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Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis

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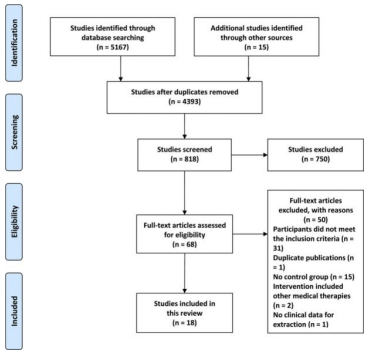
Graphical abstract



Keywords: Chinese herbal medicine, Traditional Chinese medicine, Coronavirus disease 2019, Randomized controlled trial, Systematic review, Meta-analysis

Abstract

Currently, coronavirus disease 2019 (COVID-19), which can lead to severe respiratory failure and death, is now a global pandemic with no specific anti-viral drugs or vaccines. However, It is worth noting that traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), has been widely applied in mainland China since outbreak, bringing new hope for the prevention and control of COVID-19. A comprehensive literature searching was conducted in 7 electronic databases from their inception up to June 21, 2020 to evaluate the efficacy and safety of CHM for COVID-19. Eighteen randomized controlled trials (RCTs) involving 2275 patients were enrolled. Most of CHMs were originated from classical Chinese herbal formulas. Liquoric Root (Gancao, Radix Glycyrrhizae), Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae), Forsythia Fruit (Lianqiao, Fructus Forsythiae Suspensae), and Bitter Apricot Seed (Kuxingren, Semen Armeniacae Amarum) were most frequently used Chinese herbs. The most commonly used dosage formulation was decoction. Our meta-analyses found that comparing CHM group and conventional western medicine group, CHM group has improvements in several clinical parameters including lung CT, clinical cure rate, ranging from mild to critical cases, length of hospital stay, total score of clinical symptoms, fever reduction time, symptom score of fever, number of cough reduction cases, symptom score of cough, number of fatigue reduction cases, symptom score of fatigue, disappearing time of fatigue, TCM syndrome, viral nucleic acid testing, and inflammatory biomarkers (C-reactive protein). Besides, no severe adverse effects was identified by CHM. CHM, especially classical Chinese herbal formulas, could be used as potential candidates for COVID-19 in this battle.

1. Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has broken out in *Wuhan*, China [1]. The main symptoms include fever, dry cough, and fatigue, while some patients with myalgia and diarrhea. It can lead to severe respiratory failure, acute respiratory distress syndrome, septic shock, and even death. Currently, COVID-19 outbreak is moving rapidly. As of June 21, 2020, a total of 8,949,953 confirmed cases of COVID-19 has been reported in China and 200 other countries, with 4,760,539 (53.19 %) cured cases and 467,347 (5.22 %) deaths. Unfortunately, the number of confirmed cases continues to rise due to rapid spread. World Health Organization (WHO) has defined it as a global pandemic. Worst of all, except for conventional western medicine (CWM) including antiviral drugs, antibacterial drugs, antitussive, expectorant and antiasthmatic drugs, and symptomatic and supportive therapy, no specific

anti-viral drugs or vaccines has been discovered for this virus. More efforts should be made to understand the pathophysiology and improve clinical efficacy of this new disease. Thus, it has become a major global public health problem.

In China, the pandemic is under control due to government strong measure, public surveillance, and utilization of both CWM and traditional Chinese medicine (TCM). TCM, especially Chinese herbal medicine (CHM), has been used extensively in the treatment of several acute epidemic infectious diseases including severe acute respiratory syndrome (SARS), influenza A H1N1, avian influenza, malaria, etc [2,3]. According to the research reports of World Health Organization, compared to CWM group, TCM group has achieved remarkable therapeutic effect with 3 days for average fever reduction time, 10 days for average hospital stay, low medical costs, and no death, sequelae, transfer, and infection of nurses and doctors during the SARS epidemic in 2003 [4]. Among the 564 patients with COVID-19 admitted to *Jiangxia Fangcang* TCM Hospital, 482 were cured, and the rest 82 complicated with basic diseases were transferred to designated hospitals. During the treatment, no patients turned from mild to critical cases, and no nurses and doctors were infected by COVID-19. TCM has played an indispensable role and TCM therapeutic schedule was included in the guideline on diagnosis and treatment of COVID-19 [5].

Currently, a large number of published clinical studies including case reports, case series, and randomized controlled trials (RCTs) showed that CHM could improve clinical symptom and and lung CT image, shorten fever reduction time and average length of hospital stay, and reduce the conversion rate from mild to severe, bringing new hope for clinical treatment and new drug discovery in treating COVID-19 [6,7]. Although 4 systematic reviews [[8], [9], [10], [11]] regarding *Lianhua Qingwen* granules and other CHM for COVID-19 have been published in advance respectively, serious methodological shortcomings were also identified. Non-RCTs were enrolled in the review by Dr Qi et al., which should be excluded actually [8]. For the other systematic review, more databases and RCTs should be updated in order to reduce potential bias [[9], [10], [11]]. Therefore, in this study, a systematic review of RCTs was performed to evaluate the current clinical evidence on CHM for the treatment of COVID-19.

2. Methods

This study was conducted and reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

2.1. Eligibility criteria

2.1.1. Types of studies RCTs which have evaluated the efficacy of CHM for COVID-19 were included in this study.

2.1.2. Types of participants Patients diagnosed as COVID-19 could be enrolled in this review. In order to ensure including all relevant studies, no restriction on gender, age and nationality was preseted.

2.1.3. Types of interventions CHM, which include Chinese natural herb and its processed products that originated from botanical drug, mineral, animal, chemical and biological products sources, should be used under the guidance of TCM theory. The dosage forms of CHM contain decoction, tablet, pill, powder, pellet, granule, capsule, cream formula, oral liquid, plaster, and injection [13].

Patients in the treatment group should be treated by CHM or combination of CHM and CWM. Patients in the control group should be treated by CWM or combination of CHM placebo and CWM. CWM in the treatment and control group must be identical in name, usage, dosage, etc. No restrictions on dosage forms, type, quantity, or treatment course of CHM was preseted.

RCTs will be excluded if the following conditions are met: (a) clinical experiences, theoretical discussion, reviews, commentaries, editorials, case reports, case series, and experimental studies; (b) non−COVID-19 patients; (c) other TCM therapeutic methods beyond CHM, including acupuncture, moxibustion, cupping, massage, *qigong*, *Tai Chi*, *baduanjin*, and music therapy, were applied in either treatment or control group; (d) no detailed information regarding clinical efficacy could be extracted; and (e) duplicate publications reporting the same results.

2.1.4. Types of outcome measures The primary outcome measure was defined as lung CT. The secondary outcome measures were death, clinical cure rate, ranging between mild and critical cases, length of hospital stay, clinical symptoms (total score of clinical symptoms, fever, cough, fatigue), TCM syndrome, viral nucleic acid testing, and inflammatory biomarkers including white blood cell (WBC), neutrophils (NEU), lymphocyte (LYM), and C-reactive protein (CRP).

2.2. Literature search

Relevant literatures assessing the efficacy and safety of CHM for COVID-19 were searched in 7 electronic databases including Cochrane Central Register of Controlled Trials, EMBASE, PubMed, Chinese National Knowledge Infrastructure (CNKI), VIP Information Database (VIP), Chinese Biomedical Literature Database (CBM), and Wanfang Database from inception up to June 21, 2020. The following grouped keywords were used as search strategy and modified according to different databases: ("coronavirus disease 2019" OR "COVID-19" OR "SARS-CoV-2" OR "novel coronavirus pneumonia" OR "novel coronavirus" OR "*xin xing guan zhuang bing du fei yan*" OR "*xin guan fei yan*" OR "*xin xing guan zhuang bing du*") AND ("Chinese herbal medicine" OR "traditional Chinese medicine" OR "classical Chinese herbal formulas" OR "Chinese herb" OR "Chinese herb therapy" OR "herbal medicine" OR "herb therapy" OR "herbal remedy" OR "*zhong yi yao*" OR "*zhong yao*") AND ("clinical trial" OR "clinical study" OR "randomized controlled trial"OR "randomised controlled trial" OR "*lin chuang yan jiu*" OR "*lin chuang shi yan*"). In order to reduce bias, we also retrieved the ongoing registered clinical trials and unpublished papers on CHM for COVID-19. We also manually retrieved relevant articles and clinical studies to obtain as much literature as we can. No language and status restriction was set in this review.

2.3. Study selection and data extraction

The selection of studies and data extraction were performed independently by two reviewers (Xiong XJ and Wang PQ) according to the preseted inclusion and exclusion criteria. Detailed information of enrolled study was listed as below: (a) basic characteristics of included studies: title of study, authors' name, publication date, sample size, diagnostic criteria, methodological quality, therapeutic schedule in treatment and control groups, components and dosage of CHM, withdraws, and course of treatment; (b) basic characteristics of included patients: age, gender, ratio of mild to severe cases, baseline data of body temperature, heart rate, respiration, blood pressure, previous medical history, and laboratory examination; (c) both primary and secondary outcome measures; and (d) adverse effects. If detailed information on outcome measure was lacking, the first or correspondence author of original study was contacted by email, fax, and telephone, which were recorded in the article. If no response was obtained from the authors, data was recalculated from the graphs using digital ruler software. Otherwise, it was excluded. If disagreements on data extraction were identified, a third party (Xing YW and William CC) was consulted.

2.4. Assessment of methodological quality

Methodological quality of the included trials was also assessed by 2 reviewers (Xiong XJ and Su KL) independently. According to Cochrane Collaboration's tool [14], 7 fields of risk of bias (ROB) were

evaluated as below: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each field was assessed to be “yes” (low ROB), “no” (high ROB), or “unclear” (unclear ROB).

2.5. Data analysis

Review Manager software (RevMan, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was utilized to conduct the data analysis of dichotomous and continuous outcome measures, which were extracted from the original studies. Weighted mean difference (WMD) was utilized for data measurement of continuous outcomes, while risk ratio (RR) for dichotomous outcomes. All of them were expressed with a 95 % confidence interval (CI). When no statistical heterogeneity was identified (heterogeneity test, $P \geq 0.10$, or $I^2 \leq 50$ %), fixed-effects model was selected, otherwise random-effects model was applied. Funnel plot was also used to evaluate the publication bias. It was regarded as significant difference when $P < 0.05$.

3. Results

3.1. Study selection

The flow chart of literature identification and screening is described in Fig. 1 . In total, 5182 related literatures were derived from the above 7 electronic databases. After removing duplicate publications, 4393 studies were remained. And then, we excluded 4325 studies as they are not RCT, specially, these include reviews, commentaries, editorials, case reports, case series, experimental researches, data mining articles, and irrelevant to COVID-19 after scanning titles and abstracts. Furthermore, after reading the rest 68 full papers, we further excluded 50 literatures as follows: participants did not meet the inclusion criteria (n = 31); duplicate publications (n = 1); no control group (n = 15); intervention included other medical therapies (n = 2); no clinical data for extraction (n = 1). Ultimately, 18 eligible RCTs were included [[15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32]].

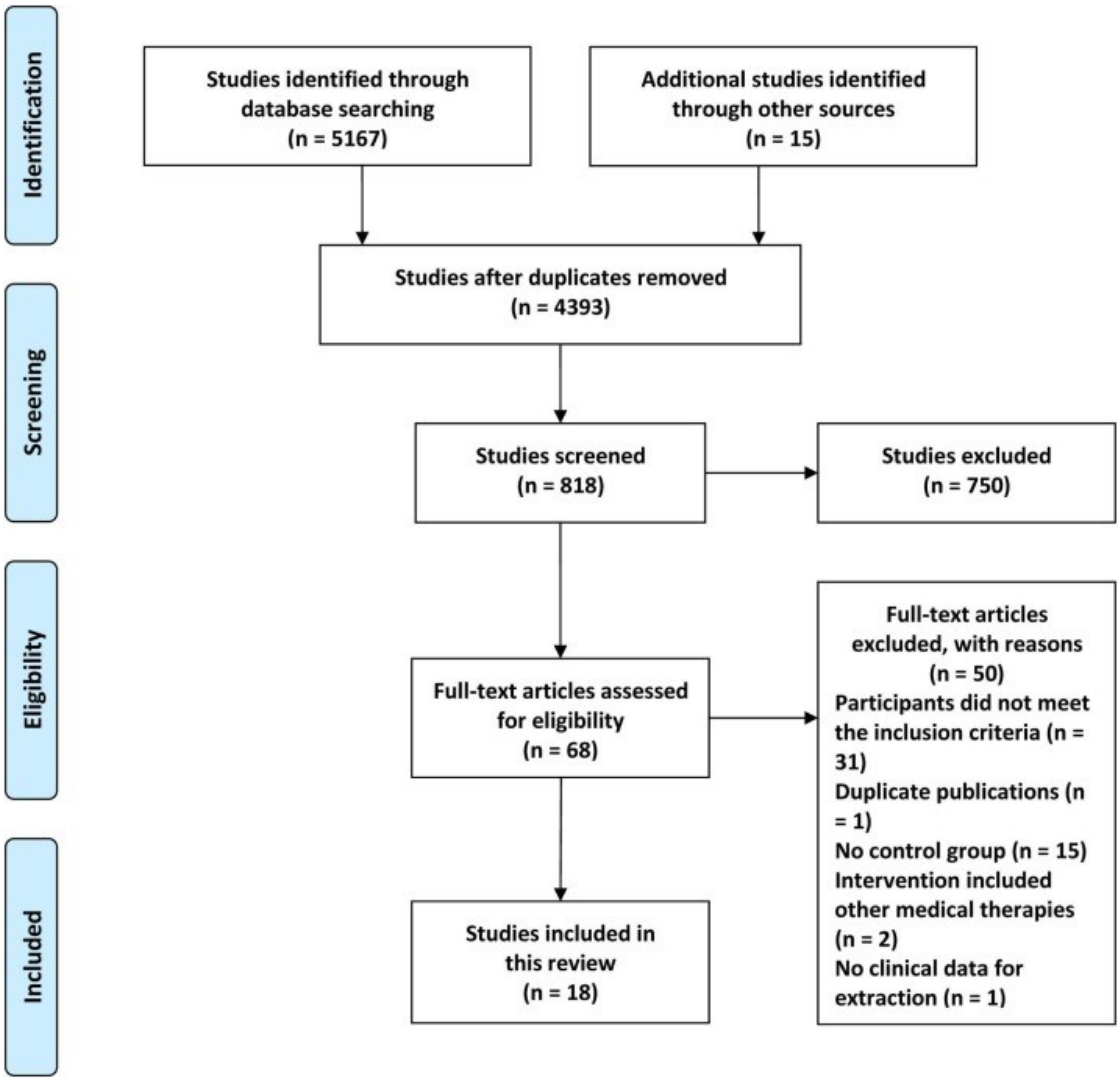


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Fig. 1

Flow diagram of study selection and identification.

3.2. Study characteristics

Basic characteristics of enrolled studies and subjects was listed in Table 1 . Among the 18 included trials, 5 were multi-centered trials [21,24,27,30,32] and the rest 13 were single-centered trials. All of the 18 studies were conducted in mainland China in 2020. One paper was online published in advance with English language [32], and the rest were in Chinese [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]. There were altogether 2275 patients enrolled in this review, with the sample size ranged from 20 to 517. All the included trials evaluated the effects of CHM combined with CWM compared to CWM alone. The name, usage, dosage of western medicine used in CHM group should be the same as used in CWM group. There is no trial utilized CHM placebo. Treatment duration varied from 5 to 15 days. Primary outcome measure was reported in 13 studies [15, 16, 17, 18, 19,21,22,24,26,28,30, 31, 32]. Death was reported in 4 trials [17,18,21,31]. Clinical cure rate was

reported in 7 trials [18,19,22,24,29,31,32]. Ranging between mild and critical cases was reported in 12 trials [[15], [16], [17], [18],20,21,24,25,28,[30], [31], [32]]. Length of hospital stay was reported in 2 trials [17,18]. All the included trials reported clinical symptoms. TCM syndrome was evalated in 5 studies [18,20,28,29,31]. Viral nucleic acid testing was reported in 4 trials [15,21,23,32]. Inflammatory biomarkers were reported in 8 trials, including WBC, NEU, LYM, and CRP [15,16,18,19,21,22,29,31]. Adverse effects were ported in 10 trials [15,16,[18], [19], [20],22,23,25,31,32].

Table 1

Basic characteristics of included trials and subjects.

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Abbreviation: C: control; CHM: Chinese herbal medicine; CWM: conventional western medicine; F: female; GDTCOVID-19: guideline for diagnosis and treatment of COVID-19; M: male; N: no; T: treatment; TCM: traditional Chinese medicine; Y: yes.

3.3. Assessment of methodological quality

As shown in Table 2 , the methodological quality of the included studies was evaluated based on the criteria in Cochrane handbook. Detailed information on sequence generation of randomization was reported in 6 trials (6/18, 33.33 %) [16,20,28,30], [31], [32]]. Specific method of allocation concealment was not described in this review. One trial reported no application of blinding [30]]. One trial only reported blinding of assessor [32]]. Detailed information regarding blinding of patient, investigator, and assessor was unclear in the rest 16 trials [[15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29],31]]. Dropouts were reported in 4 trials (4/18, 22.22 %) [15,16,20,21]].

Table 2

Methodological quality of included trials according to Cochrane handbook.

References	A	B	C	D	E	F	G	H
Huang H et al 2020 [15]	?	?	?	?	?	+	?	?
Ding XJ et al. 2020 [16]	+	?	?	?	?	+	?	?
Shi J et al. 2020 [17]	?	?	?	?	?	+	?	?
Xia WG et al. 2020 [18]	?	?	?	?	?	+	?	?
Fu XX et al. 2020 [19]	?	?	?	?	?	+	?	?
Duan C et al. 2020 [20]	+	?	?	?	?	+	?	?
Yang MB et al. 2020 [21]	?	?	?	?	?	+	?	?
Xiao Q et al. 2020 [22]	?	?	?	?	?	+	?	?
Qu XK et al. 2020 [23]	?	?	?	?	?	+	?	?
Cheng DZ et al. 2020 [24]	?	?	?	?	?	+	?	?
Lv RB et al. 2020 [25]	?	?	?	?	?	+	?	?
Wang YL et al. 2020 [26]	?	?	?	?	?	+	?	?
Yao KT et al. 2020 [27]	?	?	?	?	?	+	?	?
Qiu M et al. 2020 [28]	+	?	?	?	?	+	?	?
Liu XG et al. 2020 [29]	?	?	?	?	?	+	?	?
Sun HM et al. 2020 [30]	+	?	–	–	–	+	?	?
Yu P et al. 2020 [31]	+	?	?	?	?	+	?	?
Hu K et al. 2020 [32]	+	?	–	–	+	+	?	?

Abbreviation: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (patient); D: Blinding (investigator); E: Blinding (assessor); F: Incomplete outcome data addressed (ITT analysis); G: Free of selective reporting; H: Other potential threat to validity; +: Low risk; -: High risk;? : Unclear.

3.4. Description of single herb and CHM

Thirty-one CHM were used in this review, including *Maxing Shigan* decoction, *Chailing Pingwei* decoction, *Haoqin Qingdan* decoction, *Huopu Xialing* decoction, Modified *Buzhong Yiqi* decoction,

Pneumonia No. 1 formula, Powerful Pneumonia No. 1 formula, Pneumonia No. 2 formula, *Qingfei Touxie Fuzheng* recipe, Damp-toxin obstructing lung formula, Toxin blocking lung formula, *Qiwei* decoction, *Toujie Quwen* granules, *Shufeng Jiedu* capsules, *Lianhua Qingwen* granules and capsules, *Xuanfei Zhisou* mixture, *Shuanghuanglian* oral liquids, *Yupingfeng* granules, *Ganlu Xiaodu* pills, *Huoxiang Zhengqi* liquids, *Reyanning mixture*, *Jinhua Qinggan* granules, *Xuebijing* injection, *Tanreqing* injection, *Shengmai* injection, *Shenfu* injection, *Lianhua Qingke* granules, Maxing Xuanfei Jiedu decoction, etc. Among them, 13 (13/31, 41.94 %) were originated from classical Chinese herbal formulas, which have been used for 189–1800 years.

The frequency of each Chinese herb in this review was also summarized manually. In total, 100 Chinese herbs were included. And the top 5 ranked Chinese herbs were Liquoric Root (Gancao, Radix Glycyrrhizae) (15/31, 48.39 %), Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis) (11/31, 35.48 %), Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) (11/31, 35.48 %), Forsythia Fruit (Lianqiao, Fructus Forsythiae Suspensae) (10/31, 32.26 %), and Bitter Apricot Seed (Kuxingren, Semen Armeniacae Amarum) (10/31, 32.26 %).

Six dosage formulations of CHM were included, including decoction, granule, capsule, oral liquid, pill, and injection. The most commonly used dosage formulation was decoction (17/31, 54.84 %), followed by granule (7/31, 22.58 %), injection (4/31, 12.90 %), oral liquid (2/31, 6.45 %), capsule (2/31, 6.45 %), and pill (1/31, 3.23 %). The decoction of CHM was orally taken 1 dose every day, with about 400 mL in every dose. The administration of CHM in each trial was described in Table 1 and the compositions were summarized in Table 3 .

Table 3

Components of Chinese herbal medicine used in the included studies.

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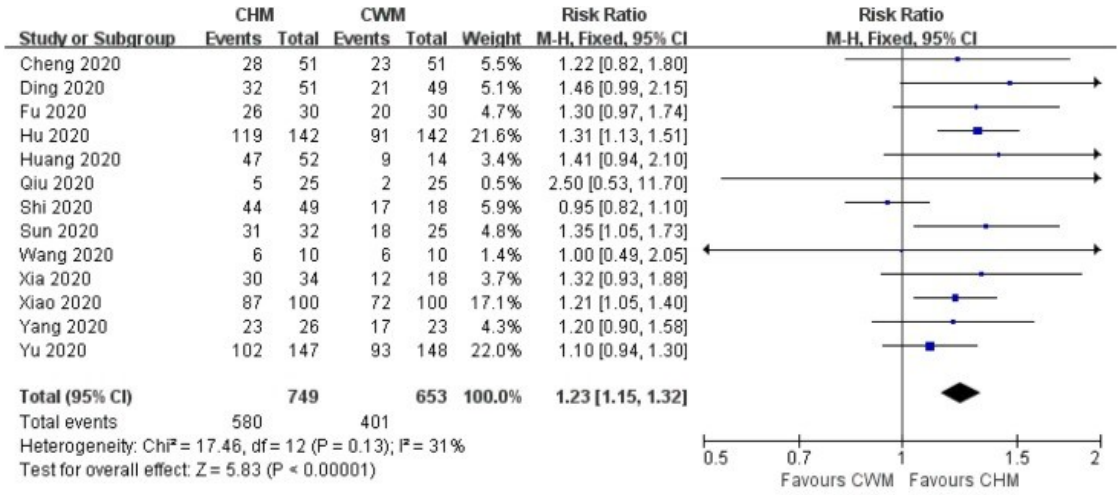
Abbreviation: CHM: Chinese herbal medicine; ▲: originated from classical Chinese herbal formulas.

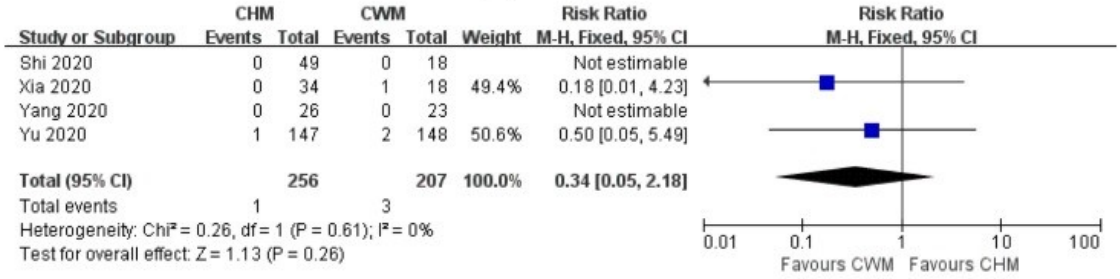
3.5. Efficacy assessment

3.5.1. Lung CT Thirteen trials assessed the efficacy of CHM on lung CT in this study [[15], [16], [17], [18],

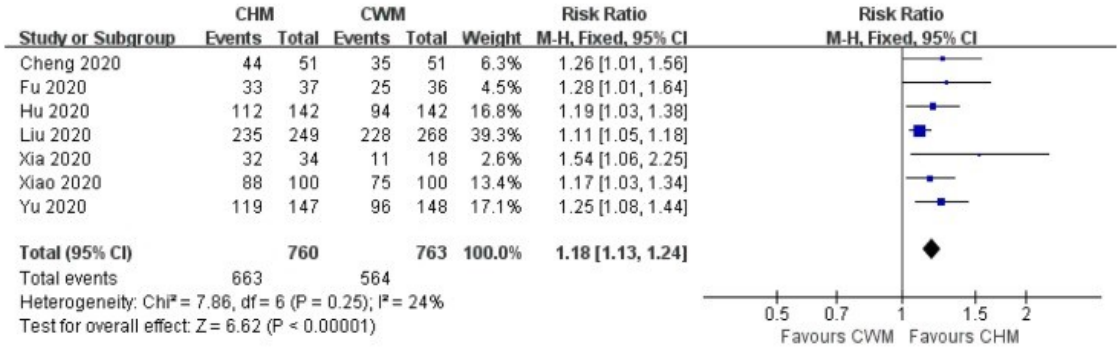
[19],21,22,24,26,28,[30], [31], [32]]. There were 749 patients in CHM group and 653 in CWM group. A significant improvement in lung CT was identified by CHM in this meta-analysis (13 trials, n = 1402; RR = 1.23; 95 % CI: 1.15–1.32; I^2 = 31 %, $P <$ 0.00001; Fig. 2 a).



(a) lung CT



(b) death



(c) clinical cure rate

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Fig. 2

Forest plot of the effects of CHM for outcomes of (a) lung CT, (b) death, and (c) clinical cure rate.

3.5.2. Death The effect of CHM on death was reported in 4 trials [17,18,21,31]. There were 256 patients in CHM group and 207 in CWM group. Meta-analysis showed no significant difference on death

between CHM and CWM (4 trials, n = 463; RR = 0.34; 95 % CI: 0.05–2.18; I^2 = 0%, P = 0.26; Fig. 2 b).

3.5.3. Clinical cure rate Clinical cure rate was defined as the following 4 discharge criterion in guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia: a) body temperature returned to normal for more than 3 days, b) respiratory symptoms improved significantly, c) pulmonary imaging showed obvious absorption of inflammation, and d) two consecutive times of novel coronavirus nucleic acid test negative in respiratory tract (the sampling interval shall be at least 1 day) [7]. Seven trials evaluated the effects of CHM on clinical cure rate [18,19,22,24,29,31,32]. There were 760 patients in CHM group and 763 in CWM group. CHM exhibited a significant improvement on clinical cure rate (7 trials, n = 1523; RR = 1.18; 95 % CI: 1.13–1.24; I^2 = 24 %, P < 0.00001; Fig. 2c).

3.5.4. Ranging between mild and critical cases Twelve trials evaluated the effects of CHM on ranging between mild and critical cases [[15], [16], [17], [18],20,21,24,25,28,[30], [31], [32]]. Among them, effects of CHM on ranging from critical to mild cases were evaluated in 2 trials [16,17]. There were 100 patients in CHM group and 67 in CWM group. Compared with CWM, no significant difference on ranging from critical to mild cases was identified (RR = 1.34; 95 % CI: 0.47–3.80; I^2 = 0%, P = 0.58; Fig. 3 a).

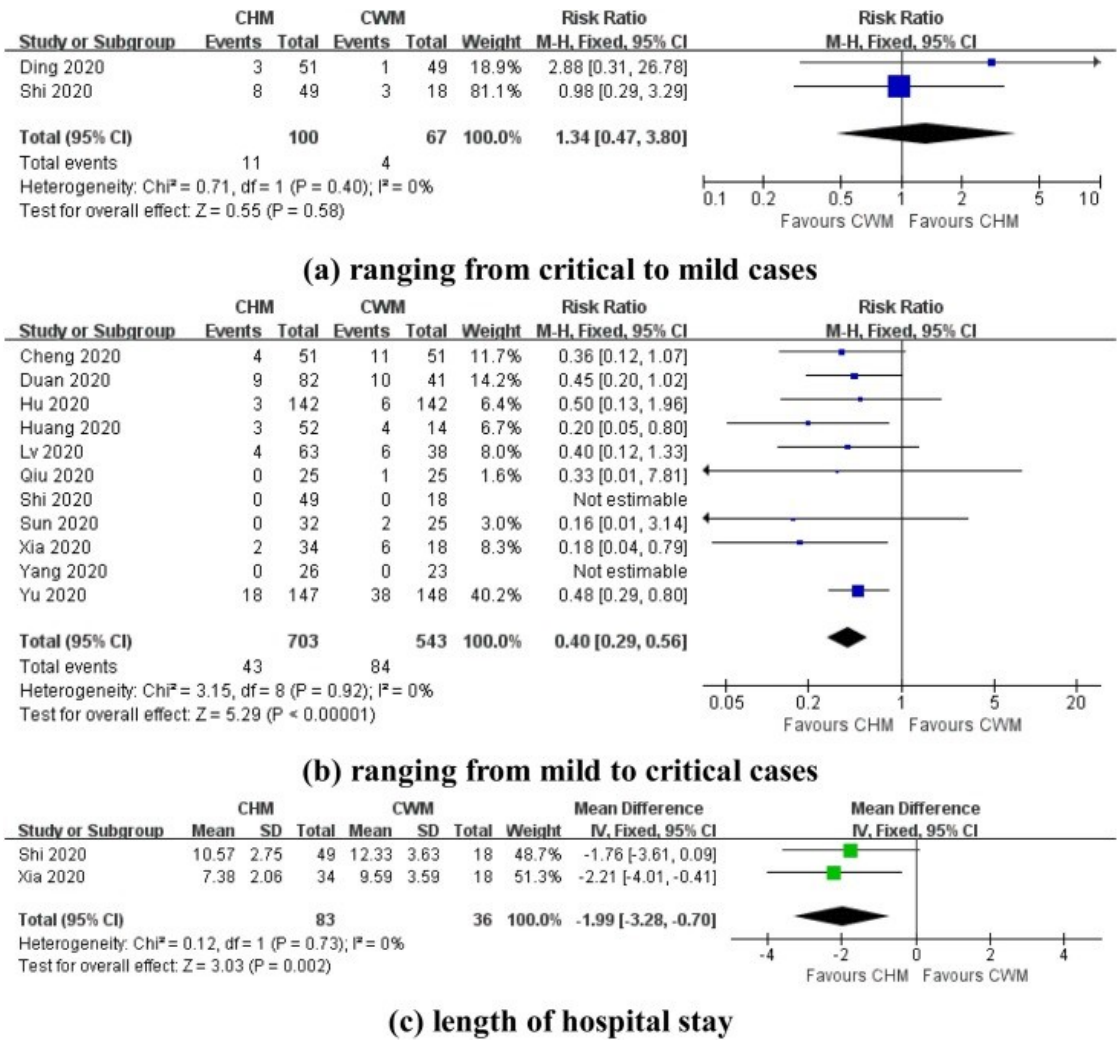

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Fig. 3

Forest plot of the effects of CHM for outcomes of (a) ranging from critical to mild cases, (b) ranging from mild to critical cases, and (c) length of hospital stay.

In addition, effects of CHM on ranging from mild to critical cases were evaluated in 11 trials [15,17,18,20,21,24,25,28,[30], [31], [32]]. There were 703 patients in CHM group and 543 in CWM group. A significant improvement on ranging from mild to critical cases was observed by CHM (11 trials, n = 1246; RR = 0.40; 95 % CI: 0.29 to 0.56; I^2 = 0%, P < 0.00001; Fig. 3b).

3.5.5. Length of hospital stay Two trials evaluating length of hospital stay were included for further analysis [17,18]. There were 83 patients in CHM group and 36 in CWM group. Meta-analysis showed a significant reduction on length of hospital stay by CHM (2 trials, n = 119; WMD: -1.99; 95 % CI: -3.28 to -0.70; I^2 = 0%, P = 0.002; Fig. 3c).

3.5.6. Clinical symptoms Clinical symptoms including fever, dry cough, expectoration, fatigue, sore throat, itchy throat, chest tightness, asthma, shortness of breath, poor appetite, diarrhea, nausea, vomiting, abdominal distention, and abdominal pain were reported in all the included studies [[15], [16],

[17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32]]. As fever, dry cough, and fatigue were main clinical symptoms of COVID-19, individual symptom score, disappearing time, number of improved cases, and total score of clinical symptom were summarized.

3.5.7. Total score of clinical symptoms Total score of clinical symptom was evaluated in 2 studies [15,17]. There were 101 patients in CHM group and 32 in CWM group. Meta-analysis revealed a significant improvement on total score of clinical symptom (2 trials, n = 133; WMD: -1.84; 95 % CI: -3.10 to -0.58; I^2 = 0%, P = 0.004; Fig. 4 a).

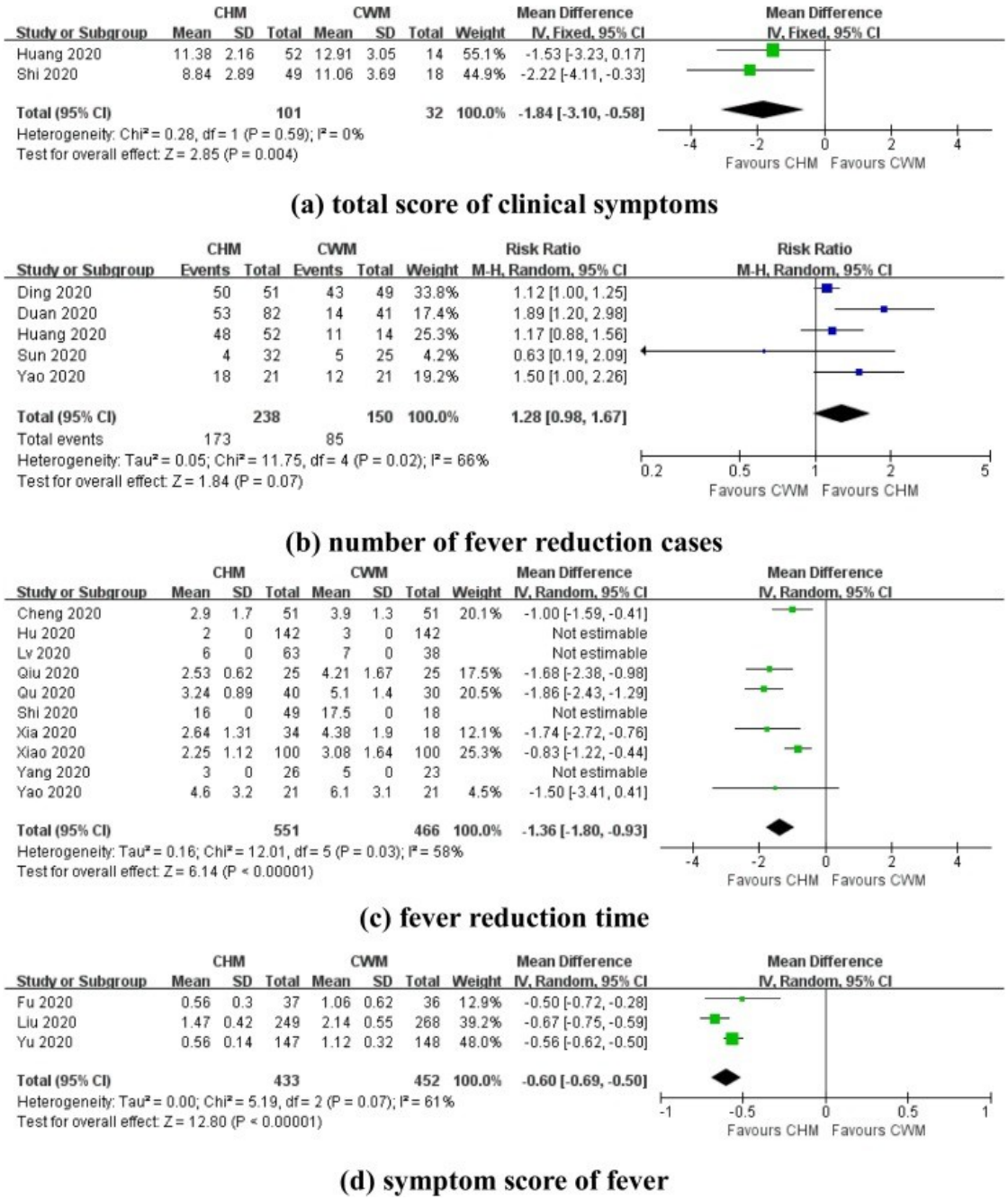

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Fig. 4

Forest plot of the effects of CHM for outcomes of (a) total score of clinical symptoms, (b) number of fever reduction cases, (c) fever reduction time, and (d) symptom score of fever.

3.5.8. Fever The symptom of fever was reported in 15 trials [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25],[27], [28], [29], [30],32]. Among them, 5 studies reported number of fever reduction cases [15,16,20,27,30], 10 reported fever reduction time [17,18,21,[16], [17], [18], [19], [20], [21], [22], [23], [24], [25],27,28,32], and 3 reported symptom score of fever [19,29,31].

In the field of number of fever reduction cases, there were 238 patients in CHM group and 150 in CWM group. Meta-analysis revealed no significant difference on fever reduction number between CHM and CWM (5 trials, n = 388; RR = 1.28; 95 % CI: 0.98–1.67; I^2 = 66 %, P = 0.07; Fig. 4b).

In the field of fever reduction time, there were 551 patients in CHM group and 466 in CWM group. The aggregated results including 10 trials suggested that fever reduction time is significantly improved by CHM (10 trials, n = 1017; WMD: -1.36; 95 % CI: -1.80 to -0.93; I^2 = 58 %, $P <$ 0.00001; Fig. 4c).

In the field of symptom score of fever, there were 433 patients in CHM group and 452 in CWM group. It has been identified that score of fever is significantly reduced by CHM (3 trials, n = 885; WMD: -0.60; 95 % CI: -0.69 to -0.50; I^2 = 61 %, $P <$ 0.00001; Fig. 4d).

3.5.9. Cough The symptom of cough was reported in all the trials, and only 14 were enrolled in this review [16,[19], [20], [21], [22], [23], [24], [25],[27], [28], [29], [30], [31], [32]]. Among them, 6 studies reported number of cough reduction cases [16,20,24,25,27,30], 4 reported symptom score of cough [19,21,29,31], and 6 reported disappearing time of cough [[22], [23], [24],28,30,32].

In the field of number of cough reduction cases, there were 240 patients in CHM group and 182 in CWM group. Meta-analysis showed a significant improvement on number of cough reduction cases by CHM (6 trials, n = 422; RR = 1.50; 95 % CI: 1.26–1.78; I^2 = 0%, $P <$ 0.00001; Fig. 5 a).

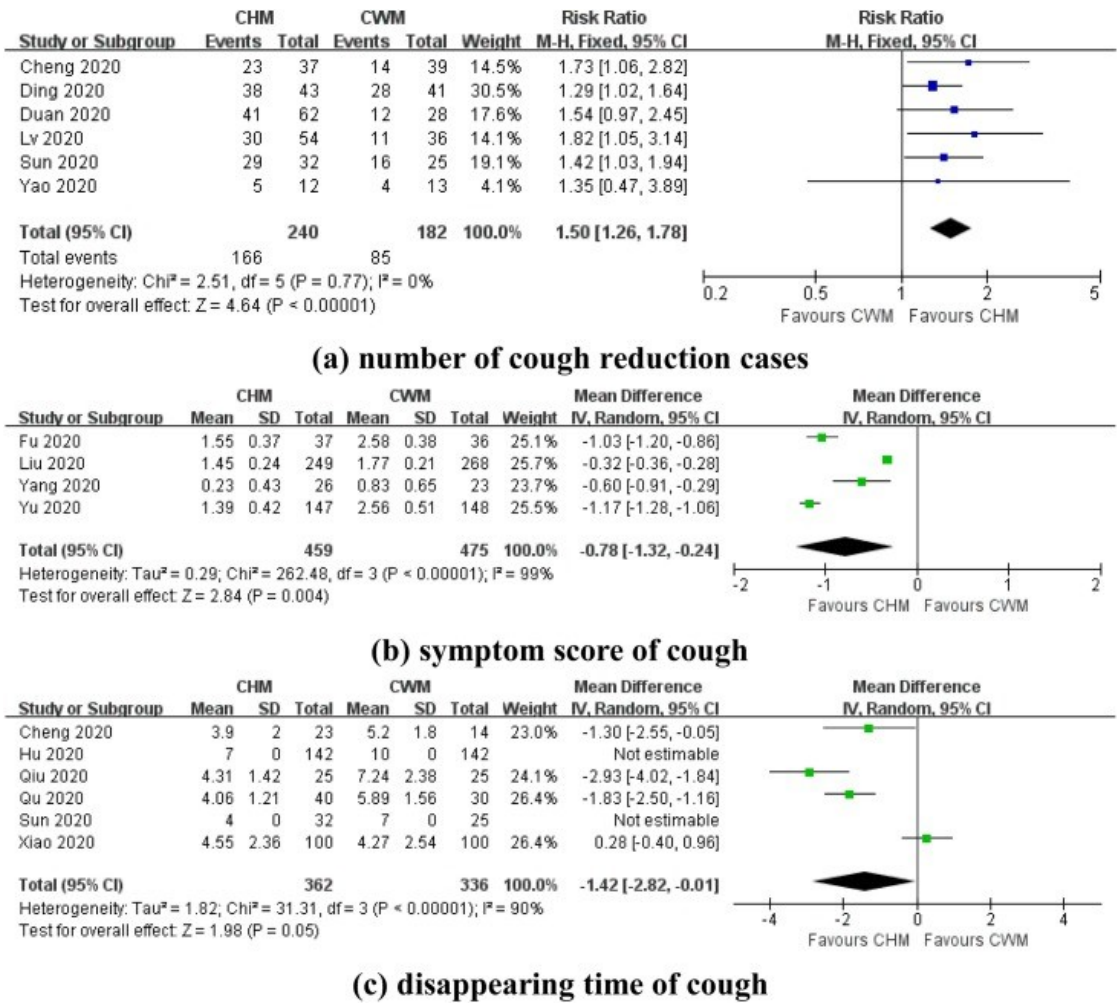

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Fig. 5

Forest plot of the effects of CHM for outcomes of (a) number of cough reduction cases, (b) symptom score of cough, and (c) disappearing time of cough.

In the field of symptom score of cough, there were 459 patients in CHM group and 475 in CWM group. The aggregated results suggested that cough is significantly improved by CHM (4 trials, n = 934; WMD: -0.78; 95 % CI: -1.32 to -0.24; I^2 = 99 %, P = 0.004; Fig. 5b).

In the field of disappearing time of cough, there were 362 patients in CHM group and 336 in CWM group. No significant difference on disappearing time of cough between CHM and CWM was identified in this study (6 trials, n = 698; WMD: -1.42; 95 % CI: -2.82 to -0.01; I^2 = 90 %, P = 0.05; Fig. 5c).

3.5.10. Fatigue The effect of CHM on fatigue was evaluated in 12 studies [[19], [20], [21], [22], [23], [24], [25],27,[29], [30], [31], [32]]. Among them, 5 studies reported number of fatigue reduction cases [20,24,25,27,30], 4 reported individual symptom score [19,21,29,31], and 4 reported disappearing time of fatigue [[22], [23], [24],32].

For number of fatigue reduction cases, there were 167 patients in CHM group and 140 in CWM group.

A significant improvement on number of fatigue reduction cases by CHM was identified in this meta-analysis (5 trials, n = 307; RR = 1.73; 95 % CI: 1.39–2.16; I^2 = 0%, $P <$ 0.00001; Fig. 6 a).

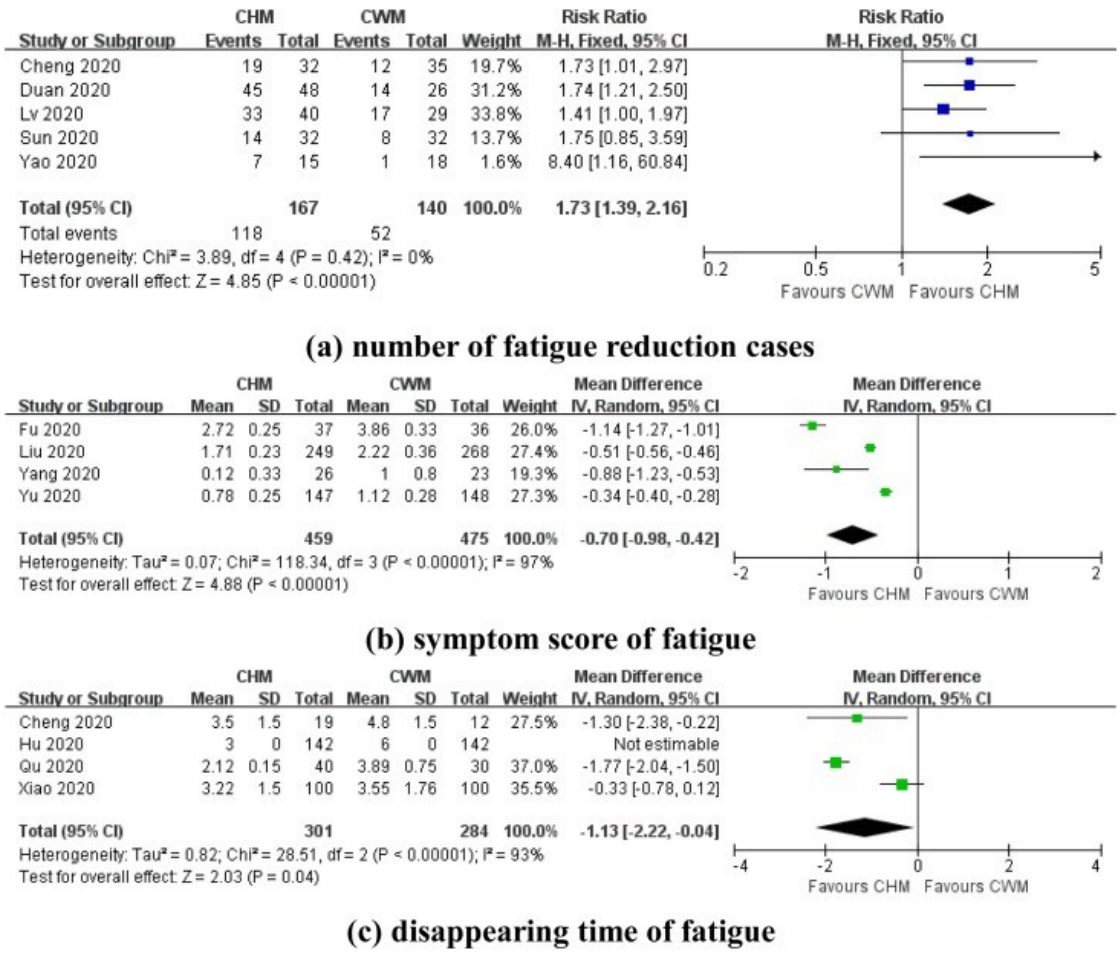

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Fig. 6

Forest plot of the effects of CHM for outcomes of (a) number of fatigue reduction cases, (b) symptom score of fatigue, and (c) disappearing time of fatigue.

For symptom score of fatigue, there were 459 patients in CHM group and 475 in CWM group. Compared to CWM, a significant improvement on symptom score of fatigue was observed by CHM (4 trials, n = 934; WMD: -0.70; 95 % CI: -0.98 to -0.42; I^2 = 97 %, $P <$ 0.00001; Fig. 6b).

For disappearing time of fatigue, there were 301 patients in CHM group and 284 in CWM group. Improvement on disappearing time of fatigue was also identified in CHM group compared to CWM group (4 trials, n = 585; WMD: -1.13; 95 % CI: -2.22 to -0.04; I^2 = 93 %, $P =$ 0.04; Fig. 6c).

3.5.11. TCM syndrome The efficacy of CHM on TCM syndrome was evalated in 5 studies [18,20,28,29,31]. Only 3 trials could be enrolled in this study. There were 141 patients in CHM group and 84 in CWM group. Meta-analysis showed significant improvement by CHM on TCM syndrome (3 trials, n = 225; WMD: -3.67; 95 % CI: -6.60 to -0.73; I^2 = 86 %, $P =$ 0.01; Fig. 7 a).

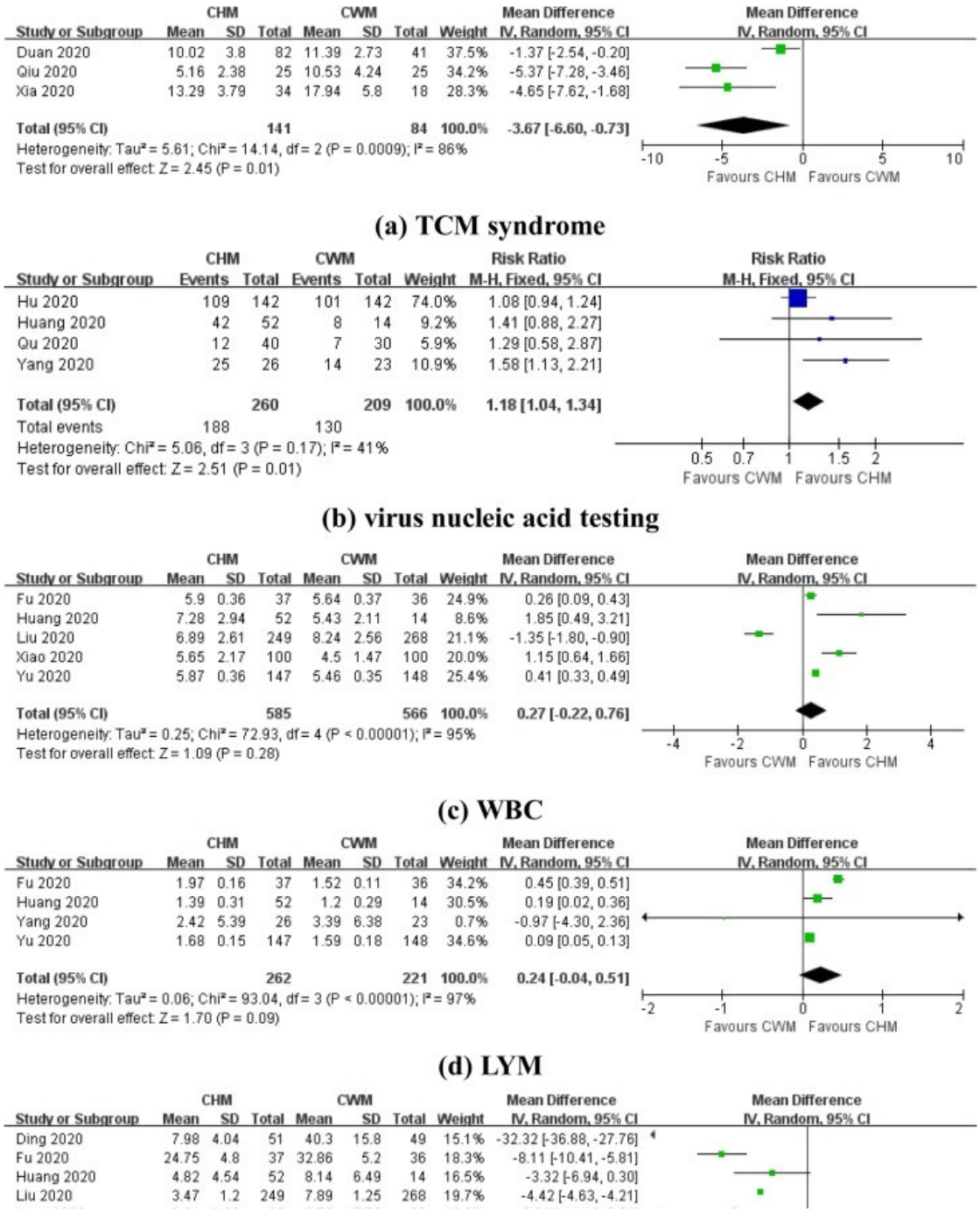

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Fig. 7

Forest plot of the effects of CHM for outcomes of (a) TCM syndrome, (b) virus nucleic acid testing, (c) WBC, (d) LYM, and (e) CRP.

3.5.12. Viral nucleic acid testing The effect of CHM on viral nucleic acid testing was reported in 4 trials [15,21,23,32]. There were 260 patients in CHM group and 209 in CWM group. A significant improvement on negative conversion rate of viral nucleic acid testing was identified by CHM when

compared with CWM (4 trials, n = 469; RR = 1.18; 95 % CI: 1.04–1.34; I^2 = 41 %, P = 0.01; Fig. 7b). Additionally, the negative conversion time of viral nucleic acid testing was reported in 1 trial [23], and a shorter time was identified in CHM group (9.32 ± 3.03 vs 11.89 ± 3.21).

3.6. Inflammatory biomarkers

3.6.1. WBC Six trials evaluated the efficacy of CHM on number of WBC [15,18,19,22,29,31]. As enumeration data was used in 1 trial [18], 5 trials were included in this study [15,19,22,29,31]. There were 585 patients in CHM group and 566 in CWM group. Meta-analysis showed no significant difference between CHM and CWM on the number of WBC in patients with COVID-19 (5 trials, n = 1151; WMD: 0.27; 95 % CI: -0.22 to 0.76; I^2 = 95 %, P = 0.28; Fig. 7c).

3.6.2. NEU For the number of NEU, 3 trials [15,18,21] involving 167 patients were enrolled. As enumeration data and percentage were used in 2 trials [15,21], meta-analysis could not be conducted accordingly. Among them, a significant improvement of NEU was identified in 1 trial [18] (P < 0.05), while negative conclusions were found in the rest 2 trials [15,21].

3.6.3. LYM Effects of CHM on the level of LYM were assessed in 6 trials [15,18,19,21,22,31]. As enumeration data and percentage were reported in 2 trials with positive conclusions [19,22], only 4 trials were included in this meta-analysis. Meta-analysis revealed no significant difference between CHM and CWM on the level of LYM (4 trials, n = 483; WMD: 0.24; 95 % CI: -0.04 to 0.51; I^2 = 97 %, P = 0.09; Fig. 7d).

3.6.4. CRP The levels of CRP at baseline and after intervention were recorded in 7 trials [15,16,18,19,21,29,31]. Although positive conclusion was identified in 1 trial [19], it could not be included in the meta-analysis due to enumeration data. Meta-analysis of the rest 6 trials revealed that CRP is significantly reduced by CHM (6 trials, n = 1100; WMD: -8.91; 95 % CI: -12.56 to -5.27; I^2 = 97 %, P < 0.00001; Fig. 7e).

3.6.5. Adverse effects In this review, 10 trials reported adverse effects (10/18, 55.56 %) [15,16,[18], [19], [20],22,23,25,31,32]. Among them, no adverse effect was identified in both CHM and CWM groups [18,19,25,31]. Adverse effects in the rest 6 trials included gastrointestinal reactions (abdominal distention, diarrhea, abdominal pain, nausea, vomiting, belching, acid reflux, poor appetite), headache, dizziness, drowsiness, abnormal liver function, renal dysfunction, and drug allergy [15,16,20,22,23,32]. All of the reported adverse effects were released spontaneously in both CHM and CWM groups. Meta-analysis identified that no significant difference between CHM and CWM was identified (9 trials, n = 1069; RR = 0.93; 95 % CI: 0.49–1.75; I^2 = 46 %, P = 0.82; Fig. 8).

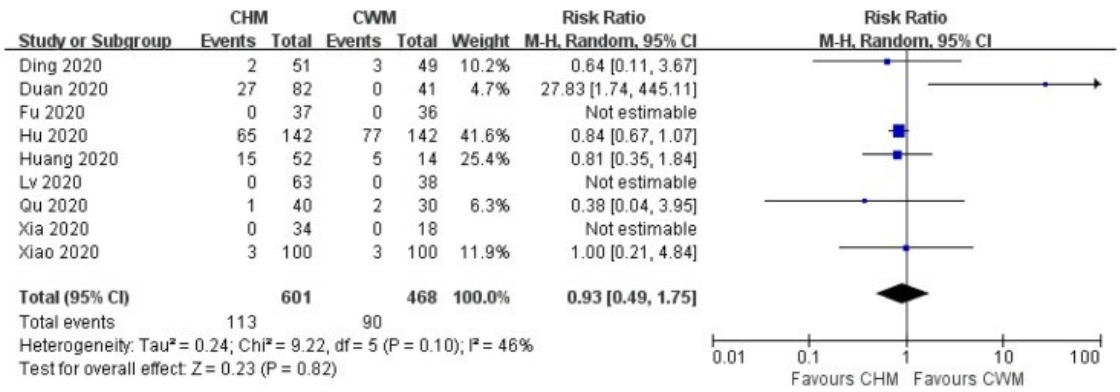

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Fig. 8

Forest plot of the reported adverse effects.

3.6.6. Publication bias Publication bias was detected by the funnel plot of lung CT. The asymmetry suggested a mild publication bias in the study (Fig. 9).

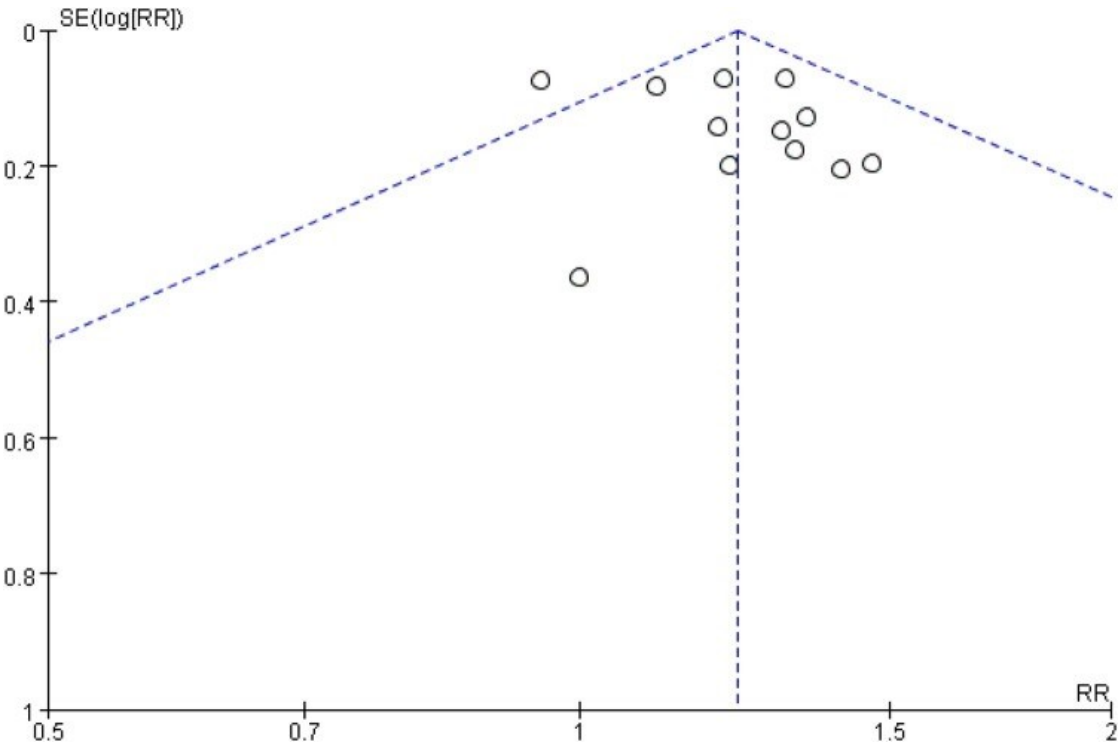

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Fig. 9

Funnel plot of outcome of lung CT.

4. Discussion

4.1. Summary of evidence

Currently, COVID-19 has become a major public health problem in the whole world [33,34]. It has been identified that clusters of fatal pneumonia could be caused by 2019 novel coronavirus (2019-nCoV), the clinical manifestation of which is greatly resembling severe acute respiratory syndrome coronavirus (SARS-CoV) [35]. During the epidemic, rapid and robust research is important to help guide clinical treatment, formulating public health policy, and new drug research and development. From the beginning of outbreak, CHM has been widely used in China and evidences of CHM for COVID-19 are emerging gradually. To our knowledge, this is the first strictly designed systematic review and meta-analysis of all the published RCTs to assess the efficacy and safety of CHM for COVID-19 in English.

In this study, several research highlights deserved our attention. Firstly, extensive literature searching of relevant clinical trials published in both Chinese and English databases was performed. In the previous published systematic reviews, only less than 5 RCTs were included. However, up to 18 trials were enrolled in our review, the conclusion of which was more persuasive and feasible. Although the number of included studies was still small, these data are very valuable and timely in light of no specific drugs and high mortality of COVID-19.

Secondly, large number of objective and subjective outcome measures including lung CT, death, clinical cure rate, ranging between mild and critical cases, length of hospital stay, clinical symptoms, TCM syndrome, viral nucleic acid testing, and inflammatory biomarkers were utilized to assess the efficacy of CHM comprehensively. This is different from the traditional evaluation of CHM that only focused on subjective indicators. The whole research findings from 18 trials involving 2275 patients showed that lung CT, clinical cure rate, ranging from mild to critical cases, length of hospital stay, total score of clinical symptoms, fever reduction time, symptom score of fever, number of cough reduction cases, symptom score of cough, number of fatigue reduction cases, symptom score of fatigue, disappearing time of fatigue, TCM syndrome, viral nucleic acid testing, and inflammatory biomarkers (CRP) were significantly improved by CHM. In my opinion, achievement of clinical efficacy is closely related to traditional medical experience and extensive use of large number of classical Chinese herbal formulas. Although there is no records in TCM, it does not affect the understanding of TCM pathogenesis and clinical treatment of COVID-19. As symptoms and signs including tongue coating and pulse are the basis of diagnosis and treatment in TCM, TCM syndrome and formulae syndrome rather than disease were focused accordingly [36]. When in treating acute infectious febrile diseases, large quantity of classical Chinese herbal formulas have been formed and accumulated in ancient times [37]. It is held that COVID-19 belong to “damp-heat epidemic” or “damp-toxin epidemic” according to TCM theory. The disease can be divided into 3 stages on the basis of different TCM pathogenesis: illness in all three *yang* channels in the mild stage, phlegm-heat obstructing the lung in the critical stage, and deficiency of lung and spleen *qi* in the recovery stage. Therefore, therapeutic principles of dispelling cold, relieving exterior, dissipating phlegm, clearing away heat, invigorating spleen, and replenishing *qi* were widely used. Classical Chinese herbal formulas including *Maxing Shigan* decoction, *Xiaochaihu* decoction, etc. were frequently applied correspondingly. What’s more, all these formulas possessed a wide range of pharmacological functions including anti-inflammatory, antiviral, antipyretic, expectorant, antiasthmatic, antitussive effects [38]. However, more researches on clinical evidence and molecular mechanism by classical Chinese herbal formulas are also warranted.

Thirdly, treatment course of CHM was also worthy of attention. The reported course ranged from 5 to 15 days. Whether CHM can play a role in such a short period of time is a widely concerned issue. Patients diagnosed as COVID-19 could develop severe pulmonary infection and acute respiratory

distress syndrome, which have a high likelihood of hospitalization in intensive care unit and death. However, TCM often held that "to treat what and when it is not ill". That is to say, although patient manifested fever in the early stage and mild stage of COVID-19, it belongs to the category of typical exterior syndrome from the perspective of TCM. If it was intervened in time at the stage of exterior syndrome, COVID-19 can be effectively blocked in ranging from mild to critical cases, thus reducing mortality, length of hospital stay, and fever reduction time.

Fourthly, in terms of adverse effects, no severe discomfort and abnormal liver and kidney function was identified in CHM group. The results indicated that CHM maybe relatively safe for COVID-19. However, as adverse effects were not reported in some studies, the safety of CHM should be observed and reported in more detailed information.

Fifthly, the most frequently used Chinese herbs were also analysed in this study. In the top 5 herbs, Liquoric Root (Gancao, Radix Glycyrrhizae) is traditionally used as "*Shi*" to harmonize the properties of different drugs. It is also widely used to resolve phlegm and relieve cough. Glycyrrhetinic acid (Fig. 10 a), the effective component of Liquoric Root (Gancao, Radix Glycyrrhizae), has a strong antitussive and expectorant effect with a dose-dependent relationship. Glycyrrhetinic acid and glycyrrhizin also possess obvious antipyretic effect. Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis) can clear away heat and reduce fire, thus treating febrile diseases, acute upper respiratory tract infection, and cough yellow phlegm. Baicalin (Fig. 10b) and baicalein (Fig. 10c), the active components of Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), can inhibit multiple viruses and bacteria, thus inhibiting inflammation. Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) is traditionally used to eliminate phlegm-dampness. In pharmacology, it possessed significant antitussive and expectant effects, with Forsythaside (Fig. 10d) as the active component. Forsythia Fruit (Lianqiao, Fructus Forsythiae Suspensae) could clear away heat and toxic material in TCM theory. It can inhibit a variety of viruses including influenza A virus, human cytomegalovirus, encephalitis B virus, respiratory syncytial virus, and herpes simplex virus, and inhibit a variety of bacteria including E.coli, staphylococcus aureus, salmonella typhi, escherichia coli, multidrug-resistant acinetobacter baumannii, and staphylococcus epidermidis [39]. Bitter Apricot Seed (Kuxingren, Semen Armeniacae Amarum) could be used to reduce qi, relieve cough and asthma, and relax bowel, thus treating cough, asthma, chest fullness, phlegm, and constipation. The main active ingredient is amygdalin (Fig. 10e), which possesses the effects of expectorant and antitussive. It is noteworthy that, oxidative stress is a negative effect produced by free radicals in the body, and is considered to be an important factor leading to apoptosis, aging and disease [40], [41], [42], [43]. Virus infection is closely related to oxidative injury, and it evokes oxidative stress and intensifies pathological process. Plant polyphenols include flavonoids, tannins, phenolic acids, etc., which have the functions of scavenging free radicals in the body, anti lipid oxidation, delaying the aging of the body, and possess the effects of bacteriostasis, anti-virus, and anti-tumor [44]. A large number of Chinese herb medicine and natural medicine, including Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Forsythia Fruit (Lianqiao, Fructus Forsythiae Suspensae), Liquoric Root (Gancao, Radix Glycyrrhizae), and so on, possess certain anti-oxidation, anti-bacterial and anti-virus effects, and can be used in treating acute respiratory infection. Our study suggested that, CHM can not only improve symptoms, reduce the number of severe patients, shorten of fever reduction time and length of hospital stay, and improve pulmonary imaging, but also possess effects of antiviral and inhibiting inflammatory reaction in the treatment of COVID-19. That is to say, CHM could be considered to treat patients in both mild and critical stages of the disease, which embodies the advantages of multi-target and overall regulation by CHM.

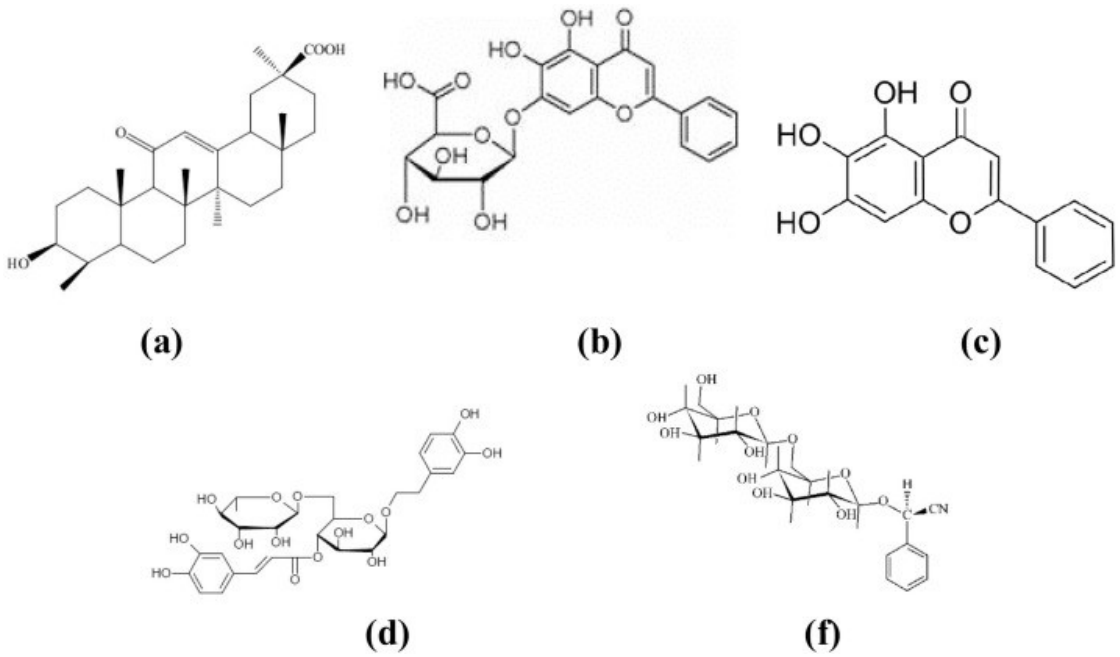

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Fig. 10

Chemical structure of the main active ingredients of most frequently used Chinese herbs for the treatment of COVID-19.

4.2. Limitations

Limitations in this review should also be taken into account as below. Firstly, poor methodological design is a very common problem in most of included trials. Significant drawbacks regarding sequence generation of randomization, concealment of allocation, reporting on blinding, dropouts, and pre-estimation of sample size should be considered in further studies. Secondly, as viral nucleic acid testing turning positive again is very common in the recovery stage of COVID-19, no trial adopted long-term follow-up.

5. Conclusions

In general, this systematic review and meta-analysis suggested that CHM maybe beneficial for the treatment of COVID-19 in improving clinical symptoms, imaging, and laboratory indicators, shortening the course of disease, and reducing the number of severe cases. However, considering the shortcomings of original trials, further rigorously designed trials following CONSORT Statement [45] and CONSORT extension for herbal medicine [46] are warranted to confirm the conclusions. CHM, especially classical Chinese herbal formulas, could be used as potential candidates for COVID-19 in this battle.

Author contributions

X.J.X. designed the paper, extracted data, carried out the statistical analysis, produced the tables and figures, and wrote the first edition of the paper. P.Q.W. selected the literature. K.L.S. evaluated the methodological quality of each trial. Y.W.X. and C.C.W. were consulted and helped to revise the manuscript. X.J.X. and K.L.S. contributed equally in this paper.

Declaration of Competing Interest

The authors declare no competing financial interests.

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