Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Systematic Review

Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis

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ABSTRACT

Background: There is currently no drug or therapy that cures COVID-19, a highly contagious and life-threatening disease.

Objective: This systematic review and meta-analysis summarized contemporary studies that report the use of Chinese herbal medicine (CHM) to treat COVID-19.

Search strategy: Six electronic databases (PubMed/MEDLINE, Cochrane Library, ScienceDirect, Google Scholar, Wanfang Data and China National Knowledge Infrastructure) were searched from their beginning to May 15, 2020 with the following search terms: traditional Chinese medicine, Chinese medicine, Chinese herbal medicine, COVID-19, new coronavirus pneumonia, SARS-CoV-2, and randomized controlled trial.

Inclusion criteria: Randomized controlled trials (RCTs) from peer-reviewed journals and non-reviewed publications were included. Further, included RCTs had a control group that was given standard care (SC; such as conventional Western medicine treatments or routine medical care), and a treatment group that was given SC plus CHM.

Data extraction and analysis: Two evaluators screened and collected literature independently; information on participants, study design, interventions, follow-up and adverse events were extracted, and risk of bias was assessed. The primary outcomes included scores that represented changes in symptoms and signs over the course of treatment. Secondary outcomes included the level of inflammatory markers, improvement of pneumonia confirmed by computed tomography (CT), and adverse events. Dichotomous data were expressed as risk ratio or hazard ratio with 95% confidence interval (CI); where time-to-event analysis was used, outcomes were expressed as odds ratio with 95% CI. Continuous data were expressed as difference in means (MD) with 95% CI, and standardized mean difference (SMD) was used when different outcome scales were pooled.

Results: Seven original studies, comprising a total of 732 adults, were included in this meta-analysis. Compared to SC alone, CHM plus SC had a superior effect on the change of symptom and sign score (−1.30 by SMD, 95% CI [−2.43, −0.16]; 3 studies; n = 261, P = 0.03), on inflammatory marker C-reactive protein (CRP, mg/L; −11.82 by MD, 95% CI [−17.95, −5.69]; 5 studies; n = 325, P = 0.0002), on number of patients with improved lung CT scans (1.34 by risk ratio, 95% CI [1.19, 1.51]; 4 studies; n = 489, P < 0.00001). No significant adverse events were recorded in the included RCTs.

Conclusion: Current evidence shows that CHM, as an adjunct treatment with standard care, helps to improve treatment outcomes in COVID-19 cases.

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Contents

1. Introduction

The outbreak of the 2019 coronavirus disease (COVID-19) was announced as a pandemic by the World Health Organization (WHO) on March 12, 2020 [1]. It is a new disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had not previously affected humans. As of June 1, 2020, there were 6,341,056 confirmed COVID-19 cases and 376,220 deaths worldwide; the ongoing case-fatality rate (CFR) was 5.93%, at that time, and most cases were still active. Within the United States (US) alone, the total infection and mortality numbers were 1,850,743 and 106,586, respectively, with the ongoing CFR of 5.76% [2,3]. In some developed European countries, the ongoing CFR reached as high as 14.13%–16.21% [2,3]. COVID-19 has immensely impacted the global economy, potentially causing a global recession [4], aside from widespread sickness, hospitalization and death. However, for now, no drug or therapy has been identified to cure this highly contagious and life-threatening disease. Despite a shortage of information regarding the efficacy and safety of the antiviral drug remdesivir for treating COVID-19, the US Food and Drug Administration (FDA) issued an emergency-use authorization for its study in suspected or laboratory-confirmed COVID-19 cases in adults and children hospitalized with a severe condition, as of May 1, 2020 [5].

China achieved success in countering the first wave of the COVID-19 epidemic by the middle of March 2020. As of June 1, 2020, there were 82,954 confirmed COVID-19 cases and 4634 deaths (CFR 5.59%, almost all are closed cases) in China [2,3]; this is much less than those in many Western countries. All confirmed cases were treated with standard care under the guidelines issued by the National Health Commission (NHC) and State Administration of Traditional Chinese Medicine of China [6]. Multiple Chinese herbal therapies were recommended by NHC in the interim guidelines for the treatment of COVID-19 (*Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*) [6], and 91.5% (or 74,187) of COVID-19 patients were treated with Chinese herbal medicine (CHM) [7]. CHM was used alone in some of the mild or ordinary cases (in the US, called "moderate"). From a larger perspective, compared with the treatments in Western countries, the use of CHM in countering COVID-19 is undoubtedly a unique experience [8–29]. CHM may have played an important role in countering this deadly disease. For example, it was reported that the use of CHM *Qingfei Paidu Decoction* (or with modification) plus standard care, across 30 COVID-19 hospitals in 14 provinces and on a total 1476 adult patients, there was a total symptom relief rate of 90.0%–94.8% over a treatment course of 3–9 days [14–16,19]. Based on these experiences with large patient numbers, *Qingfei Paidu Decoction* has been recommended by China's NHC for COVID-19 [6] and used widely, either as the original formula or by customizing it to the patient's actual condition. In five cohort studies [25–29], 255 patients with COVID-19 were treated with CHM plus standard care, compared with 208 patients in the control groups, treated only with standard care. The reports showed that CHM plus standard care had a superior effect on change of the overall scores of clinical symptoms and signs, especially on the outcomes of "days to fever relief"; on "number converting to severe case"; on the "number of computed tomography (CT) improvement"; on the "days of hospitalization" and on the "number of cured." In other words, the results showed that adding CHM to

standard care can significantly improve COVID-19 recovery without increasing adverse effects [25–29].

Traditional Chinese medicine (TCM, or acupuncture and Oriental medicine) has been developed over thousands of years [7,30]. It not only plays an important role in the health care system in China, but also is used in many countries and regions around the world, such as the US, United Kingdom, Canada, and Australia [7]. With its unique theory, treatment strategies and perspectives on the nature of illness and disorders, CHM, a major branch of TCM, has been incorporated into daily healthcare practice in China [30–33]. In particular, it has been used to manage COVID-19 [6–29]. Instead of mainly focusing on drugs to combat diseases, such as coronavirus, CHM uses treatments with multiple targets that may act through modulating a patient's immune response, improving a patient's symptoms, or countering the pathogen directly. CHM also emphasizes individualization of treatments based on an individual's signs and symptoms; this differs from conventional Western medical care that generally standardizes treatments for patients with the same disease. Individualization of CHM formulas makes the evaluation of its clinical efficacy difficult within the framework of the standard randomized controlled trials (RCTs). There was a concern that the use of CHM to treat COVID-19 was not scientifically approved [34]. Therefore, rigorous and objective evaluation of clinical research using CHM to treat COVID-19 is needed, and evidence obtained from RCTs will be more convincing.

This study provides a systematic review and meta-analysis of current RCTs evaluating the use of CHM as an adjuvant to standard care in the treatment of COVID-19.

2. Materials and methods

2.1. Literature search

2.1.1. Search strategies

Six electronic databases were searched, including PubMed/MEDLINE (PubMed.gov), Cochrane Library (cochranelibrary.com), ScienceDirect (ScienceDirect.com), Google Scholar (scholar.google.com), Wanfang data (wanfangdata.com.cn), and China National Knowledge Infrastructure (CNKI.net). The timeframe used for the database queries was from the earliest indexed studies to May 15, 2020. Keyword searches were used to return relevant research. Search words included traditional Chinese medicine, Chinese medicine, Chinese herbal medicine, COVID-19, new coronavirus pneumonia, SARS-CoV-2, clinical trial, and randomized controlled trial. Papers provided by experts were also accepted.

2.1.2. Inclusion criteria

Literature which used CHM as the treatment for COVID-19 was included, regardless the age, gender, or severity of the condition. Studies designed as RCTs that were published in both peer-reviewed and non-peer reviewed journals were included. The included studies had a control group that used standard care (SC; i.e. conventional Western medicine treatments or routine medical care); they also had an experimental group that used both SC and a form of CHM, such as herbal decoctions, the National Medical Products Administration (also known as "China's FDA")-approved patent herbal medicines, and herbal extract injections [6]. Symptom and sign score was used as the primary outcome.

2.1.3. Exclusion criteria

Papers published as case reports, case series and cohort studies were excluded. Papers unrelated to the current review topic, including results of the effects on drugs, non-CHM interventions such as natural medicines, acupuncture or moxibustion, and non-clinical reports such as letters, opinions, comments and reviews, were excluded. Duplicated studies were also removed after browsing literature returned from database searches.

2.2. Literature screening and data extraction

2.2.1. Screening process

The above online databases were searched with the strategy described. All unrelated literature was removed.

2.2.2. Data extraction

The extracted data include the first author, the time trial or treatment was conducted, location, sample size of each group (intervention/control), study design, methods, interventions, control measures, patients' gender and age, disease stage, adverse effects and treatment results. All literature selected was managed by EndNote x8 (downloaded from Clarivate Web of Science group [35]).

The primary outcome was a score measured by the summary of changes in the main symptoms and signs of the condition; secondary outcomes included the level of inflammatory markers, such as C-reactive protein (CRP), high-sensitivity CRP, procalcitonin (PCT), interleukin 6 (IL-6), erythrocyte sedimentation rate, tumor necrosis factor-α (TNF-α), tumor necrosis factor-γ, white blood cells, neutrophils and lymphocytes, and number of patients whose conditions had been improved and confirmed by lung CT scans, as well as adverse events. Other outcomes, such as effectiveness rate, number of patients hospitalized, score of Hamilton anxiety scale, and service satisfactory score, were also included.

2.3. Literature quality evaluation

2.3.1. Bias risk assessment

The Cochrane manual 5.1.0 risk assessment tool was used to quantify the risk of bias.

2.3.2. Heterogeneity assessment

Potential heterogeneity in included RCTs was assessed by using the I^2 statistic. When substantial heterogeneity was found (I^2 statistic more than 50%), then the sources of such heterogeneity were assessed by rechecking the data or by subgroup analysis based on clinical and methodological variety factors, for instance, participant factors (severity of the condition), outcome measure factors (validation of scoring system) or treatment factors (dose or preparations of interventions), to explain the differences.

2.4. Statistical methods

2.4.1. Effective quantity selection

Statistical analysis was carried out using the ReviewManager 5.3 (RevMan; the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). The inverse-variance method in RevMan was adopted and the random-effect model was used because the CHM formulas, dosage forms and days of administration were variable among the included studies. Dichotomous data with positive outcome (favor to intervention group) were expressed as risk ratio (RR) or hazard ratio (HR) with 95% confidence interval (CI) where time-to-event analysis was used; dichotomous data with negative outcome (favor to control group) were expressed as odds ratio (OR) with 95% CI. A higher number of events that expressed with RR indicated better improvement of the condition. Continuous data were expressed as difference in means (MD) with 95% CI and standardized mean difference (SMD) was used where different outcome scales were pooled [36]. Where data were express as interquartile range (IQR), the standard deviation (SD) was estimated from IQR by SD = IQR/1.35 as recommended by the Cochrane Handbook 6 [36].

2.4.2. Data synthesis

For the included RCTs, data were synthesized by different judgment indicators, such as symptom and sign score or specific symptom score, and 95% CI of effect value was calculated. Forest plots were used to express the effect estimate across the included stud-

ies when same outcome measures were employed. The potential source of heterogeneity of these results was explored by performing sensitivity analysis using characteristics of participants (severity of the condition), outcome measure (validation of scoring system) or interventions (dose or preparations of interventions).

Study selection and data extraction were performed critically and independently by two evaluators (Fan AY and Gu S). For this systematic review and meta-analysis, patients received CHM plus SC were placed in experiental group and SC alone in control group.

3. Results

3.1. Literature retrieval situation

A total of 865 articles were retrieved from six databases, with the search words set on 2.1.1 Search strategies. Additional one was identified through experts' referrals. Of these studies, 763 were not relevant to the study objectives, including 759 drug or epidemiology reports and four on studies of acupuncture or moxibustion. Seventy-five articles were further excluded after reading the full text, including two duplicate articles, 16 opinion pieces, 33 reviews, 11 histories, eight pharmacological studies and five flu-related studies. Among the remaining 28 CHM clinical papers on COVID-19, there were 21 non-RCTs, including six case reports, ten case series, and five cohort studies, which were all excluded. A total of seven articles documenting RCTs were finally included in the current systematic review and meta-analysis (Fig. 1).

3.2. Systematic review and meta-analysis

There were seven RCTs [37–43] that compared the effects of CHMs plus SC to SC alone among adults who had been diagnosed with COVID-19 and received treatment of CHMs plus SC or SC alone, based on the interim guideline for COVID-19 by China NHC [6]. All studies were published online in Chinese or English between March 3, 2020 and May 5, 2020. All were open-label, two-arm RCTs with 1:1 or 2:1 random assignment. Samples sizes ranged from 42 to 284 participants.

3.2.1. Participants

In these RCTs, a total of 732 participants aged above 18 years were recruited from public hospitals in Wuhan [37,38,41–43] and Guangzhou [39,40], China between January and March 2020, during the COVID-19 epidemic. The conditions of the recruited participants were mild, ordinary, severe or critical, and patients were treated in either out-patient departments [38] or isolated wards of in-patient departments [37,39–41].

3.2.2. Interventions

In addition to SC, oral CHMs (decoction, extracted granules or capsules) were provided to the treatment groups for 5–15 days. Duan et al. [38] used *Jinhua Qinggan* (JQ) granules. Hu et al. [42] reported a formula for *Lianhuaqingwen* (LH) capsules, a CHM developed during the severe acute respiratory syndrome (SARS) epidemic from 2002 to 2003 [44,45]. Both JQ and LH were developed or repurposed in 2009 to treat mild cases of the pan-

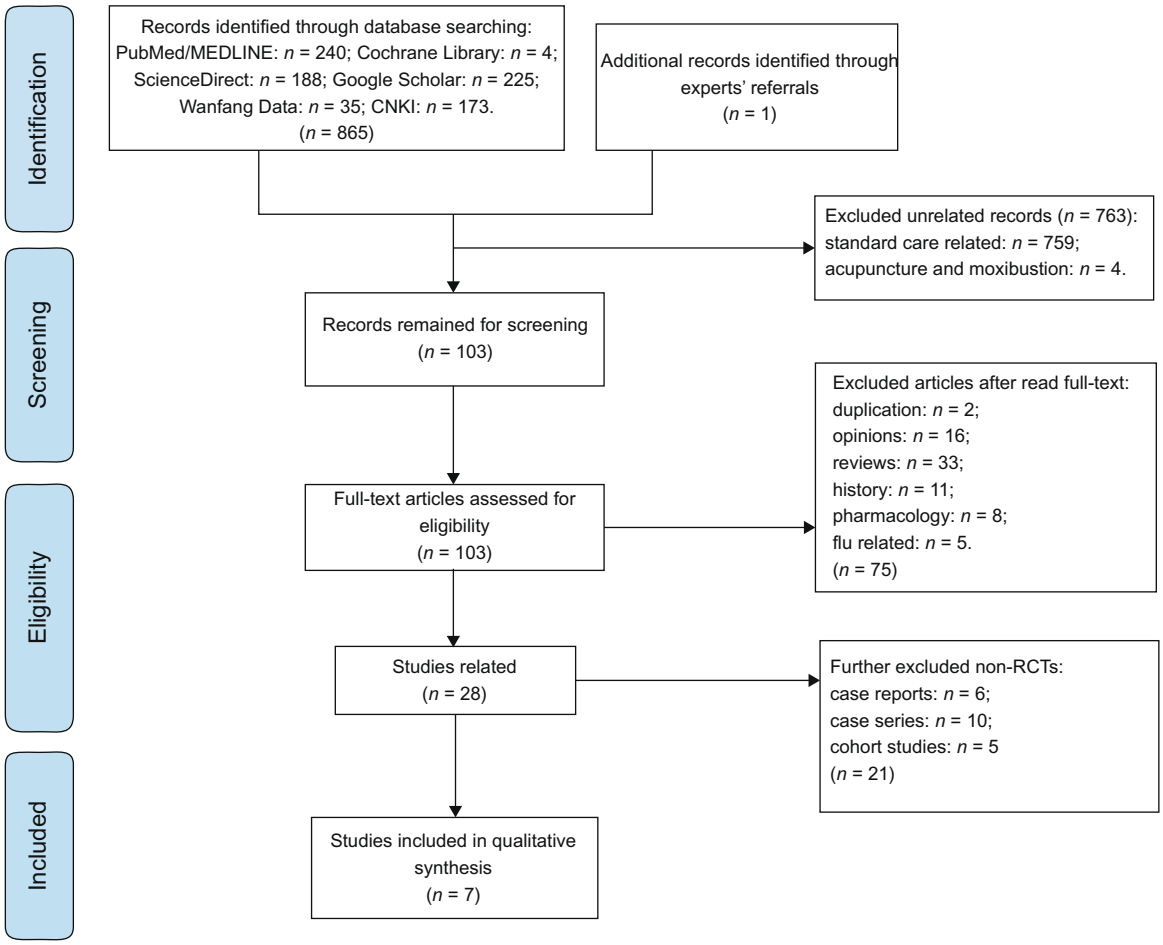

Fig. 1. Flow chart on literature retrieval. CNKI: China National Knowledge Infrastructure; RCT: randomized controlled trial.

demic H1N1 flu [46]. The other studies employed team-created [37,41], expert-created [39,40], or classical formulae [42,43]. The most commonly used CHMs were Mahuang (Herba Ephedrae), Kuxingren (Semen Armeniacae Amarum), Shigao (Fibrosum Gypsum) (five studies); the second most common group of CHMs was Jinyinhua (Flos Lonicerae Japonicae) and Lianqiao (Fructus Forsythiae) (four studies); another three studies used Huangqin (Radix Scutellariae) and Taizishen (Radix Pseudostellariae).

3.2.3. Comparison

All studies used SC as comparative intervention, based on the interim guidelines for COVID-19 care issued by the Chinese NHC [6]. These included application of antivirals and antibiotics, systemic corticosteroids, and other supporting treatments.

3.2.4. Outcomes

Improvement of participants' symptoms, inflammatory markers, numbers of patients whose conditions had been improved and confirmed by lung CT findings, or adverse events were reported by most of the included studies as their primary measures for evaluating the efficacy and safety of CHMs. The effect estimates were re-calculated with data extracted from the included studies. Data of cardinal symptoms such as fever, cough, fatigue, or dyspnea were retrieved at "outcome of improvement of participants' symptoms" in this review. Table 1 summarizes details of the included studies.

3.2.5. Assessment of risk of bias

All included RCTs claimed to have grouped participants randomly, but only Ding et al. [37], Duan et al. [38], Fu et al. [39], Hu et al. [42] and Ye et al. [43] included a method of randomization. No blinding was used in any of the included studies. No reporting bias was detected, as all stated study outcomes were reported by the included studies. Fig. 2 outlines the percentage of risk of bias among the included studies and Fig. 3 provides a summary of risk of bias for each of the included studies.

3.2.6. Meta-analysis for detecting the overall effects of CHMs

All included studies reported favorable results in groups receiving CHM plus SC compared to SC alone. As each of these studies had a relatively small sample size, meta-analysis was performed to improve statistical power to confirm the overall treatment effect.

3.2.7. Symptoms and signs score

Duan et al. [38] used a symptoms and signs scoring system as an outcome for detecting treatment effects. The score ranged from 0 to 65, where higher scores indicate worsening of the condition. Fu et al. [39] used a score ranging from 5 to 20, and Fu et al. [40] applied the same scoring system but used the range of 0 to 30. The scoring systems were not validated. Both Fu et al. [39] and Fu et al. [40] reported a score based on single symptoms or signs, such as fever, cough, or fatigue. The scores for fever in [38–40] were pooled in this review. The forest plot comparing signs and symptoms scores shows that the CHM + SC group was 1.30 lower (by SMD, 95% CI [−2.43, −0.16]; 3 studies; n = 261, Fig. 4.) than SC alone. However, significant heterogeneity was also present (I^2 = 94%). This may be due to the different scoring methods used among these three studies.

3.2.8. Inflammatory markers

A variety of inflammatory markers, including CRP and PCT, were used in five studies [37,39–41,43]. Data from Ye et al. [43] were expressed as median and IQR. The SD was estimated from IQR (SD = IQR/1.35) and pooled for meta-analysis. The forest plot of comparison showed the volume of CRP (mg/L) in CHM plus SC groups was −11.82 (by MD, 95% CI [−17.95, −5.69]; 5 studies; n = 325, Fig. 5). However, significant heterogeneity was also detected (I^2 = 97%).

3.2.9. Lung CT scan findings

Four studies [37,39,41,42] reported the number of participants with improvements after treatment with CHM plus SC, reflected in their lung CT scan results. The number of participants in the CHM plus SC group was higher (by RR 1.34, 95% CI [1.19, 1.51]; 4 studies; n = 489, Fig. 6), and no heterogeneity was detected (I^2 = 0%).

3.2.10. Adverse events

Ding et al. [37] reported two mild liver dysfunction cases in the experimental group and three cases in the control group. There were 27 participants who complained of diarrhea in the experimental group and none in the control group in the study by Duan et al. [38]. There was no significant difference in the number of adverse events experienced by control and treatment groups in four studies [39–42]. Hu et al. [42] reported that the participants did not experience adverse events, and Ye et al. [43] did not report adverse events.

4. Discussion

The clinical literature on treating COVID-19 with CHMs, published as case reports, case series, cohort studies and RCTs, constitutes a full evidence chain [8–29,37–43]. These studies appear to support one another, indicating that the addition of CHMs to standard care for COVID-19 is beneficial, even though there were differences among the studies. There were some constitutional differences in CHM groups in the different studies, as there were in the controls (See content in Table 1 for the detail). However, within each study, there were not significant differences in patient demographics, health parameters or standard care between study groups. In this systematic review and meta-analysis, the CHM plus SC groups were combined among studies, even though they may have used different CHMs, and compared against the control group receiving SC alone. All CHMs and SC drugs or therapies used in these studies were recommended by China's NHC [6]. SC generally includes antiviral medicines (such as arbidol, lopinavir-ritonavir, remdesivir and α-interferon), antibacterial medicines (such as moxifloxacin, levofloxacin, azithromycin, cephalosporins and penicillin), systemic corticosteroids, supporting medicines (such as γ globulin and methylprednisolone), and oxygen therapy and breathing support [6].

Large-scale RCTs are considered to be a source of high-confidence clinical data. However, they are difficult to perform in highly contagious and high-CFR diseases, like COVID-19. For diseases like this, other types of clinical studies have shown their value, especially cohort studies, although they were retrospective [25–29]. Some case reports were published during the early days of the COVID-19 outbreak. As no effective antiviral treatment has been demonstrated so far, researchers have worked urgently to find a remedy for COVID-19. During the COVID-19 epidemic in China, case reports provided early evidence that CHMs may not only help the recovery of mild or ordinary cases, but also might be an adjunctive therapy in the rescue of severe cases [8–13]. Reports of successful treatments in these cases provided some confidence in the treatment of COVID-19, and may have helped to dispel some of the social panic associated with COVID-19 [8–13]. Case studies of CHMs used to treat COVID-19 were exploratory; however, most of the published reports provided clear evidence of CHM efficacy with low rates of adverse events. Case series were published in the later months of the COVID-19 epidemic, and they included larger numbers of patients and provided more information [14–23]. There were no control groups, no blinding, significant heterogeneity in outcomes and lack of reporting long-term efficacy and follow-up. However, considering the urgency of patients' treatment needs, absence of RCT data when the COVID-19 outbreak began, and limited resources, the early case reports and case series provided valuable information for combining CHM with SC. Some reports did not focus on the safety of CHMs; however, when used

Table 1
Characteristics of included randomized controlled trials.

Study	Sample size (T/C)	Disease stage	Intervention		Outcomes	Effect size
			Treatment	Control		
Ding et al. [37]	51/49	All	Oral intake of QF decoction modified based on individual needs, bid for 10 d, plus SC	SC (antivirals and antibiotics)	① Number of participants with improvement of symptoms	① Fever: RR 1.12 (1.00, 1.25), $P = 0.051$; cough: RR 1.36 (1.09, 1.70), $P = 0.006$; dyspnea: RR 2.20 (1.11, 4.39), $P = 0.024$
					② Inflammatory markers	② ESR: MD −41.60 (−46.02, −37.18), $P < 0.01$; CRP: MD −32.32 (−36.88, −27.76), $P = 0.019$; IL-6: MD −17.60 (−32.74, −2.46), $P = 0.023$; TNF-α: MD −6.86 (−9.46, −4.26), $P = 0.000$; TNF-γ: MD −0.40 (−11.53, 10.73), $P = 0.943$
					③ CT findings	③ RR 1.46 (0.99, 2.15), $P = 0.053$.
					④ Adverse events	④ OR 0.96 (0.26, 3.53), $P = 0.946$.
Duan et al. [38]	82/41	Mild	Oral intake of JQ granules, 15 g tid for 5 d, plus SC	SC (antivirals or antibiotics)	① Number of participants with improvement of symptoms	① Fever: RR 1.51 (1.07, 2.14), $P = 0.019$; cough: RR 3.09 (1.49, 6.41), $P = 0.002$; fatigue: RR 1.44 (0.98, 2.11), $P = 0.060$
					② CM symptoms and signs score	② MD −1.37 (−2.54, −0.20), $P = 0.041$
					③ Number of hospitalized	③ OR 0.38 (0.14, 1.03), $P = 0.057$
					④ Hamilton anxiety scale	④ MD −2.42 (−4.09, −0.75), $P = 0.005$
					⑤ Service satisfactory score	⑤ MD −0.27 (−0.96, 0.42), $P = 0.443$
					⑥ Adverse events	⑥ OR 41.13 (2.44, 693.89), $P = 0.09$
Fu et al. [39]	32/33	Mild and ordinary	Oral intake of TJ granules, bid for 10 d (did not state dose), plus SC	SC (arbidol 0.2, tid; ambroxol 30 mg, tid, 10 d)	① Effectiveness rate	① RR 15.47 (4.03, 59.44), $P = 0.000$
					② CM symptoms and signs score	② Fever: MD −0.80 (−0.95, −0.65), $P = 0.000$; cough: MD −0.63 (−0.80, −0.46), $P = 0.000$; fatigue: MD −0.34 (−0.45, −0.23), $P = 0.000$
					③ Inflammatory markers	③ WBC: MD 0.36 (0.20, 0.52), $P = 0.000$; LYM count (10^9/L): MD 0.26 (0.20, 0.32), $P = 0.000$; LYM%: MD 5.18% (4.11%, 6.25%), $P = 0.000$; NEU%: MD −4.58% (−5.81%, −3.35%), $P = 0.000$; CPR: MD −9.11 (−11.52, −6.70), $P = 0.000$; PCT: MD −0.02 (−0.02, −0.01), $P = 0.000$; D-dimer (μg/L): MD −42.50 (−84.55, −0.45), $P = 0.052$
					④ CT findings	④ RR 1.30 (0.97, 1.74), $P = 0.075$
					⑤ Rate of conversion of severe cases	⑤ OR 0.32 (0.03, 3.28), $P = 0.338$
Fu et al. [40]	37/36	Ordinary	Oral intake of TJ granules, bid for 15 d (did not state dose) plus SC	SC (arbidol 0.2, tid, 10 d; ambroxol 30 mg, tid, 15 d)	① Effectiveness rate	① RR 1.28 (1.01, 1.64), $P = 0.044$
					② CM symptoms and signs score	② Fever: MD −0.50 (−0.72, −0.28), $P = 0.000$; cough: MD −1.03 (−1.20, −0.86), $P = 0.000$; fatigue: MD −1.14 (−1.27, −1.01), $P = 0.000$; dyspnea: MD −0.18 (−0.37, 0.01), $P = 0.06$.
					③ Inflammatory markers	③ WBC: MD 0.26 (0.09, 0.43), $P = 0.003$; LYM count (10^9/L): MD 0.45 (0.39, 0.51), $P = 0.000$; LYM%: MD 3.18% (2.17%, 4.19%), $P = 0.000$; CPR: MD −8.11 (−10.41, −5.81), $P = 0.000$; $CD4^+$/$CD8^+$: MD 0.88 (0.79, 0.97), $P = 0.000$
					④ Hospital discharge rate	④ RR 1.42 (0.76, 2.62), $P = 0.268$
Hu et al. [42]	142/142	Not reported	LH capsule, 4 capsules bid, for 14 d plus SC	SC (antivirals, antibiotics, immune modulators, systemic corticosteroids)	① Rate of symptoms recovery at day 14	① RR 1.11 (1.01, 1.22), $P = 0.023$
					② Time to symptom recovery	② HR 1.7 (1.3–2.2), $P < 0.010$
					③ Rate of clinical recovery	③ RR 1.19 (1.03, 1.38), $P = 0.018$
					④ Rate of recovery of CT	④ RR 1.31 (1.13, 1.51), $P = 0.000$
					⑤ Conversion rate of viral assay	⑤ RR 1.08 (0.94, 1.24), $P = 0.280$
					⑥ Rate of conversion of severe cases	⑥ OR 0.49 (0.12, 2.00), $P = 0.318$
					⑦ Adverse events	⑦ OR 0.71 (0.45, 1.14), $P = 0.154$
Ye et al. [43]	28/14	Severe	Oral intake of CHM formulae (MX or SFT decoction), 200 mL, bid for 7 d plus SC	SC (antivirals, antibiotics, immune modulators, systemic corticosteroids)	① COVID-19 severity scale (number of death at day 3)	① OR 0.48 (0.03, 8.32), $P = 0.615$
					② Overall survival rate on day 14	② RR 1.04 (0.88, 1.22), $P = 0.647$
					③ Proportion of participants with	③ OR 3.56 (0.50, 25.56), $P = 0.206$

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size (T/C)	Disease stage	Intervention		Outcomes	Effect size
			Treatment	Control		
					no improvement at day 7	
					④ Inflammatory markers at day 7	④ WBC: MD 1.79 (−0.27 to 4.08), P = 0.104; LYM (10^9/L): MD −0.07 (−0.53 to 0.27), P = 0.696; NEU (10^9/L): MD 1.38 (−0.56 to 3.33), P = 0.167; ESR: MD −12.45 (−29.3, 13.2), P = 0.308; PCT: MD 0 (0.00, 0.03), P = 0.322; CRP: MD −1.63 (−6.62, 1.30), P = 0.329; HSCRP: MD −0.19 (−0.19, 146.7), P = 0.755
					⑤ Number of antibiotic use	⑤ OR 1.84 (0.41, 8.33), P = 0.428
Zhang et al. [41]	22/23	Ordinary	Oral intake of JW *granules*, tid for 7 d (did not state dose), plus SC	SC (did not state details)	① Number of day with improvement of symptoms and signs	① Fever: MD −2.52 (−3.30, −1.74), P = 0.000; dry cough: MD −1.89 (−2.62, −1.16), P = 0.000; dyspnea: MD −2.48 (−3.10, −1.86), P = 0.000; fatigue: MD −2.35 (−2.91, −1.79), P = 0.000
					② Inflammatory markers	② WBC: MD −0.25 (−1.85, 1.35), P = 0.761; LYM%: MD 14.90% (10.43%, 19.37%), P = 0.000; CRP: MD −6.88 (−8.05, −5.71), P = 0.000
					③ CT findings	③ RR 2.51 (1.06, 5.95), P = 0.036

These seven included studies are all open-label parallel RCTs with participants aged above 18 years. Fu et al. published two reports in different journals. Continuous data in Ye et al. were expressed as median and interquartile range. It was assumed that the effect estimates between groups were presented as MD with 95% confidence interval. bid: twice a day; CHM: Chinese herbal medicine; CM: Chinese medicine; CRP: C-reactive protein (mg/L); CT: computerized tomography; ESR: erythrocyte sedimentation rate (mm/H); HR: hazard ratio; HSCRP: high-sensitivity CRP (mg/L); IL-6: interleukin 6 (pg/mL); JQ: Jinhua Qinggan granules; JW: Jiaweidayuan granules; LH: Lianhuaqingwen capsule; LYM: lymphocytes; MD: mean difference; MX: Maxinshigan-dayuanyin decoction; NE: not estimable (where no event occurred in both groups); NEU: neutrophils; OR: odds ratio; PCT: procalcitonin (ng/L); QF: Qingfeitouxiefuzheng decoction; RCT: randomized controlled trial; RR: risk ratio; SC: standard care; SFF: Shengfutang decoction; T/C: treatment group/control group; tid: three times a day; TJ: Toujieqingwen granules; TNF-α: tumor necrosis factor-α (pg/mL); TNF-γ: tumor necrosis factor-γ (pg/mL); WBC: white blood cell ($\times 10^9$/L).

correctly, it is generally believed that CHMs lead to few serious adverse reactions [15]. Published more recently, cohort studies [25–29] have included more COVID-19 patients and added control groups. Before RCT data were available, these cohort studies provided more solid evidence than case reports or case series. The cohort studies from different regions of China supported one another, indicating that treatment with CHMs decreased the rate of mild-ordinary cases becoming severe cases. This information was critical for reducing the number of severe cases and then lowering the fatality rate. Also, evidence from the cohort studies showed the value of CHMs in the treatment of COVID-19, whether in mild, ordinary, severe, or critical cases.

There was preliminary evidence from the seven RCTs included in this analysis that CHMs may have helped to improve clinical outcomes, such as symptoms and signs, CRP level or lung CT scan findings, in COVID-19 cases during the epidemic in China. Ding et al. [37] used a team-created CHM decoction to treat 51 cases of COVID-19 for 10 days and reported a significant decrease of CRP in the CHM plus SC group (MD −32.32, 95% CI [−36.88, −27.76], n = 100). Duan et al. [38] repurposed existing CHM granules, which had been designed for mild cases of the 2009 H1N1 influenza pandemic, to treat 82 cases of COVID-19. Reduction in scores used to track signs and symptoms was greater in the CHM plus SC groups, compared to SC alone (MD −1.37, 95% CI [−2.54, −0.20], n = 123). Two studies by Fu et al [39,40] were conducted by the same team and published as two separate reports in different journals with divided data. The two studies used the same scoring system for their outcome measures, but the scoring range was different (5–20 *vs* 0–30). The reliability and validity of the scoring system remains in doubt, although the decrease in CRP was more obvious in the CHM plus SC group in both of these studies. Hu et al. [42] repurposed an existing CHM capsule to treat COVID-19 and reported a favorable result, as confirmed by primary and secondary outcomes including rate of symptom improvement or clinical recovery at the endpoint. The study of Ye et al. [43] was a pilot RCT that tested the feasibility of two sets of classical CHM decoctions plus SC for patients with severe COVID-19. It reported a marginal effect in which the experimental group may have had a higher overall survival rate than the control group (RR 1.04, 95% CI [0.88, 1.22], n = 42). Zhang et al. [41] provided team-created CHM granules that were given to 22 patients with COVID-19; they reported a significant improvement of the condition that was confirmed by CT scan findings (RR 2.51, 95% CI [1.06, −5.95], n = 45). No severe adverse events were reported in any of the seven included studies. Although all included studies stated a favorable effect of including CHM with SC, the effect may be overestimated due to potential high risk of performance bias (no blinding to the participants) across the studies. However, open-label studies have the benefit of low cost and ease of participant recruitment; they supplement blinded studies, which are not always feasible [44]. It is recommended that validated scoring systems for symptoms and signs be used in future studies to improve the consistency of outcome measures [45].

It is worth noting that these herbal medicine granules, decoctions, or patent herbal medicines share an obvious characteristic: many of them consist of two sets of herbs. The first set is Jinyinhua (Flos Lonicerae Japonicae), Lianqiao (Fructus Forsythiae), Huangqin (Radix Scutellariae) and Shigao (Fibrosum Gypsum), which have clear antiviral, antibacterial or anti-inflammatory activities; the second set of commonly used CHMs is Mahuang (Herba Ephedrae) and Kuxingren (Semen Armeniacae Amarum), which can help to relieve respiratory congestion and coughing. Among the herbal products or formula used in the included studies, Lianhua Qingwen granule was developed during the SARS epidemic in 2002–2003 [46,47]. Recently it was reported that Lianhua Qingwen had antiviral and anti-inflammatory activity against SARS-CoV-2 and decreased inflammatory cytokines TNF-α, IL-6, CC chemokine ligand-2/MCP-1, and CXC chemokine ligand-10/IP-10 in an experimental study [48]. The JQ granule was developed for mild cases

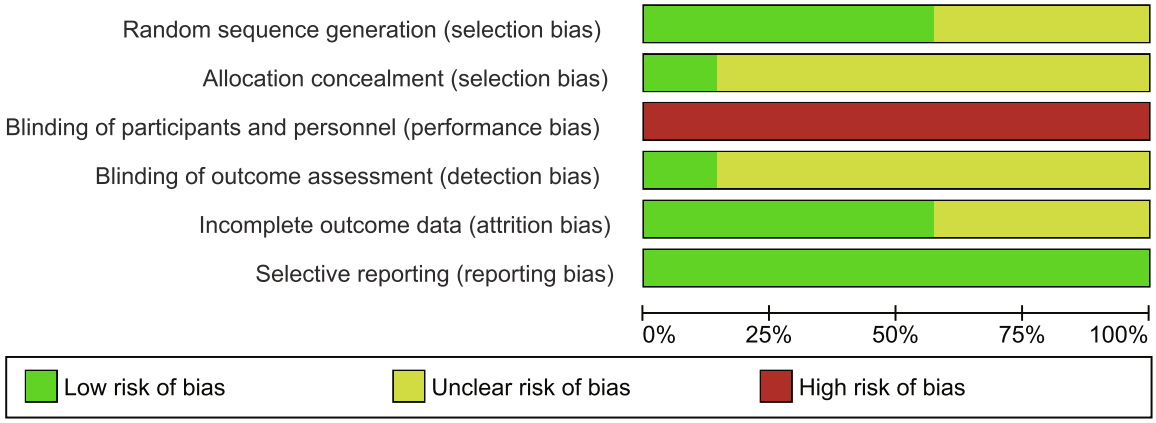

Fig. 2. Risk of bias graph for randomized controlled trials included in this study.

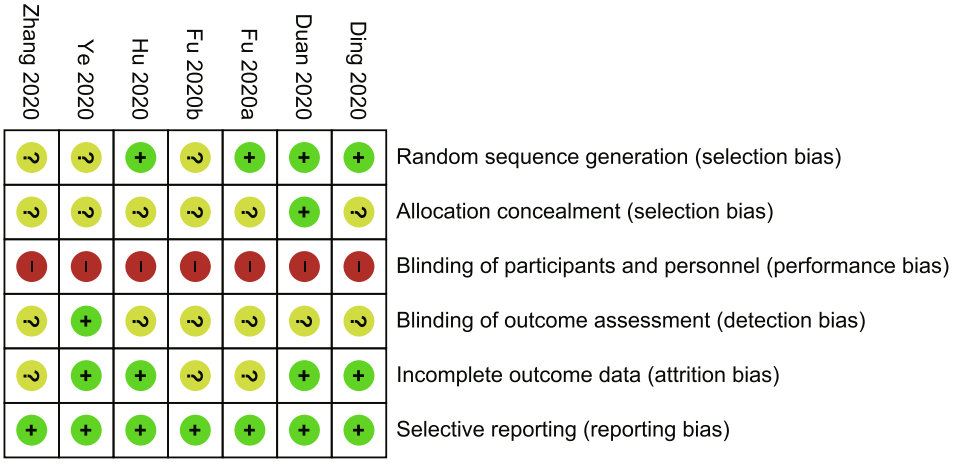

Fig. 3. Risk of bias summary in randomized controlled trials included in this study. Fu et al. published two reports (2020a [39] and 2020b [40]) in different journals.

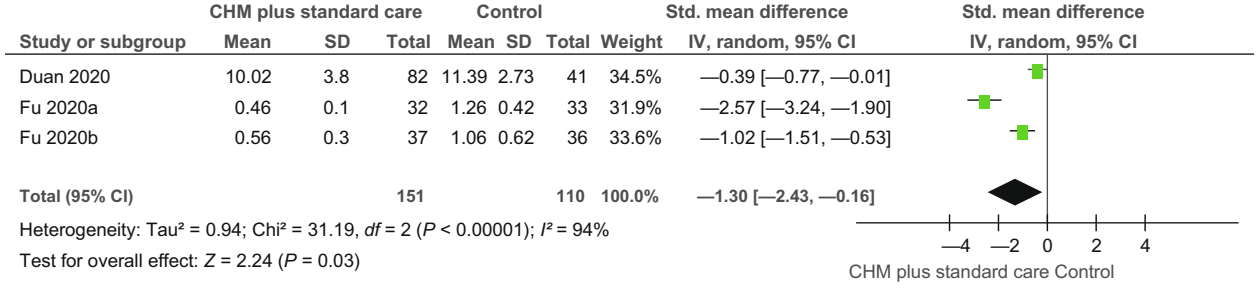

Fig. 4. Comparison of symptoms and signs score between CHM plus standard care and standard care. CHM: Chinese herbal medicine; SD: standard deviation; Std: standard; CI: confidence interval; IV: inverse-variance.

of H1N1 during the influenza pandemic of 2009 [49], and the Shuanghuanglian formula has protection for acute lung injury through anti-inflammatory and anti-oxidative activities [50]. They are over-the-counter herbal medicines approved by China's National Medical Products Administration. Because they have wide-spectrum anti-infection and anti-inflammatory activities, they have been used to treat various respiratory infections, including influenza, and have had good outcomes in COVID-19 treatment. At the present time, no specific antiviral drug has been proven effective for treating patients with COVID-19; recent RCTs have shown that both lopinavir-ritonavir [51] and remdesivir [52] did not have significant clinical benefits, even though many people had hoped that they would.

There are several limitations to this analysis aside from those discussed above. Firstly, very few RCTs studying the efficacy of CHM for COVID-19 have been published; there are only seven included in our review. Therefore, publication bias was not assessed. Secondly, the sample size in each RCT was small. Thirdly, due to the quick onset of COVID-19, researchers did not set up unified clinical trial protocols with consensus, which led to confusion in primary outcomes, secondary outcomes, and course of treatment. Some studies did not mention their primary outcomes. Even though the studies had the same primary outcome, the assessment methods were very different. For example, some studies used scores for symptoms and sign, while others used the score of each main symptom, or the days to specific symptom relief. This creates

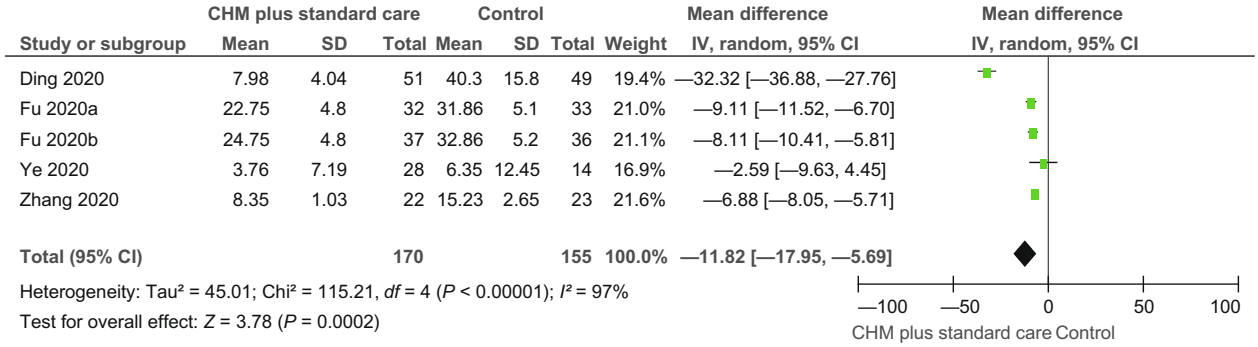

Fig. 5. Comparison of CRP between CHM plus standard care and standard care. CRP: C-reactive protein; CHM: Chinese herbal medicine; SD: standard deviation; CI: confidence interval; IV: inverse-variance.

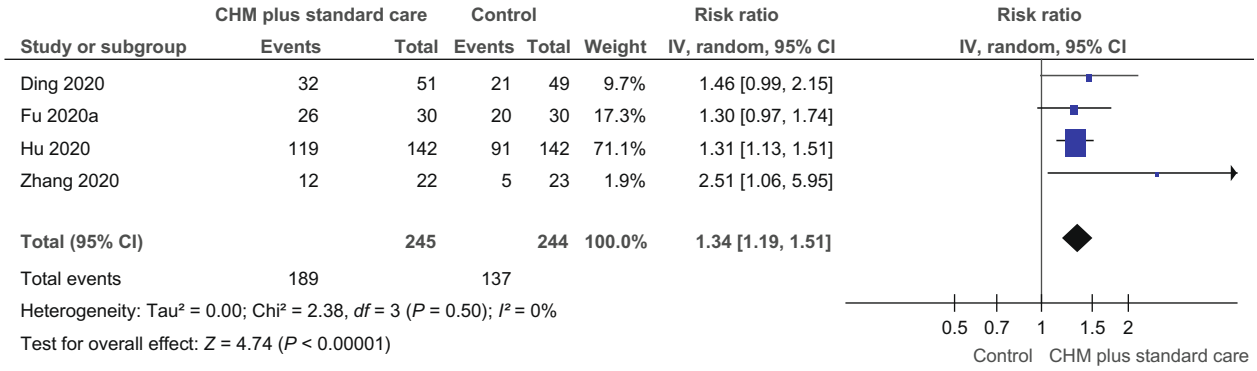

Fig. 6. Comparison of number of participants with improvement confirmed by lung CT scan findings between CHM plus standard care and standard care. CHM: Chinese herbal medicine; CI: confidence interval; CT: Computed tomography; IV: inverse-variance.

a problem for meta-analysis where homogeneous data are pooled to estimate the effect size across multiple studies. Finally, it is difficult to perform a clinical trial with a specific herbal formula, even though we grouped all related modifications together for analysis. In the typical practice of CHM, Chinese medicine doctors use an individualized treatment strategy, and each patient is given an individualized herbal formula that includes modifications to address their specific needs. This kind of individualized treatment might be more effective for a patient's condition than using fixed formulas, as it is more customized treatment. This might lead to more significant results being recorded in clinical studies. Based on the above reasons, more large-scale double-blinded placebo-controlled trials with rigorous evidence-based medicine methodology are warranted to further test the efficacy and safety of CHM for COVID-19.

5. Conclusion

Based on this systematic review and meta-analysis, it is clear that adding CHM to standard care improves the symptoms and signs of COVID-19 patients, decreases the inflammation marker CRP level and accelerates absorption of lung infection lesions. Evidence from some studies even suggests that CHM as a co-therapy may even lower the fatality rate. CHM has been recommended and included in the interim guidelines for the treatment of COVID-19 by the Chinese officials as Chinese medicine is on the mainstream health care system in China. For those countries where CHM has not been regulated or approved as one kind of medicine or therapy, the above CHMs should be used in conjunction with conventional medical care for patients with COVID-19.

Authors' contribution

AYF and SG conducted the study selections and data extraction. AYF, SG and SFA drafted, revised and finalized the manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest. Due to the limitation of the authors' personal backgrounds, experiences and perspectives, this article may have some omissions, limitations, and errors; comments or corrections are welcomed and appreciated.

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