	27
Laboratory indicators	26
CT	25
Effective rate	24
Severe conversion rate	23
Curative rate	22
Rate of 2019-nCoV RT-PCR negativity	20
Improvement of symptoms	18
Adverse reactions	16
Accompanying symptoms disappear rate	14
Safety measurements	12
Serum cytokine levels	11
Time to 2019-nCoV RT-PCR negativity	10

Note: Outcomes (frequency <10): Lung functions, Quality of life, Survival rate, Rate of aggravation, Duration of mechanical ventilation, Nucleic acid detection, Hospitalization rate, Recovery time, The frequency of oxygenation; Outcomes (Frequency <5): TCM symptoms, Time to return to normal for laboratory measures, Chest radiograph, Score of clinical symptoms, Dosage and treatment time of broad-spectrum antiviral drug, Body temperature, Disease duration, HAMD (Hamilton Depression Scale), IES-R (Impact of Event Scale-Revised), Pcl-c (The PTSD Checklist Civilian Version), Rate of severe patients, The rate of appearance of main symptoms, Usage of hormone, Length of ICU stay, Frequency of respiratory progression, Rate of chest imaging recovery, Biological results, Blood pressure, Chronic conditions, COVID-19 attack rate, Duration of oxygen intaking, HAMA (Hamilton Anxiety Scale), Kidney function, Liver function, The incidence of sequelae, Productivity of healthy baby, Severity of dyspnea on Visual Analogue Scale or Borg Scale, St Georges respiratory questionnaire (SGRQ), Turn to intensive rate, The score of TCM symptom, Proportion of participants with fever, Proportion of participants with one or more adverse events, PSQI (Pittsburgh Sleep Quality Index), SAS (Self-Rating Anxiety Scale), SDS (Self-Rating Depression Scale), 6-min walk test (6MWT), Viral load, Clinical remission rate, Converting to clinical diagnosis rate, CPR (cardiopulmonary resuscitation), Disappearance time of pulmonary shadows in X ray, Discomfort symptoms, Duration of each symptom, Frequency of composite events, Medical image, Mental health, Pregnancy condition, Recurrence rate after cure, Respiratory parameters (FiO2, PaO2, PEEP, and PaCO2), Time to clinical response (TTCR), Sequential organ failure assessment (SOFA).

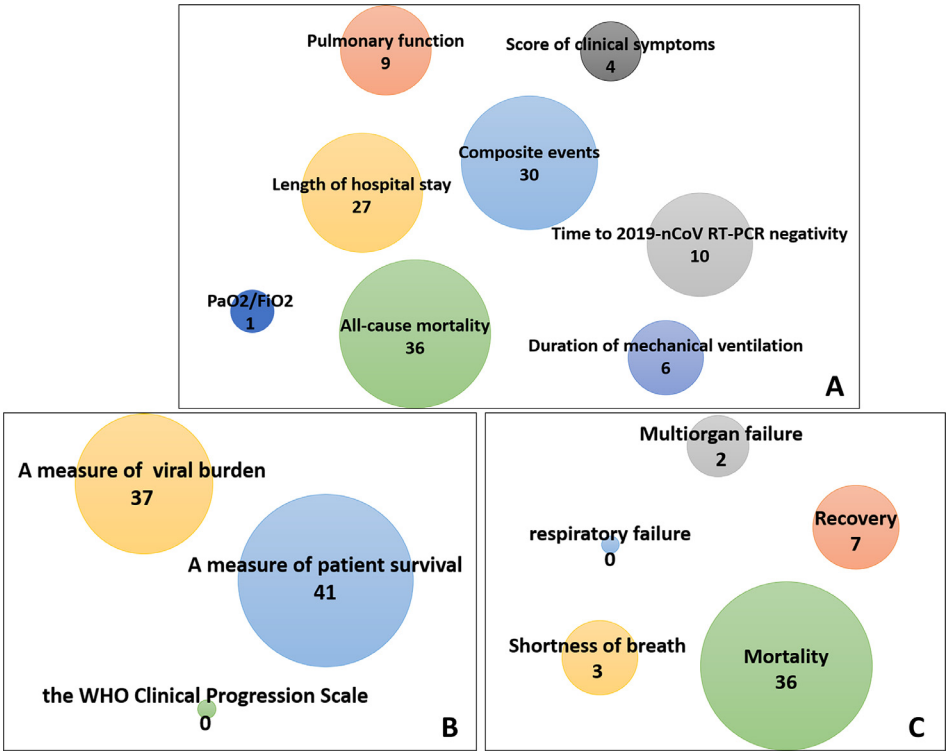

Figure 4. The usage frequency of core outcomes. (A) COS for Clinical Trials on Coronavirus Disease 2019 (COS-COVID), (B) A Minimal Common Outcome Measure Set for COVID-19 Clinical Research, and (C) COS for Trials in People with COVID-19

Disease 2019(COS-COVID) [15] are shown in Figure 4A. Fifty-eight protocols[27-33,35,36,38-40,43-51,54-58,60-73,75-80,82,85-89,92-97] used at least one outcome of the COS, of which six protocols[43,50,54,60,79,97] reported the maximum number of core outcomes, i.e., up to four. Time to 2019-nCoV RT-PCR negativity, the score of clinical symptoms, PaO_2/FiO_2, duration of mechanical ventilation, and pulmonary function were not reported in most SR protocols. Especially, PaO_2 and FiO_2 were reported in only one protocol[43] (Figure 4A).

3.8.1.2. A Minimal Common Outcome Measure Set for COVID-19 Clinical Research. Three outcomes of *A Minimal Common Outcome Measure Set for COVID-19 Clinical Research*[16] are depicted in Figure 4B. Forty-nine protocols[27,28,31,32,36-40,43-57,60,62,63,65-69,71-73,75-79,82,85-89,95-97] employed at least one outcome of the COS. Twenty-six protocols[27,28,32,38,45-49,54-57,63,65,67,71-73,75,76,78,79,82,88,97] reported the maximum number of core outcomes, i.e., up to 2. The WHO Clinical Progression Scale was not employed in any of the protocols (Figure 4B).

3.8.1.3. COS for Trials in People with COVID-19. Five outcomes of *COS for Trials in People with COVID-19*[17] are shown in Figure 4C. Forty protocols[27,28,31,32,36,38-40,43-47,50,51,54-57,60,62,63,65,70-73,75-78,82,85-89,92,95,96] used at least one outcome of the COS, of which mortality was most frequently employed (n = 36).[27,28,31,32,36,38,40,43-47,51,54-57,60,62,63,65,71-73,75-78,82,85-89,95,96] A few protocols used respiratory failure, multiorgan failure, shortness of breath, and recovery as the outcomes (Figure 4C).

4. Discussion

After analyzing the protocols of SRs on TCM for COVID-19 registered in PROSPERO, we found that more than half were similar and were aimed at similar clinical conditions. Furthermore, their participants, interventions, control, and outcomes (PICO) were comparable and hence not innovative.

Protocol registration is the first and critical step in the process of SR. The purpose of registration is to ensure transparency and usability of the protocols. Therefore, the design of the protocols must be rigorous.

SRs are characterized by a systematic and replicable methodology and presentation, which involve a comprehensive search and a systematic integration of the search results.[98] Several clinical studies pertaining to TCM for COVID-19 have been published in Chinese journals and have been listed in Chinese databases. Therefore, Chinese databases and English databases both are important. Twenty-six protocols[33,34,36,39,40,43,44,46,50,54,55,59-62,68,70-73,75,78,81,82,89,92] did not perform a comprehensive search on Chinese databases, which may lead to data missing, selection bias and language constraints. Besides, 30 protocols[27-34,45-47,50,53,55-58,64,68,70,77,79,80,82-84,87,88,92,97] additionally searched clinical trial protocol platforms, which are the key sources of SRs and warrant attention.

SR is a synthesis of all the relevant studies on a specific clinical topic.[99] The homogeneity of the included studies is critical to the reliability of the evidence synthesis results. SRs of RCTs are located on the top of the evidence pyramid.[100] Most protocols reported the specific type of studies included, and RCT was the most common one. However, two protocols[29,89] only reported that all trials were included and did not describe the specific type of trials, and two[94,95] did not report the included studies.

PICO, a method to construct clinical problems,[101] needs to be strictly defined for accurate clinical questions and meaningful SRs. However, only 18 protocols[34,35,37,41,42,49,54,57,58,69,73,75,84,85,88,89,96,97] identified the specific type of participants, such as disease severity, patient age, symptoms, and population. In addition, four protocols[29,33,39,43] were not rigorous in the criteria for the included participants.

Differences in the diagnostic criteria of the participants mean that the comparability of the subjects is low, which reduces the credibility of the comprehensive results.

TCM was the most widely used intervention in the protocols, but only 28 protocols[29-31,33-35,37,39,40,47,63,66-68,74,75,77,78,80,83,85-87,90-92,94,95] reported the specific medicine. Some protocols only reported the name of the Chinese medicine and did not provide information on dosage form, dosage frequency, course of treatment, and follow-up time, which may weaken the evidence evaluation and decision-making of the SR.

A total of 76 kinds of outcomes were reported in the included protocols. Among the three outcomes reported most frequently (>35 times), only mortality was recommended by the COSs. The outcome of a protocol is the key point for evaluating the effect of the intervention. COS is an agreed-upon standard set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or healthcare.[102] COS can not only improve the practicability of the results but also reduce the inhomogeneity and the risk of selective reporting of the outcomes in clinical trials and enhance the value of the research results.[103] Therefore, the use of COS in SRs/meta-analysis of evidence evaluation and decision-making is advocated.[15] At present, three COSs[15-17] for COVID-19 have been published. *Clinical Trials on Coronavirus Disease 2019 (COS-COVID)*[15] was published on March 18, 2020. Since then, 70 protocols[27-96] have been registered, of which 57 used these core outcomes.[27-33,35,36,38-40,43-51,54-58,60-73,75-80,82,85-89,92-96] *A Minimal Common Outcome Measure Set for COVID-19 Clinical Research*[16] was published on June 14, 2020. The included protocols that were registered before its publication were 66,[27-35,41-97] of which 44 used these core outcomes;[27,28,31,32,43-57,60,62,63,65-69,71-73,75-79,82,85-89,95-97] 5 protocols[36-40] were registered after its publication, all of which used the outcomes. *COS for Trials in People with COVID-19*[17] was published on August 14, 2020. Prior to its publication, 71 included protocols were registered, of which 40 used these core outcomes.[27,28,31,32,36,38-40,43-47,50,51,54-57,60,62,63,65,70-73,75-78,82,85-89,92,95,96] However, 10 protocols did not use any of the outcomes among the three COSs.[34,41,42,59,74,81,83,84,90,91] Failing to use the COS might mean that the results of the studies could not be combined, thereby hampering the research value.[103-105]

COVID-19 is now the hot research topic worldwide. Until August 2020, 148 COVID-19 clinical studies on TCM have been registered in the China Clinical Trial Registration Center (http://www.chictr.org.cn/) and ClinicalTrials.gov (http://www.clinicaltrials.gov) (Supplement 3). At the same time, up to 71 SR protocols on TCM for COVID-19 have been registered in PROSPERO. It was found that the growth rate of TCM clinical studies did not catch up with that of the SRs. The TCM SRs for COVID-19 may be over-registered. Researchers should focus on trying to solve the contentious issues associated with COVID-19, including vaccines, public health, mental health, and economics,[2] instead of repeating studies.[106] Multiple clinical studies have been carried out. However, most of these terminated due to limited clinical resource. Uncompleted clinical studies will not be included in SRs, which may weaken the quality of evidence. Moreover, similar SRs being conducted by different research groups is a waste of time. In addition, some organizations have registered nearly 20 protocols in the short term, which may lead to inefficient management of the procedural conduct of single research, thereby influencing the reliability of the results.

Based on the result of this study, several points need to be considering and improving. First, SR should not be repeated within a short time. Secondly, an innovative and rigorous SR should be registered and implemented, enhancing the value of the obtained information. Thirdly, a comprehensive search should be carried out to locate all relevant published and unpublished literature.[98] Chinese databases and clinical trial registration platforms should be adopted. Rigorous inclusion criteria for COVID-19 patients should be devised based on authoritative diagnostic guidelines. The details of the intervention must be clearly reported, rather than general "TCM" or "Acupuncture". The main outcomes need to refer to the published COSs. Finally, correct outcome measures should be reported.

This study performed an overview of the SR protocols included in PROSPERO. So the results of this study can not be generalized to all the protocols of SRs for COVID-19 with TCM. Generally, SR protocols for COVID-19 with TCM are not rigorous enough. Some problems, such as non-specific PICO, incomprehensive literature retrieval and improper outcome measures, need to be solved in future studies.

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Author contributions

Conceptualization: JZ and HW.
Investigation: HH, ZJ, CF, WP, and ZC.
Formal Analysis: HH, ZJ, CF, WP, and ZC.
Writing – Original Draft: HH and ZJ.
Writing – Review & Editing: JZ and HW.

Conflict of Interest

The authors have no conflict of interests to declare.

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Ethical statement

This study is an overview of the literature; thus, ethical approval was not needed.

Data availability

The data used to support the findings of this study are included within the article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100774.

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