Chinese herbal medicine used with or without conventional western therapy for COVID-19: an evidence review of clinical studies

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Abstract

Objective To present the evidence of the effectiveness and safety of Chinese herbal medicine (CHM) used with or without conventional western therapy on COVID-19.

Methods Clinical studies on effectiveness and safety of CHM for COVID-19 were included. We summarized general characteristics of included studies, evaluated methodological quality of randomized controlled trials (RCTs) using the Cochrane risk of bias tool, analyzed the use of CHM, used Revman 5.4 software to present the risk ratio (RR) or mean difference (MD) with their 95% confidence interval (CI) to estimate the effectiveness and safety of CHM.

Results A total of 58 clinical studies were identified including RCTs (17.24%, 10), non-randomized controlled trials (1.72%, 1), retrospective studies with a control group (18.97%, 11), case-series (20.69%, 12) and case-reports (41.38%, 24). No high methodological quality RCTs were identified. The most frequently tested Chinese patent medicine, Chinese herbal medicine injection or prescribed herbal decoction were: Lianhua Qingwen granule/capsule, Xuebijing injection and Maxing Shigan Tang. In terms of aggravation rate, pooled analyses showed that there had statistical differences between the intervention group and the comparator group (RR 0.46, 95% CI 0.30 to 0.68, 7 RCTs; RR 0.37, 95% CI 0.22 to 0.64, 4 retrospective studies with control group), that is, CHM plus conventional western therapy appeared better than conventional western therapy in reducing aggravation rate. In addition, compared with conventional western therapy, CHM plus conventional western therapy had potential advantages in increasing the resolution rate and shortening the duration of fever, cough and fatigue, improving the negative conversion rate of nucleic acid test, and increasing the number of patients with inflammatory disappearance or shortening the time from receiving treatment to beginning of inflammation disappearance. For adverse events, pooled data showed that there was no statistical difference between the CHM and the control groups.

Conclusion Current low certainty evidence suggests that there maybe a tendency that CHM plus conventional western therapy is superior to conventional western therapy alone. The use of CHM did not increase the risk of adverse events.

1 Introduction

Novel coronavirus pneumonia (NCP), officially named as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO)[1], is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) which has affected the general population. The main symptoms of COVID-19 are fever, dry cough and fatigue, and may be accompanied by nasal congestion, runny nose, sore throat, diarrhea, or loss of taste and smell anosmia.[2] In traditional Chinese medicine, COVID-19 is classified within the pestilential (Yibing, 疫病) category. The National Health Commission of the People's Republic of China has incorporated COVID-19 into the category B infectious diseases as stipulated in the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases, and carried out prevention and control management following category A infectious diseases. On 11 March 2020, the director-general of World Health Organization (WHO), Dr Tedros Adhanom Ghebreyesus, declared that COVID-19 was now characterized as a pandemic[3], that is, COVID-19 had spread worldwide, and posed a great challenge and threat to the existing public health resources.

At present, there is no specific and effective therapy for the treatment and prevention of this disease.[4,5] Traditional Chinese medicine (TCM) has accumulated thousands of years of experience on the use of Chinese herbal medicine (CHM) to prevent and treat infectious diseases[6]. Its success was initially substantiated by modern human clinical research on severe acute respiratory syndrome (SARS) and H1N1 influenza epidemics, suggesting that using historical CHM experience may be a worthwhile approach.[7] As this current epidemic escalated into a pandemic, the National Health Commission of the People's Republic of China has released multiple editions of guidelines for the diagnosis and treatment of COVID-19 (hereinafter referred to as GDT of COVID-19). In the third edition[8], CHM was recommended for the treatment of COVID-19, and all relevant medical institutions were required to actively encourage of the use of CHM in the treatment of COVID-19. The early application of CHM during the COVID-19 pandemic and appeared to have a potentially beneficial effects. CHM has increasingly shown its potential in the treatment and prevention for infectious diseases, and has received widespread attention.

To further probe the role of CHM used with or without conventional western therapy on the treatment of COVID-19, an evidence-based approach was employed to systematically collate, analyze and evaluate clinical studies on the effectiveness and safety of using CHM for COVID-19.

2 Materials and methods

2.1 Inclusion and exclusion criteria of studies

The following criteria were used to identify relevant studies.

Inclusion criteria were as follows: (1) Clinical studies which aimed to evaluate the effectiveness and/or safety of CHM used with or without conventional western therapy in patients with COVID-19; (2) There were no limits on the study design and could be randomized controlled trials (RCT), non-randomized controlled trials (non-RCT), cohort studies, case series, case reports or other study designs; (3) Participants were patients diagnosed with COVID-19. Disease severity could be mild, common, severe or critical, as prescribed in the guideline for the diagnosis and treatment of COVID-19 formulated by the National Health Commission of the People's Republic of China. There was no limitation on participants' age, gender and their ethnicity, or the setting of the studies; (4) The interventions in the experimental group were CHM and included prescribed herbal decoctions, oral

Chinese patent medicines (capsules, tablets or granules) or Chinese herbal medicine injection, or CHM combined with comparators. For controlled clinical studies, comparators could be conventional western therapy or placebo.

Exclusion criteria were: (1) The full text of the studies could not be obtained; (2) Any duplicated articles; (3) Registered clinical studies but had not started or completed; (4) Clinical studies that had been registered and completed but had not published research data, and the data which could not be obtained by contacting the authors; (5) If the registered protocol and published articles were from the same study, the protocol was excluded.

2.2 Retrieval platforms and search strategies of studies

Studies were retrieved through nine electronic databases including: China National Knowledge Infrastructure (CNKI, as of April 30, 2020), Wanfang Database (from January 1 to April 30, 2020), the China Science Technology Journal Database (VIP, from January 1 to April 30, 2020), SinoMed (from January 1 to April 30, 2020), PubMed (from January 1 to April 30, 2020), Embase (from January 1 to April 30, 2020), BioRxiv (as of April 30, 2020), MedRxiv (as of April 30, 2020), arXiv (as of April 30, 2020) and clinical trial registration platforms (CTRPs) including ClinicalTrials.gov (www.clinicaltrials.gov, as of April 30, 2020) and Chinese Clinical Trial Registry (ChiCTR, www.chictr.org/cn, as of April 30, 2020).

For the databases/CTRPs with COVID-19 thematic platforms, including CNKI and ClinicalTrials.gov, the search was performed directly in the COVID-19 thematic platform. For Wanfang, VIP, SinoMed, PubMed and Embase, search terms were used. The search terms included Xinxing Guanzhuang Bingdu Bing (新型冠状病毒病), Xinguan Feiyan (新冠肺炎), 2019 Guanzhuang Bingdu Bing (2019 冠状病毒病), coronavirus disease-19, COVID-19, 2019 novel coronavirus, 2019-nCOV, NCP, Zhongyi (中医), Zhongyao (中药), Caoyao (草药), Tangji (汤剂), Zhongchengyao (中成药), Zhusheji (注射剂), Zhongxiyi Jiehe (中西医结合), Chinese medicine, traditional Chinese medicine, herbal medicine, decoction, patent medicine, injection, integrated Chinese and western medicine. For ChiCTR, title search was carried out using Xinxing Guangzhuang Bingdu (新型冠状病毒) and COVID-19 as search terms. For BioRxiv, MedRxiv and arXiv, title or abstract search was carried out using COVID-19 as search terms. Appendix 1 shows the search strategies for the nine electronic databases and CTRP.

Before submission, we updated the search and included the latest published studies that met the inclusion criteria.

2.3 Study selection and data extraction

Published studies were screened according to the inclusion/exclusion criteria by titles, abstracts and (or) full texts of the published articles. Registered studies were screened according to the inclusion/exclusion criteria by reading the titles and details of registered protocols. SBL, YYZ, CS, CHL, YQL, BYL and ZYT were responsible for the selection of articles.

Excel 2010 was used to provide the data sheets for extraction. Extracted items include first author's name or registered protocol's ID, study titles, the country in which the study was carried out, study design, characteristics of participants (such as sample size, age, gender, severity of COVID-19, etc.), details of interventions and outcomes, etc. For each included study, two authors independently extracted and checked the data. The inconsistencies were resolved by the two authors through

consultation. If any disagreements, a third author (JPL) was consulted. LSB, YYZ, YQL, CS, BYL, ND, YJ, XWZ, CHL, YPZ and MX participated in data extraction in pair.

2.4 Outcomes

Primary outcomes included cure rate, mortality rate and aggravation rate.

Secondary outcomes included the disappearance rate or the duration of main symptoms (including fever, cough and fatigue), negative conversion rate of nucleic acid test for SARS-Cov-2, inflammatory disappearance on chest CT, length of hospitalization and adverse events.

2.5 Design of this review and data synthesis

This is an evidence review of clinical studies on the effectiveness and safety of CHM used with or without conventional western therapy on COVID-19. Initially, we summarized the general characteristics of the included studies and then the methodological quality of included RCTs was assessed by SBL and YQL using the Cochrane risk of bias tool[9]. Subsequently, counts and percentages were applied to analyze the use of CHM. Lastly, we evaluated the effectiveness and safety of CHM used with or without conventional western therapy on COVID-19. For studies without control group, such as case series and case reports, we only presented these findings qualitatively as they were not sufficient to probe the therapeutic effect of CHM for COVID-19 due to the absence of control and a high risk of bias in case selection. For studies with control group, we used Cochrane Collaboration Review Manager 5.4 (Revman 5.4) software to conduct meta-analysis of the data. We presented binary data as a risk ratio (RR) with its 95% confidence interval (CI), and continuous data as a mean difference (MD) with its 95% CI. Considering potential sources of clinical heterogeneity, the random-effect model (REM) was used for meta-analysis. We planned to conduct the following subgroup analysis for the primary outcomes if data were available: (1) subgroup analysis based on the severity of COVID-19, to detect whether the effectiveness of CHM is related to the severity; (2) subgroup analysis based on the use of CHM with or without conventional western therapy, to detect whether CHM alone or whether CHM plus conventional western therapy is more beneficial for treatment of COVID-19.

3 Results

3.1 Search results

Fig.1 shows the flow diagram for the searching and screening of published articles. A total of 4763 published articles were retrieved from the above-mentioned nine open electronic databases, of which 102 articles were selected by reading full-texts and 54 were removed for various reasons. Finally, 48[10-57] published articles (representing 48 completed studies) met the inclusion criteria. Before submission, we updated the search and included 10 further completed studies[58-67] that met the inclusion criteria. Fig. 2 shows the flow diagram for searching and screening of registered clinical studies. A total of 1669 registered protocols were retrieved from the above-mentioned two CTRPs and 50 registered protocols (50 registered clinical studies) meeting the inclusion criteria. However, all the 50 registered studies were excluded due to their status as ‘not yet started’ or ‘in progress’.

Therefore, 58 published articles[10-67] (representing 58 completed studies) were included in our review.

Insert Fig.1

Insert Fig.2

3.2 The characteristics of included 58 clinical studies

All the 58 clinical studies were conducted in China. Of these, 52 were published in Chinese[10-15,17,18,20-53,57-66] and 6 were in English[16,19,54-56,67]. Among the included studies, 10 (17.24%) were RCTs[10-16, 58-59, 67], one (1.72%) was non-RCT[17], 11 (18.97%) were retrospective studies with control group[18-27,60], 12 (20.69%) were case-series[28-37,61,62], 24 (41.38%) were case-reports[38-57,63-66].

Of 2773 COVID-19 patients involved in the included studies, 1921 (69.28%) received CHM. The level of severity of COVID-19 involved non-serious (including mild and common) and serious (including severe and critical). Of the included 58 studies, 29 (50.00%) studies[10-14,17,18,20,23,25,27,28,34-38,41,49-51,57-61,63,66,67] included only non-serious patients, 12 (20.69%) studies[16,22,30,31,44,45,47,48,53,55,56,65] included only serious patients, 11 (18.97%)[15,19,24,26,29,32,39,42,46,54,62] included both non-serious and serious patients, and the remaining 6 (10.34%) studies[21,33,40,43,52,64] did not report the level of severity of COVID-19.

Of the included 58 studies, 8 (13.79%)[29,40,42,51,56,57,63,64] involved the alone use of CHM, and 51 (87.93%)[10-28,30-39,41,43-50,52-56,58-62,65,66] involved CHM used in combination with conventional western therapy (such as abidor, ganciclovir, lopinavir, oxygen inhalation, nutritional support, etc.). The course of treatment varied from 4 to 15 days.

Table 1 shows the characteristics of the 58 included studies.

Insert Table 1

3.3 Methodological quality of RCTs

In terms of the random sequence generation methods of the included 10 RCTs[10-16,58,59,67], 6 RCTs[10-13,58,67] used random number tables, 2 trials[15,16] used a simple random allocation method and the remaining 2 RCTs[14,59] only mentioned random without describing the detailed randomization method. Two RCTs[16,67] performed allocation concealment. Therefore, the risk of selection (allocation) bias was unclear for the majority of the included RCTs due to lack of information on allocation concealment. Due to no trials used blinding to participants and personnel, the performance bias of all the included trials was judged as high-risk. Two RCTs[16,67] performed outcome assessor blinding and the remaining 8 RCTs[10-15,58,59] did not report relevant information, thus the detection bias for majority of the included RCTs was judged as unclear-risk. In terms of attrition bias, 8 RCTs[11-13,15,16,58,59,67] were assessed as low-risk of bias due to complete outcome data or incomplete outcome data being adequately addressed, 2 RCTs[10,14] were assessed as high-risk due to incomplete outcome data that were not adequately addressed. Two RCTs[16,67] registered the study protocol and reported the registration information. By comparison, we found that there was no selective reporting of outcomes in these two RCTs, so their reporting bias was evaluated as low-risk. Since the protocols or registration information of the other 8 included RCTs[10-15,58,59] were not available, the selective reporting of outcomes in these RCTs could not be judged and the reporting bias of these was assessed unclear-risk. All 10 RCTs reported the comparability of baseline data, so they were assessed as having a low-risk of other bias.

Fig.3 demonstrates the risk of bias of included 10 RCTs.

Insert Fig.3

3.4 Analysis of the use of CHM

For the type of CHM, 24 (41.38%) studies[10-14,17-19,23-27,31,34,36,38,39,51,53,54,56,57,60] tested oral Chinese patent medicine, 40 (68.97%) studies[15,16,21,22,24,26,28-35,37,39-53,55,58,59,61-66,67] tested prescribed herbal decoction, and 7 (12.07%) studies[20,22,24,31,34,41,65] tested Chinese herbal medicine injection.

The top ten CHMs used were Maxing Shigan Tang [麻杏石甘汤, 15.52% (9/58)], Lianhua Qingwen granule/capsule [连花清瘟颗粒/胶囊, 15.52% (9/58)], Xuebijing injection [血必净注射剂, 8.62% (5/58)], Dayuanyin [达原饮, 8.62% (5/58)], Shufeng Jiedu capsule[疏风解毒胶囊, 8.62% (5/58)], Qingfei Paidu Tang [清肺排毒汤, 6.90% (4/58)], Xiaochaihu Tang [小柴胡汤, 6.90% (4/58)], Ganlu Xiaodu Dan [甘露消毒丹, 5.17% (3/58)], Liujunzi Tang [六君子汤, 5.17% (3/58)] and Toujie Quwen granule [透解祛瘟颗粒, 5.17% (3/58)]. Of which, the most frequently used Chinese patent medicine, Chinese herbal medicine injection and prescribed herbal decoction were Lianhua Qingwen granule/capsule [连花清瘟颗粒/胶囊], Xuebijing injection [血必净注射剂], and Maxing Shigan Tang [麻杏石甘汤], respectively.

Table 2 lists the CHM used at least twice.

Insert Table 2

3.5 Effectiveness and safety of CHM in the treatment or adjuvant treatment of COVID-19

3.5.1 Analysis for studies with control group

3.5.1.1 Primary outcomes

3.5.1.1.1 Cure rate

Five studies including one RCT[14] and 4 retrospective studies with control group[21-24] reported this outcome. All 5 studies adopted the judgment criteria of the GDT of COVID-19 for cure: (1) the body temperature returned to normal for longer than three days; (2) the respiratory symptoms improved significantly; (3) the pulmonary imaging showed that the inflammation has obviously disappeared; (4) the respiratory pathogenic nucleic acid, (the sampling time interval of 2 tests was at least 1day or 24 hours), and the results were both negative.

All 5 studies compared CHM plus conventional western therapy with conventional western therapy. After analyzing separately according to the study design, the results regardless of RCTs or retrospective studies with control group showed that there was no statistical difference between the experimental and control groups (RR 1.42, 95% CI 0.76 to 2.62, 1 RCT; RR 1.20, 95% CI 0.98 to 1.48, 4 retrospective studies with control group).

Insert Fig.4

3.5.1.1.2 Aggravation rate

A total of 13 studies[10-13,16,18,21,24,26,27,58,60,67] that compared CHM plus conventional western therapy with conventional western therapy reported on this outcome. Of these, 2 retrospective studies with a control group[26,27] reported that there were no patients who experienced aggravation in either the experimental or control group. After analyzing separately according to the study design of the

remaining 11 studies, the results of RCTs or retrospective studies with control group both showed that CHM plus conventional western therapy was better than conventional western therapy alone in reducing aggravation rate (RR 0.46, 95% CI 0.30 to 0.68, 7 RCTs[10-13,16,58,67]; RR 0.37, 95% CI 0.22 to 0.64, 4 retrospective studies with control group[18,21,24,26,27,60]). Fig.5 illustrates the details of these results.

Insert Fig.5

3.5.1.1.3 Mortality rate

Five studies[10,16,22,24,67] that compared CHM plus conventional western therapy with conventional western therapy reported this outcome. After analyzing separately according to the study design, the results regardless of RCTs or retrospective studies with control group showed that there was no statistical difference between the experimental and control groups (RR 0.45, 95% CI 0.09 to 2.13, 3 RCTs[10,16.67]; RR 0.66, 95% CI 0.35 to 1.27, 2 retrospective studies with control group[22,24]).

Insert Fig.6

3.5.1.2 Secondary outcomes

The results on secondary outcomes are shown in Table 3.

Insert Table 3

3.5.1.2.1 The disappearance rate and the duration of main symptoms (fever, cough and fatigue)

a. The disappearance rate of main symptoms

A total of 6 studies[11,12,15,18,25,60] including 3 RCTs[11,12,15] and 3 retrospective studies with control group[18,25,60] reported the disappearance rate of main symptoms. All studies compared CHM plus conventional western therapy with conventional western therapy. Of these, the number of studies that reported the disappearance rate of fever, cough and fatigue was 6[11,12,15,18,25,60], 6[11,12,15,18,25,60] and 5[11,12,18,25,60], respectively.

Studies which explored the resolution rate for fever, after analyzing separately according to the study design, although the pooled data of retrospective studies with control group showed that CHM plus conventional western therapy was better than conventional western therapy alone (RR 1.34, 95% CI 1.13 to 1.58, 3 retrospective studies with control group), the pooled result of RCTs showed that there was no statistical difference between the experimental and control groups (RR 1.18, 95% CI 0.88 to 1.60, 3 RCTs, I^2 = 69%).

Regarding studies which investigated the disappearance rate of cough, the results of RCTs or retrospective studies with control group both showed that CHM in combination with conventional western therapy was superior to conventional western therapy alone (RR 1.37, 95% CI 1.15 to 1.64, 3 RCTs; RR 1.82, 95% CI 1.22 to 2.71, 3 retrospective studies with control group).

Studies reporting the disappearance rate of fatigue following COVID-19, the results regardless of RCTs or retrospective studies with control group showed that CHM plus conventional western therapy had a higher disappearance rate than conventional western therapy alone (RR 1.37, 95% CI 1.02 to 1.83, 2 RCTs; RR 1.48, 95% CI 1.14 to 1.93, 3 retrospective studies with control group).

b. The duration (time to resolution) of main symptoms

A total of 10 studies[17,18,21,23-25,58-60,67] including 3 RCTs[58,59,67], 1 non-RCT[17] and 6 retrospective studies with control group[18,21,23-25,60] reported the duration of main symptoms and all of them compared CHM plus conventional western therapy with conventional western therapy. Of these, the number of studies that reported the duration of fever, cough and fatigue was 10[17,18,21,23-25,58-60,67], 7[17,18,21,23,58-60] and 6[17,18,23,58-60], respectively.

For the duration of fever, one study[67] reported that, the CHM group exhibited a significant improvement in time to fever resolution (P = 0.035) compared with the control group. After analyzing separately in light of the other 9 studies' design[17,18,21,23-25,58-60], the results regardless of RCTs, non-RCT or retrospective studies with control group showed that CHM plus conventional western therapy was better than conventional western therapy alone (MD -2.08 days, 95% CI -2.90 to -1.26, 2 RCTs, I^2 = 60%; MD -0.83 days, 95% CI -1.22 to -0.44, 1 RCT; MD -1.54 days, 95% CI -1.82 to -1.26, 6 retrospective studies with control group).

In shortening the duration of cough, the results regardless of RCTs or retrospective studies with control group showed that CHM plus conventional western therapy was superior to conventional western therapy alone (MD -2.34 days, 95% CI -3.32 to -1.37, 2 RCTs, I^2 = 56%; MD -1.68 days, 95% CI -1.92 to -1.43, 4 retrospective studies with control group). However, the results from one non-RCT showed that there was no statistical difference between the experimental and control groups (MD 0.28 days, 95% CI -0.40 to 0.96, 1 non-RCT).

Regarding those studies reporting the duration of fatigue as secondary outcome, both RCTs and retrospective studies with control group showed better effect for the CHM plus conventional western therapy when compared with conventional western therapy alone (MD -2.35 days, 95% CI -2.91 to -1.79, 1 RCT; MD -1.75 days, 95% CI -2.01 to -1.49, 3 retrospective studies with control group). However, the result from one non-RCT showed that there was no statistical difference between the two groups (MD -0.33 days, 95% CI -0.78 to 0.12, 1 non-RCT).

3.5.1.2.2 Negative conversion rate of nucleic acid test for SARS-Cov-19

A total of 3 retrospective studies with control group[20,23,27] reported this outcome and all compared CHM plus conventional western therapy with conventional western therapy. Pooled data from 3 studies showed that CHM in combination with conventional western therapy was superior to conventional western therapy alone (RR 1.32, 95% CI 1.05 to 1.66) in improving the negative conversion rate of nucleic acid test for SARS-Cov-19.

3.5.1.2.3 Inflammatory disappearance on chest CT

A total of 16 studies[10,12,13,15,17-22,24,26,27,58-60] reported this outcome and all compared CHM plus conventional western therapy with conventional western therapy.

Of these, 14 studies[10,12,13,15,17,18,20,22,24,26,27,58-60] reported the number of patients with inflammatory disappearance on chest CT (assessed as effective, effective rate = the number of patients with inflammatory disappearance on chest CT / the total number of patients in experimental or control group × 100%). After analyzing separately according to the study design, the results regardless of RCTs or non-RCT showed that CHM plus conventional western therapy was better than conventional western therapy alone (RR1.28, 95% CI 1.10 to 1.49, 6 RCTs; RR 1.21, 95% CI 1.05 to 1.40, 1 non-RCT). However, the pooled results from 7 retrospective studies with control group showed that there

was no statistical difference between the experimental and control groups (RR 1.23, 95% CI 1.00 to 1.52, 7 retrospective studies with control group, I^2 = 67%).

The other 2 retrospective studies with control group[19,21] reported the time from receiving treatment to the beginning of inflammation disappearance and the pooled analysis from the 2 studies showed that CHM plus conventional western therapy was superior to conventional western therapy alone in shortening the time (MD -2.23 days, 95% CI -2.46 to -2.00, 2 retrospective studies with control group).

3.5.1.2.4 Length of hospitalization

A total of 4 retrospective studies with control group[22,24,26,58] reported length of time in hospital as an outcome. All 4 studies compared CHM plus conventional western therapy with conventional western therapy. The pooled analysis from the 4 studies showed that there was no statistical difference between the experimental and control groups (MD -0.42 days, 95% CI -3.49 to 2.64, I^2 = 95%) in shortening the length of hospitalization.

3.5.1.2.5 Adverse events

A total of 16 studies[10,11,13-15,17,19-24,27,59,60,67] reported this outcome and all compared CHM plus conventional western therapy with conventional western therapy. Of these, 8 studies[10,13,14,19,24,27,59,60] reported that no adverse events occurred in either the experimental or control group. Pooled data from the other 8 studies[11,15,17,20-23,67] showed that there was no statistical difference between the experimental and control groups (RR 2.06, 95% CI 0.34 to 12.38, 3 RCTs[11,15,67]; RR 1.00, 95% CI 0.21 to 4.84, 1 non-RCT[17]; RR 0.87, 95% CI 0.26 to 2.93, 4 retrospective studies with control group[20-23]). The adverse events reported in these 8 studies were mild abdominal pain, diarrhea, nausea, vomiting and drug allergy, etc.

3.5.1.3 Subgroup analysis

As all controlled studies compared CHM plus conventional western therapy with conventional western therapy, we failed to perform the subgroup analysis based on the use of CHM with or without conventional western therapy. Therefore, we only conducted the subgroup analysis based on the level of severity of COVID-19 (non-serious, serious or a mix of non-serious and serious) for primary outcomes.

With regard to cure rate, although a pooled data of 5 studies that reported this outcome showed that CHM plus conventional western therapy was superior to conventional western therapy in improving it (RR 1.21, 95% CI [1.01, 1.45]), the results of the subgroup analysis based on the level of severity of COVID-19 showed that there was no statistical difference between the experimental and control groups (RR 1.69, 95% CI 0.72 to 3.92, 2 studies[14,23] involving 143 non-serious patients; RR 1.17, 95% CI 0.91 to 1.50, 1 study[22] involving 103 serious patients; RR 1.23, 95% CI 0.87 to 1.72, 2 studies[21,24] involving 112 patients, a mix of non-serious and serious, I^2 = 62%).

Regarding aggravation rate, a total of 11 studies[10-13,16,18,21,24,58,60,67] that reported this outcome were used to conduct meta-analysis, and the results from the 11 studies showed that CHM plus conventional western therapy was better than conventional western therapy alone in reducing aggravation rate (RR 0.42, 95% CI 0.31 to 0.59). Of which, 8 studies[10-13,18,58,60,67] included only patients with non-serious COVID-19, and pooled data from the 8 studies showed that CHM plus conventional western therapy was better than conventional western therapy (RR 0.42, 95% CI 0.29 to

0.61, 8 studies). One study[16] included only patients with serious COVID-19, the results showed that there was no statistical difference between the experimental and control groups (RR 1.00, 95% CI 0.10 to 10.11, 1 study). The remaining 2 studies[21,24] included both non-serious patients and serious patients with COVID-19, and the results from the 2 studies showed a lower aggravation rate in the experimental group compared with the control group (RR 0.36, 95% CI 0.14 to 0.93, 2 studies).

For mortality rate, a total of 5 studies[10,16,22,24,67] were included, and pooled data from 5 studies showed that there was no statistical difference between the experimental and control groups (RR 0.62, 95% CI [0.34, 1.14]) in reducing mortality rate. The results of the subgroup analysis based on the level of severity of COVID-19 showed that there was also no statistical difference between the two groups (RR 0.43, 95% CI 0.06 to 2.86, 2 study[10,67] involving 342 non-serious patients; RR 0.69, 95% CI 0.36 to 1.31, 2 studies[16,22] involving 145 serious patients; RR 0.18, 95% CI 0.01 to 4.23, 1 study[24] involving 52 patients, a mix of non-serious and serious).

3.5.2 Analysis of case series and case reports

A total of 12 case series[28-37,61,62] and 24 case reports[38-57,63-66] were included in our review. Of which, one case series[29] and 7 case reports[40,42,51,56,57,63,64] involving 111 patients only used CHM, and 11 case series[28,30-37,61,62] and 19 case reports[38,39,41,43-50,52-56,65,66] involving 828 patients used CHM plus conventional western therapy. The authors of the 36 articles concluded that CHM with or without conventional western therapy was beneficial for the treatment of COVID-19.

With regard to 111 patients who received CHM treatment for a period of time from 4 to 11 days, one case series and one case report involving 100 patients reported that 42 patients were cured (42/100), 7 case reports involving 13 patients reported that 13 patients were negative for nucleic acid test (13/13), one case series and 6 case reports involving 54 patients reported that 30 patients with the disappearance of fever (30/54), one case series and one case report involving 71 patients reported that 17 patients with the disappearance of cough (17/71), one case series involving 75 patients reported that 20 patients with the disappearance of fatigue (20/75), one case series and 5 case reports involving 96 patients reported that 87 patients (87/96) showed improvement of inflammatory disappearance on chest CT.

For 828 patients who received CHM plus conventional western therapy for a period of time from 6 to 15 days, 4 case series and 6 case reports involving 641 patients reported that 561 patients were cured (561/641), 6 case series and 16 case reports involving 182 patients reported that 179 patients were negative for nucleic acid test (179/182), 5 case series and 13 case reports involving 271 patients reported that 258 patients with the disappearance of fever (258/271), 5 case series and 3 case reports involving 437 patients reported that 284 patients with the disappearance of cough (284/437), 5 case series and 2 case reports involving 327 patients reported that 212 patients with the disappearance of fatigue (212/327), and 3 case series and 11 case reports involving 525 patients reported that 483 patients (483/525) showed improvement of inflammatory disappearance on chest CT. In addition, there were 3 case series which reported adverse events. Of these, 2 case series reported that no adverse events occurred, and the remaining reported that 7 patients with the treatment of CHM plus conventional western therapy experienced adverse events including vomiting (4), dizziness (2) and rash (1).

4 Discussion

Although RCT is the gold standard to evaluate the effectiveness of interventions, but it cannot answer all important questions about a given intervention.[68] Considering the characteristics of sudden

acute infectious diseases and the practical problems of ethics and informed consent, the implementation of RCT faces more challenges under conventional medical conditions.[69] Many questions in medical research are investigated in observational studies having a role in research into the benefits and harms of medical interventions[68,70], having an important reference for the preliminary evaluation of the effectiveness of CHM and clinical decision-making. In this case, other types of studies (eg. non-RCT, retrospective studies, case-series) were included in our review.

4.1 Summary of the main findings

A total of 58 clinical studies whose purpose were to evaluate the effectiveness of CHM used with or without conventional western therapy on COVID-19 were included. The included studies involved RCTs, non-RCT, retrospective studies with control group, case-series and case-reports. In total the studies involved 2773 COVID-19 patients, 1921 (69.28%) of them received CHM. The severity of COVID-19 varied from non-serious (mild and common) and serious (severe and critical). Most of the studies used a combination of CHM and conventional western therapy. Analysis of the frequency of different CHM indicated that the most frequently used Chinese patent medicine, Chinese herbal medicine injection and prescribed herbal decoction were Lianhua Qingwen granule/capsule, Xuebijing injection, and Maxing Shigan Tang, respectively.

This review suggested that CHM in combination with conventional western therapy appeared better than conventional western therapy alone in reducing aggravation rate, increasing the disappearance rate or shortening the duration of main symptoms (fever, cough and fatigue), improving the negative conversion rate of nucleic acid test, and increasing the number of patients with inflammatory disappearance according to chest CT or alternative demonstrated a reduction in the time needed from receiving treatment to beginning of inflammation disappearance. For the primary outcomes, subgroup analyses were conducted based on the level of severity of COVID-19 and suggested that CHM in combination with conventional western therapy had more significant effect than conventional western therapy in reducing aggravation rate for non-serious patients.

In terms of reducing mortality rate and shortening the length of hospitalization, there was no statistical difference between the CHM combined conventional western therapy group and the conventional western therapy group. Although some studies have reported adverse events (eg. mild abdominal pain, diarrhea, nausea and vomiting) in the CHM plus conventional western therapy group, but there was also no statistical difference between the experimental and control groups. This suggests that the use of CHM did not increase the risk of adverse events.

Although in this review there were no pooled results for CHM used alone from controlled studies for COVID-19, one case-series and seven case-reports that were included reported that CHM alone may play a positive therapeutic role in the treatment of COVID-19.

4.2 Strengths and limitations

This review systematically collected the evidence from clinical studies whose purpose was to evaluate the effect and safety of CHM with or without conventional western therapy on COVID-19. Relevant clinical studies were analyzed from the aspects of general characteristics, quality assessment, analysis of the use of CHM and comprehensive effect and safety evaluation of CHM for COVID-19 patients, providing important evidence for future related research.

However, this review did not summarize the specific administration methods of CHM in all included studies, especially considering the complexity of prescribed herbal decoction use, which

may require further specific research in the future. Therefore, this review cannot be directly used to guide clinical practice. In addition, all included studies were conducted in China, whether this evidence is equally applicable to other countries outside China needs further international study.

4.3 Implications for further research

The benefits for the use of CHM for COVID-19 needs to be verified by more rigorous designed and implemented clinical trials, especially randomized controlled trials. The following points should be noted when conducting relevant RCTs: (1) Clear reporting of random allocation and random concealment; (2) Application of blinding to participants, personnel (doctors), outcome evaluators and statistical analysts; (3) Design and register the study protocol; (4) Definition of important outcomes, such as time to cure, aggravation and mortality; (5) Selection of CHM: considering the difficulty in the use of herbal decoction (eg, dosage of herbal medicien, especially about its use outside China), we suggest that trials of Chinese patent medicine or herbal injection should be given priority to verify the effects and safety of these two, so as to find safe, effective and convenient medications to cure more COVID-19 patients as soon as possible. Unfortunately, in our this research, we did not to perform subgroup analysis on Chinese patent medicine, herbal injection and prescribed herbal decoction. But next, we will give priority to the relevant evidence review of existing clinical studies on the treatment of COVID-19 with Chinese patent medicine.

5 Conclusion

Current low certainty evidence suggests that there maybe a tendency that CHM plus conventional western therapy is superior to conventional western therapy alone. The use of CHM did not increase the risk of adverse events.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

JPL and SBL conceived and designed the review. SBL, YYZ, CS, YQL, BYL, CHL and ZYT were responsible for the searching, screening and selecting studies. LSB, YYZ, QY, CS, BYL, ND, YJ, XWZ, CHL, YPZ and MX participated in data extraction. SBL and YQL assessed the risk of bias of the included trials. SBL performed the statistical analysis. YYZ, YQL, BYL and ND helped to perform the statistical analysis. SBL drafted the manuscript. JPL, YZ, NR, CS and YYZ were all involved in critically revising the manuscript. All authors have read and approved the final manuscript. All authors approved the final version of the article, including the authorship list.

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Statement

All data included in this study were supported by nine electronic databases for published studies and two clinical trial registration platforms. Appendix 1 shows the details of the nine databases and two clinical trial registration platforms.

Appendix 1 Search strategies for the nine electronic databases and clinical trial registration platforms (CTRP)

Databases/ CTRP	Search strategy	Time limit
CNKI	Since CNKI has set up a thematic platform for COVID - 19, the "treatment" section of the platform was selected for manual retrieval.	As of April 30, 2020
VIP	#1: M = Xinxing Guangzhuang Bingdu Bing(新型冠状病毒病) OR Xinguan Feiyan (新冠肺炎) OR 2019 Guanzhuang Bingdu (2019 冠状病毒病) OR COVID-19 OR 2019-nCOV OR NCP #2: M = Zhongyi (中医) OR Zhongyao (中药) OR Caoyao (草药) OR Tangji (汤剂) OR Zhongchengyao (中成药) OR Zhusheji (注射剂) OR Zhongxiyi Jiehe (中西医结合) #3: #1 AND #2	From January 1 to April 30, 2020
Wanfang	#1: Major Topic: "Xinxing Guangzhuang Bingdu Bing (新型冠状病毒病)" + "Xinguan Feiyan (新冠肺炎)" + " 2019 Guanzhuang Bingdu Bing (2019 冠状病毒病)" + "COVID-19" + "2019-nCOV" + "NCP" #2: Major Topic: "Zhongyi (中医)" + "Zhongyao (中药)" + "Caoyao (草药)" + "Tangji (汤剂)" + "Zhongchengyao (中成药)" + "Zhusheji (注射剂)" + "Zhongxiyi Jiehe (中西医结合)" #3: #1 AND #2	From January 1 to April 30, 2020

SinoMed	#1: ("Xinxing Guangzhuang Bingdu Bing (新型冠状病毒病)"[标题:智能] OR "Xinguan Feiyan (新冠肺炎)"[标题:智能] OR "2019 Guanzhuang Bingdu Bing (2019 冠状病毒病)"[标题:智能] OR "COVID-19"[标题:智能] OR "2019-nCOV"[标题:智能] OR "NCP"[标题:智能]) #2: ("Zhongyi (中医)"[标题:智能] OR "Zhongyao (中药)"[标题:智能] OR "Caoyao (草药)"[标题:智能] OR "Tangji (汤剂)"[标题:智能] OR "Zhongchengyao (中成药)"[标题:智能] OR "Zhusheji (注射剂)"[标题:智能] OR "Zhongxiyi Jiehe (中西医结合)"[标题:智能]) #3: #1 AND #2	From January 1 to April 30, 2020
PubMed	(((corona virus disease-19 OR COVID-19 OR 2019 novel coronavirus OR 2019-nCOV OR NCP[MeSH Major Topic])) AND (Chinese medicine OR traditional Chinese medicine OR herbal medicine OR decoction OR patent medicine OR injection OR integrated Chinese and western medicine[MeSH Major Topic])) AND ("2020/01/01"[Date - Publication] : "2020/04/30"[Date - Publication])	From January 1 to April 30, 2020
Emabse	#1: ab,ti: corona virus disease-19 OR COVID-19 OR 2019 novel coronavirus OR 2019-nCOV OR NCP #2: ab,ti: Chinese medicine OR traditional Chinese medicine OR herbal medicine OR decoction OR patent medicine OR injection OR integrated Chinese and western medicine #3: #1 AND #2	From January 1 to April 30, 2020
ChiCTR	Title search was carried out using Xinxing Guangzhuang Bingdu (新型冠状病毒) and COVID-19 as search terms.	As of April 30, 2020
ClinicalTrials.gov	Searched in covid-19 special registration section.	As of April 30, 2020
BioRxiv, MedRxiv, arxiv	Title or abstract search was carried out using COVID-19 as search terms.	As of April 30, 2020

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Figure legends

Fig.1 Flow diagram for searching and screening of published articles

Fig.2 Flow diagram for searching and screening of registered clinical studies

Fig.3 Risk of bias graph of included 10 RCTs

Fig.4 Forest plot of cure rate: CHM plus conventional western therapy versus conventional western therapy

Fig.5 Forest plot of aggravation rate: CHM plus conventional western therapy versus conventional western therapy

Fig.6 Forest plot of mortality rate: CHM plus conventional western therapy versus conventional western therapy

Table 1 The characteristics of included studies of Chinese herbal medicine for COVID-19

Study ID	Sample size (M/F)	Age (year)	The severity (*) of COVID-19	Type of Chinese herbal medicine	Conventional western therapy (Yes/No)	Course of treatment	Outcomes	Author's conclusion towards the role of Chinese herbal medicine in the treatment or adjuvant treatment of COVID-19 (positive/negative)
Study type 1: randomized controlled trials (9, 15.79%)								
Yu P[10]	T:82/65 C:89/59	T:48.27±9.56 C:47.25±8.67	Non-serious	Chinese patent medicine	Yes	7 days	②③⑬	Positive
Duan C[11]	T:39/43 C:23/18	T:51.99±13.88 C:50.29±13.17	Non-serious	Chinese patent medicine	Yes	5 days	②④⑤⑥⑪⑬	Positive
Sun HM[12]	T:17/15 C:11/14	T:45.4±14.10 C:42.0±11.70	Non-serious	Chinese patent medicine	Yes	14 days	②④⑤⑥⑪	Positive
Fu XXa[13]	T:17/15 C:19/14	T:43.26±7.15 C:43.68±6.45	Non-serious	Chinese patent medicine	Yes	10 days	②⑪⑬	Positive
Fu XXb[14]	T:19/18 C:19/17	T:45.26±7.25 C:44.68±7.45	Non-serious	Chinese patent medicine	Yes	15 days	①⑬	Positive
Ding XJ[15]	T:39/12 C:39/10	T:54.7±21.3 C:50.8±23.5	T: 46 (non-serious) / 5 (serious) C: 11 (non-serious) / 4 (serious)	Prescribed herbal decoction	Yes	10 days	④⑤⑪⑬	Positive
Ye YA[16]	T:2/26 C:4/10	T:53.5-69 C:47-67	Serious	Prescribed herbal decoction	Yes	7 days	②③	Positive
Qiu M[58]	T:13/12 C:14/11	T: 53.35±18.35 C:51.32±14.62	Non-serious	Prescribed herbal decoction	Yes	10 days	②⑦⑧⑪	Positive
Zhang CT[59]	T:9/13 C:10/13	T:53.7 ±3.5 C:55.6±4.2	Non-serious	Prescribed herbal decoction	Yes	7 days	⑦⑧⑨⑪⑬	Positive
Wang JB[67]	T:14/10 C:12/11	T:46.8±14.4 C:51.4±17.6	Non-serious¶	Prescribed herbal decoction	Yes	14 days	②③⑦⑬	Positive
Study type 2: Non-randomized controlled trial (1, 1.75%)								
Xiao Q[17]	T:64/36 C:66/34	T:60.90±8.70 C:62.20±7.50	non-serious	Chinese patent medicine	Yes	14 days	⑦⑧⑨⑪⑬	Positive
Study type 3: Retrospective studies with control group (11, 19.30%)								
Cheng DZa[18]	T:26/25 C:27/24	T:55.5±12.3 C:55.8±11.6	non-serious	Chinese patent medicine	Yes	7 days	②④⑤⑥⑦⑧⑨⑪	Positive
Liu ZL[19]	T:21/23 C:16/20	T:50.73 C:51.75	T: 37 (non-serious) / 7 (serious) C: 28 (non-serious) / 8 (serious)	Chinese patent medicine	Yes	7 days	⑪⑬	Positive
Zhang CY[20]	T:10/12 C:12/10	T:25-73 C:19-67	Non-serious	Chinese herbal medicine injection	Yes	7 days	⑩⑪⑬	Positive
Li KY[21]	T:15/15 C:13/17	T:53.600±0.259 C:50.433±0.338	T: 3 (serious)/27(not reported) C: 2 (serious)/28(not reported)	Prescribed herbal decoction	Yes	Not reported	①②⑦⑧⑪⑬	Positive
Yang Q[22]	T:28/23 C: 24/28	T:61.57±1.84 C:66.35±1.82	Serious	Prescribed herbal decoction + Chinese herbal medicine injection	Yes	Not reported	①③⑪⑫⑬	Positive
Qu XK[23]	T:25/15 C:16/14	T:40.65±8.23 C:39.82±6.40	Non-serious	Chinese patent medicine	Yes	10 days	①⑦⑧⑨⑩⑬	Positive
Xia WG[24]	T:17/17 C:6/12	T:54.18±13.08 C:53.67±12.70	T: 27 (non-serious) / 7 (serious) C: 13 (non-serious) / 4 (serious)	Chinese patent medicine + Chinese herbal medicine injection + prescribed herbal decoction	Yes	5-10 days	①②③⑦⑪⑫⑬	Positive
Yao KT[25]	T:16/5 C:12/9	T:57.1±14.0 C:62.4±12.3	Non-serious	Chinese patent medicine	Yes	Not reported	④⑤⑥⑦	Positive
Shi J[26]	T:26/23 C:10/8	T:47.94±14.46 C:46.72±17.40	T: 41 (non-serious) / 8 (serious) C: 15 (non-serious) / 3 (serious)	Chinese patent medicine + prescribed herbal decoction	Yes	Not reported	②⑪⑫	Positive
Yang MB[27]	T:16/10 C:9/14	T:50.35±13.37 C:47.17±16.57	Non-serious	Chinese patent medicine	Yes	7 days	②⑩⑪⑬	Positive
Chen L[60]	T:14/20 C:15/19	T:65.06±10.63 C:64.35±10.34	Non-serious	Chinese patent medicine	Yes	7 days	②④⑤⑥⑦⑧⑨⑪⑫⑬	Positive
Study type 4: case-series (12, 21.05%)								

Zhang Y[28]	9/15	49.96±12.79 (27-69)	Non-serious	Prescribed herbal decoction	Yes	6-14 days	NA	Positive
Wang RQ[29]	52/46	42.70±16.86	87 (non-serious) / 11 (serious)	Prescribed herbal decoction	No	9 days	NA	Positive
Xie YF[30]	8	35-79	Serious	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Li SY[31]	3/3	42-79	Serious	Chinese patent medicine + Chinese herbal medicine injection + prescribed herbal decoction	Yes	Not reported	NA	Positive
Ba YM[32]	243/208	43-66	399 (non-serious) / 46 (serious)	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Liu MJ[33]	36	NR	Not reported	Prescribed herbal decoction	Yes	14 days	NA	Positive
Huang LJ[34]	38/33	41.3±16.7	Non-serious	Chinese patent medicine + Chinese herbal medicine injection + prescribed herbal decoction	Yes	Not reported	NA	Positive
Xie YF[35]	27	2-68	Non-serious	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Cheng DZ b[36]	29/25	60.1±16.98 (25-95)	Non-serious	Chinese patent medicine	Yes	8. 0 ± 4. 10 days	NA	Positive
Zhou YJ[37]	17/23	19-68	Non-serious	Prescribed herbal decoction	Yes	14 days	NA	Positive
Qu YF[61]	23/17	61.2±16.5 (24-79)	Non-serious	Prescribed herbal decoction	Yes	7 days	NA	Positive
Shi TF[62]	15/25	43.9±16.3 (20-94)	32 (non-serious) / 8 (serious)	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Study type 5: case-reports (24, 42.11%)								
Fu XX[38]	1/1	32, 46	Non-serious	Chinese patent medicine	Yes	10/14 days	NA	Positive
Tian ZH[39]	2/3	24, 28, 36, 40, 49	2 (non-serious) / 3 (serious)	prescribed herbal decoction + Chinese patent medicine	Yes	9 days	NA	Positive
Dong L[40]	1M	56	Not reported	Prescribed herbal decoction	No	11 day	NA	Positive
Shi L[41]	2M	45, 48	Non-serious	Prescribed herbal decoction + Chinese herbal medicine injection	Yes	7/18 days	NA	Positive
Li GW[42]	1/1	35, 36	1 (non-serious) / 1 (serious)	Prescribed herbal decoction	No	4/6 days	NA	Positive
Zhao DK[43]	1F	41	Not reported	Prescribed herbal decoction	Yes	9 days	NA	Positive
He Q[44]	2M	25, 29	Serious	Prescribed herbal decoction	Yes	8/6 days	NA	Positive
Yang HM[45]	1F	74	Serious	Prescribed herbal decoction	Yes	15 days	NA	Positive
Wang YC[46]	2M	33, 54	1 (non-serious) / 1 (serious)	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Li WN[47]	1F	71	Serious	Prescribed herbal decoction	Yes	Not reported	NA	Positive
Feng QM[48]	1F	51	Serious	Prescribed herbal decoction	Yes	15 days	NA	Positive
Xu JC[49]	1M	35	Non-serious	Prescribed herbal decoction	Yes	12 days	NA	Positive
Liu Y[50]	1F	38	Non-serious	Prescribed herbal decoction	Yes	7 days	NA	Positive
Li XH[51]	2F	17, 45	Non-serious	Chinese patent medicine + prescribed herbal decoction	No	9 days	NA	Positive
Lin JZ[52]	1F	35	Not reported	Prescribed herbal decoction	Yes	12 days	NA	Positive
Hu ML[53]	1F	61	Serious	Chinese patent medicine + prescribed herbal decoction	Yes	11 days	NA	Positive
Wang ZW[54]	3/1	19，32，63，63	2 (non-serious) / 2 (serious)	Chinese patent medicine	Yes	Not reported	NA	Positive
Deng Z[55]	1F	39	Serious	Prescribed herbal decoction	Yes	Not reported	NA	Positive
L Ni[56]	1/2	27, 51, 53	Serious	Chinese patent medicine	1 Yes / 2 No	Not reported	NA	Positive
Gao XS[57]	1F	42	Non-serious	Chinese patent medicine	No	7 days	NA	Positive
Li DF[63]	1/1	68, 47	Non-serious	Prescribed herbal decoction	No	Not reported	NA	Positive
Lai YG[64]	1/2	56, 61, 60	1 (non-serious) / 2 (not	Prescribed herbal	No	6/7 days	NA	Positive

			reported)	decoction				
Wang HF[65]	1/1	45, 32	Serious	Chinese herbal medicine injection + prescribed herbal decoction	Yes	12/14days	NA	Positive
Wang H[66]	1/1	63, 49	Non-serious	Prescribed herbal decoction	Yes	10/14 days	NA	Positive

Note: M, male; F, female; T, treatment group involving Chinese herbal medicine; C, controlled group not involving Chinese herbal medicine; Yes, the intervention involved in this study was Chinese herbal medicine combined with conventional western therapy; No, the intervention involved in this trial was Chinese herbal medicines alone, not combined with conventional western therapy; NA, not applicable; Positive, Chinese herbal medicine has benefits on the treatment or adjuvant treatment of COVID-19; negative, Chinese herbal medicine has no benefits on the treatment or adjuvant treatment of COVID-19, or can even make the disease worse.
The severity (*) was classified according to the guidelines for the diagnosis and treatment of COVID-19 released by the National Health Commission of the People's Republic of China. We divide them into two categories of non-serious (including mild and common) and serious (including severe and critical). ¶ All participants in this trial were screened from patients of suspected COVID-19. Although the article did not state the COVID-19 severity of the participants included in the trial, we speculated that the COVID-19 severity of these participants should be non-serious (in light of the clinical knowledge of COVID-19).
Outcomes: ① cure rate; ② aggravation rate; ③ mortality rate; ④ the disappearance rate of fever; ⑤ the disappearance rate of cough; ⑥ the disappearance rate of fatigue;⑦ the duration of fever; ⑧ the duration of cough; ⑨ the duration of fatigue; ⑩ negative conversion rate of nucleic acid test; ⑪ inflammatory disappearance on chest CT; ⑫ Length of hospitalization; ⑬ adverse events.

Table 2 Chinese herbal medicine used twice or more frequently

The name of Chinese herbal medicine (CHM)	Frequency (N)	Percentage
Type 1 of CHM: prescribed herbal decoction		
Maxing Shigan Tang [麻杏石甘汤]	9	15.52%
Dayuanyin [达原饮]	5	8.62%
Qingfei Paidu Tang [清肺排毒汤]	4	6.90%
Xiaochaihu Tang [小柴胡汤]	4	6.90%
Ganlu Xiaodu Dan [甘露消毒丹]	3	5.17%
Liujunzi Tang [六君子汤]	3	5.17%
Sanren Tang [三仁汤]	2	3.45%
Feiyan No.1 Fang [肺炎 1 号方]	2	3.45%
Xiaoqinglong Tang [小青龙汤]	2	3.45%
Wulingsan [五苓散]	2	3.45%
Type 2 of CHM: Chinese patent medicine		
Lianhua Qingwen granule/capsule [连花清瘟颗粒/胶囊]	9	15.52%
Shufeng Jiedu gapsule[疏风解毒胶囊]	5	8.62%
Toujie Quwen granule [透解祛瘟颗粒]	3	5.17%
Jinhua Qinggan granule [金花清感颗粒]	2	3.45%
Shuanghuanglian oral liquid [双黄连口服液]	2	3.45%
Type 2 of CHM: Chinese herbal medicine injection		
Xuebijing injection [血必净注射剂]	5	8.62%
Xiyanping injection [喜炎平注射液]	2	3.45%
Tanreqing injection [痰热清注射液]	2	3.45%
Shenfu injection [参附注射液]	2	3.45%
Shengmai injection [生脉注射液]	2	3.45%

Note: Frequency refers to the number of included studies using the CHM. Such as, the frequency of Maxing Shigan Tang is 9, which means that nine included studies used Maxing Shigan Tang.
Percentage = (N/58) * 100%

Table 3 The pooled results of secondary outcomes of CHM used with or without conventional western therapy for COVID-19

Comparisons and outcomes	Design of the included study	Number of study	Number of participant	The pooled results	References
Chinese herbal medicine + conventional western therapy versus conventional western therapy					
●The disappearance rate of fever	RCT	3	232	RR 1.18, 95% CI 0.88 to 1.60, I^2 = 69%	11, 12, 15
	Retrospective study with control group	3	163	RR 1.34, 95% CI 1.13 to 1.58,	18, 25, 60
●The disappearance rate of cough	RCT	3	264	RR 1.37, 95% CI 1.15 to 1.64,	11, 12, 15
	Retrospective	3	156	RR 1.82, 95% CI 1.22 to 2.71,	18, 25, 60

	study with control group				
●The disappearance rate of fatigue	RCT	2	147	RR 1.37, 95% CI 1.02 to 1.83,	11, 12
	Retrospective study with control group	3	126	RR 1.48, 95% CI 1.14 to 1.93	18, 25, 60
●The duration of fever	RCT	2	95	MD -2.08 days, 95% CI -2.90 to -1.26, I^2 = 60%	58, 59
	Non-RCT	1	200	MD -0.83 days, 95% CI -1.22 to -0.44	17
	Retrospective study with control group	6	322	MD -1.54 days, 95% CI -1.82 to -1.26	18, 21, 23-25, 60
●The duration of cough	RCT	2	95	MD -2.34 days, 95% CI -3.32 to -1.37, I^2 = 56%	58, 59
	Non-RCT	1	200	(MD 0.28 days, 95% CI -0.40 to 0.96	17
	Retrospective study with control group	4	214	MD -1.68 days, 95% CI [-1.92, -1.43]	18, 21, 23, 60
●The duration of fatigue	RCT	1	45	(MD -2.35 days, 95% CI -2.91 to -1.79	59
	Non-RCT	1	200	MD -0.33 days, 95% CI -0.78 to 0.12	17
	Retrospective study with control group	3	136	MD -1.75 days, 95% CI -2.01 to -1.49	18, 23, 60
●Negative conversion rate of nucleic acid test	Retrospective study with control group	3	163	RR 1.32, 95% CI 1.05 to 1.66	20, 23, 27
●The effective rate of inflammatory disappearance on chest CT	RCT	6	607	RR 1.28, 95% CI 1.10 to 1.49	10, 12, 13, 15, 58, 59
	Non-RCT	1	200	RR 1.21, 95% CI 1.05 to 1.40	17
	Retrospective study with control group	7	484	RR 1.23, 95% CI 1.00 to 1.52, I^2 = 67%	18, 20, 22, 24, 26, 27, 60
●The time from receiving treatment to the beginning of inflammation disappearance	Retrospective study with control group	2	140	MD -2.23 days, 95% CI -2.46 to -2.00	19, 21
●Length of hospitalization	Retrospective study with control group	4	290	MD -0.42 days, 95% CI -3.49 to 2.64, I^2 = 95%	22, 24, 26, 60
●Adverse events	RCT	3	270	RR 2.06, 95% CI 0.34 to 12.38	11, 15, 67
	Non-RCT	1	200	RR 1.00, 95% CI 0.21 to 4.84	17
	Retrospective studies with control group	4	276	RR 0.87, 95% CI 0.26 to 2.93	20-23
Chinese herbal medicine versus conventional western therapy		None			

Note: RR, risk ratio; MD, mean difference; CI, confidence interval; RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial.