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Effect of Chinese herbal medicine (CHM) as an adjunctive therapy in distinct stages of patients with COVID-19: A systematic review and meta-analysis

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Abstract

Background

The pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory disease coronavirus 2 (SARS-CoV-2), has led to millions of infected cases and deaths worldwide. Clinical practice and clinical trials in China suggested that integrated Chinese herbal medicine (CHM) and conventional Western monotherapy (ICW) have achieved significant clinical effectiveness in treating COVID-19 patients.

Objectives

This article aims to systematically evaluate the effects of ICW in treating patients at distinct stages of COVID-19. The most frequently used components of the CHM formulas have been summarized to define the most promising drug candidates.

Methods

In this meta-analysis, seven databases up to May 20, 2024, were systematically searched to collect relevant randomized controlled trials (RCTs) and cohort studies (CSs). Difference in mean (MD) or ratio risk (RR) with 95% confidence interval (CI) was utilized for data processing analysis.

Results

A total of 46 studies, consisting of 24 RCTs and 22 CSs, and 10492 patients were included. ICW group showed significant improvement over the conventional Western monotherapy (CWM) group at all stages of COVID-19 patients. ICW therapy was effective in improving recovery rate of chest CT (RR = 1.21, 95%CI [1.13,1.29]), shortening negativity time of nucleic acid (MD = -2.14,95% CI [-3.70, -0.58]), suppressing the transition of mild/moderate patients into severe conditions (RR = 0.45, 95% CI [0.33,0.62]), and reducing mortality

(RR = 0.45, 95% CI [0.37,0.55]) for severe/critical COVID-19. Furthermore, compared with severe/critical patients, mild/moderate COVID-19 patients proved more effective after being treated with ICW therapy. They had a higher recovery rate of chest CT manifestations (75.4% vs. 69.1%), shorter negativity time of nucleic acid (9.21 d vs. 14.89 d), reduced time to clinical symptom reduction (3.85d vs. 11d) and shortened days of hospital stays (15.9d vs 19.1d). As for inflammatory markers analysis, ICW regimens decreased the level of lymphocytes in mild/moderate and severe/critical patients (MD = -0.15, 95% CI [-0.18, -0.13]), but no statistical difference was observed in white blood cell count and neutrophils count (MD = 0.02, 95% CI [-0.14, -0.18]; MD = 0.22,95% CI [-0.7, 1.15], respectively). A different tendency was found in the C-reactive protein level, which significantly decreased at the early stage of COVID-19 in the ICW group (MD = 2.56, 95%CI [1.28,3.83]).

Conclusion

This meta-analysis demonstrates the significant superiority of ICW over single western monotherapy in improving clinical efficacy at distinct stages of Chinese COVID-19 patients. Subgroup analysis further showed that the earlier intervention of CHM may contribute to a better therapeutic effect.

Trial registration

PROSPERO ID: CRD42023401200.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen of coronavirus disease 2019 (COVID-19), a fast-spreading disease that affects millions of people around the world [1]. Mild patients presented with fever, fatigue, and dry cough, and severe patients may experience dyspnea, acute respiratory distress syndrome (ARDS), and even multiple organ dysfunction syndrome (MODS) [2].

A variety of antiviral drugs, monoclonal antibodies, and immunomodulatory drugs have been proposed as treatments for sars-cov-2 infection [3–5]. Especially Paxlovid, a new oral novel coronavirus treatment drug, with the advantages of being not easily resistant to the drug and effective against mutants, has reduced the risk of hospitalization or death of COVID-19 patients by 89% [6]. However, Paxlovid contains CYP3A4 enzyme inhibitor ritonavir, which may interact with many drugs and affect liver and kidney function, mainly limiting drug users and increasing the drug risk of older adults with underlying diseases [7].

According to the Chinese Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition) [8], Dayuan decoction is recommended in the mild stage; for the moderate cases, Xiaochuhu decoction and Maxingshigan decoction are recommended. In the later stage, Chinese herbal formulas are considered to be administered by injection. All these prescriptions provided pharmacological efficiency on anti-inflammatory, antiviral, antipyretic, expectorant, antiasthmatic, and antitussive, with multiple targets that may act by modulating the patient's immune response, directly fighting the pathogen, and improving the patient's symptoms [9]. All these factors indicate that Chinese herbal medicine (CHM) has superior advantages in the current COVID-19 pandemic as adjunctive therapy combined with conventional Western monotherapy (CWM) [10].

At present, a considerable meta-analysis has indicated that CHM plus Western medicine treatment of COVID-19 can reduce the exacerbation rate of pneumonia and shorten the antipyretic time [11–13]. However, these studies did not restrict enrollment, probably because most early trials were not specifically divided subjects according to clinical syndrome types. There were specific differences in the treatment and prognosis of COVID-19 patients at different stages. This meta-analysis, rigorous and objective, discusses a series of existing randomized controlled trials (RCTs), prospective cohort studies (PCSs), and retrospective cohort studies (RCSs) comparing ICW therapy with CWM in distinct stages of COVID-19 patients, evaluating the effectiveness of ICW therapy, and summarizing commonly used ingredients from prescriptions included, figuring out the most promising candidates, which may aid in the development of facilitating conventional treatment.

Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Review, Meta-Analysis (PRISMA) statement and the statement by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [14, 15].

Search strategy

A structured and comprehensive search was performed in PubMed, Embase, Cochrane Library, Wan Fang Database, VIP Information Database, SinoMed, and China National Knowledge Infrastructure (CNKI) until May 20, 2024. The literature search strategy was developed using the patient characteristics, intervention, comparison, and outcomes framework [16]. (S1 Table for detailed search strategy of English databases and S2 Table for Chinese databases).

Eligibility criteria

Types of studies. Published randomized controlled trials (RCTs), prospective cohort studies (PCSs), or retrospective cohort studies (RCSs) regarding the comparison between ICW with CWM therapy on COVID-19 patients were included in this meta-analysis.

Stages of participants. Participants were patients with a precise diagnosis of COVID-19, aged≥18 years. According to the clinical manifestations, the patients with COVID-19 were divided into four stages [17]: 1) Mild stage, with mild clinical symptoms and no pneumonia in imaging; 2) Moderate stage, patients mainly had symptoms of fever and respiratory symptoms with imaging manifestations of pneumonia; 3) Severe stage, adults who met any of the following criteria: respiratory rate≥30 breaths/min; resting state oxygen saturation≤93%; arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2)≤300 mmHg. Patients with more than 50% of lesions progressing within 24 to 48 hours on lung imaging should be treated as severe cases; 4) Critical stage, meeting any of the following conditions: respiratory failure requiring mechanical ventilation; the presence of shock; other organ failure requiring ICU monitoring and treatment.

In this meta-analysis, patients at distinct stages were divided into the mild/moderate group or severe/critical group according to the clinical classification of COVID-19, and enrolled patients in each study should more than 40.

Methods of interventions. Patients in the ICW group were treated by the combination of Chinese herbal medicine and conventional Western medicine therapy, and the conventional Western monotherapy group (CWM) was only treated by Western medicine therapy.

CWM therapy included general treatment, antiviral medicines, antibacterial medicines, oral corticosteroids, nutrition therapy, supplemental oxygen, and mechanical ventilation.

CHM treatment contains Chinese medicine such as decoction, granule, capsule, liquid, and injection.

Types of outcome measures. The outcome indicators of this meta-analysis are based on an evidence-based clinical practice guideline [2], consensus [8], and present meta-analysis [11–13].

Primary endpoints

- Improvement rate of chest CT.

- Severe conversion rate of mild/moderate patients.

- Mortality rate of severe/critical patients.

- Negativity time of nucleic acid.

Secondary endpoints

- Clinical improvement rate and time of main symptoms (fever, cough, breathlessness, fatigue).

- Length of hospital stays.

- Inflammatory markers included the level of white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), and C-reactive protein (CRP) on the change from baseline.

Exclusion criteria.

- Non-CHM interventions such as natural medicines, acupuncture, or moxibustion.

- Articles with inconsistent outcome indicators and incomplete index data.

- Reviews, case reports, Master/PhD thesis, and unpublished clinical trials.

Data extraction

Data were extracted from included studies, and the characteristics of study design, course of the treatment, characteristics of included patients (clinical type, comorbidity), treatment regimen of experiment/control, and outcome measures were documented. Study screening and data extraction were conducted independently by two reviewers (Gu and Xiao), and any inconsistencies were settled by the protocol of the Complex meta-analysis Data Extraction Recommendations [18].

Risk of bias, evidence profile, and heterogeneity assessment

Bias risk was assessed and verified by two authors (Gu and Xiao) using the Cochrane Collaborative Bias Risk Tool for RCTs and Newcastle-Ottawa (NOS) for cohort studies (CSs) [19, 20]. The quality of the evidence for the primary endpoints was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [21]. The level of evidence for each outcome was classified by risk of bias, imprecision, inconsistency, indirectness, and publication bias. Disagreements were settled through discussion. We used the I^2 statistic to measure heterogeneity between the trials in each analysis; $I^2 < 50\%$ was an acceptable level of insignificant heterogeneity.

Data analysis

A pairwise meta-analysis was performed using the statistical platform R 4.1.2. Difference in means (MD) with 95% confidence interval (CI) was utilized for data measurement of

continuous outcomes, while ratio risk (RR) with 95%CI for dichotomous data. For data synthesis, we used random or fixed effect models with or without significant heterogeneity ($I^2 >$ 50% was apparent heterogeneity). We conducted sensitivity analyses by excluding each study and changing statistical models to assess whether the results changed significantly due to individual studies. Subgroup analysis was also performed based on various clinical and methodological factors. $P < 0.05$ was considered statistically significant.

Results

Study characteristics

A structured and comprehensive search was performed in 7 databases up to May 20, 2024. 14265 relevant literatures were retrieved, after moving duplicates (n = 7284), 6981 literatures were screened based on title and abstract, then 265 studies were qualified for full-text review. 46 studies were included in the meta-analysis; 6 articles were excluded due to insufficient data; 132 articles enrolled patients who did not have a clear definition of the type of COVID-19 or the sample size was less than 40; 42 articles studies were not RCT, PCS or RCS; the intervention of 37 articles was not ICW and CWM; 2 articles were Master/PhD thesis. The reasons for excluded studies at the full-reading stage were described in S3 Table. 50 trials in 46 articles with 10492 patients were finally included for analysis (ICW, 63.1%; CWM, 36.9%) [22–66]. Our study contained 24 RCTs [25, 26, 28–30, 36–38, 44, 46, 48–58, 61, 65, 66], 2 PCSs [40, 47] and 20 RCSs [22–24, 27, 31–35, 39, 41–43, 45, 59, 60, 62–64, 67], 7 studies [22, 28, 29, 39, 48, 52, 56] were multicentral and the rest 38 were single-central. 2 studies [41, 53]conducted three-armed trials, and another 2 studies [39, 45] contained two double-arm trials. 8 studies [46, 48, 51, 52, 55–57, 65] were open-label. The flow diagram of the study's screening regarding the PRISMA 2020 statement is summarized in Fig 1. Among eligible patients, the ratio of mild/moderate COVID-19 was 83%, and severe/critical COVID-19 was 17%. The relevant information is described in S4 Table.

Risk of bias

8 studies [46, 48, 51, 52, 55–57, 65] were open-label trials in which patients and assessors were aware of the study design, and 10 studies [25, 26, 28–30, 36–38, 44, 53]didn't describe the performance of allocation concealment (S1 Fig), both of them may confuse the subjective outcomes measurements. 14 RCSs [22, 27, 31–33, 39, 41–43, 45, 59, 60, 62, 63] did not have a detailed description of the target disease history, and all RCSs except Yuanyuan Wang et al. [64] matching patients in a 1:1 ratio using propensity score, controlled only by the main confounding factors. Of note, the experimental group and control group with no response rates were different in trials conducted by Chao Qun Huang, et al. [39], and we deduct points accordingly (S5 Table).

Description of CHM prescription

The frequency of each Chinese herb in recipes and the recommend prescriptions at each stage were summarized (S2 Fig). Among all ingredients documented in this study, Semen Armeniacae Amarum (Kuxingren) (2.43%) combined with Herba Ephedrae (Mahuang) (2.43%) were the top-ranked Chinese herb pair and Radix Glycyrrhizae (Gancao) (6.25%) was the top-ranked single Chinese herb among COVID-19 ranging from mild to severe cases. Fructus Forsythiae Suspensae (Lianqiao) (2.39%) plus Flos Lonicerae (Jinyinhua) (2.39%) were frequently recommended for mild/moderate stage. While for severe/ critical COVID-19, the most widely
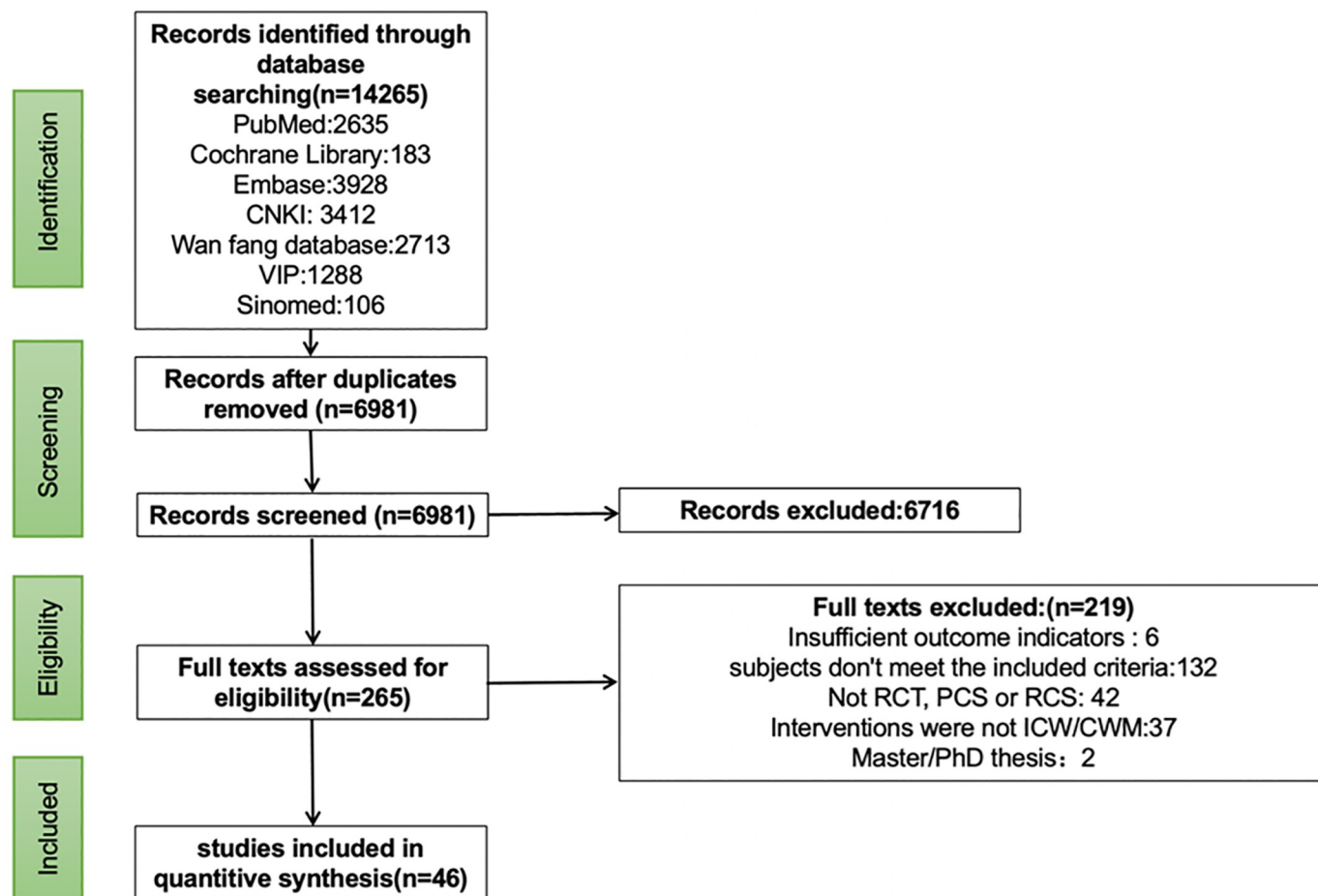
Fig 1. Flow diagram for the identification of studies included.

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used Chinese herb pairs were Radix Paeoniae Rubra (Chishao) (6.33%) plus Szechuan Lovage Rhizome (Chuanxiong) (2.53%).

Five dosage formulations of CHM were included, including decoction (43.4%), granule (30.2%), capsule (7.5%), injection (7.5%), and tablet (3.8%). The most widely used dosage formulations for the early stage were decoction and granule, followed by capsule and tablet. When it came to a later stage, injection was commonly recommended. Further, twice daily (56.7%) and thrice daily (36.7%) were the most frequently usage of CHM. The details of CHM prescriptions are summarized in S6 Table.

Primary endpoints

Improvement rate of chest CT. The recovery rate of chest CT manifestations was reported in 17 trials [22–24, 26–29, 32, 38, 39, 41, 44, 46, 56, 61, 64]. Overall, the ICW group (72.9%,95%CI [0.59; 0.85]) was associated with fewer chest radiograph abnormalities in all stages of COVID-19(RR = 1.21, 95%CI [1.13,1.29]; $P<0.01$; I^2 = 0%) and proved to be remarkably superior to the CWM therapy (58.3%,95%CI [0.46; 0.7]) (Fig 2a). Additionally, the pooled recovery rate of chest CT with added CHM was 75.4% (95%CI [0.56,0.9]) in the mild/moderate patients versus 69.1% (95%CI [0.47,0.87]) in the severe/critical cases.

Fig 2. Forest plot of the improvement in primary endpoints. (a). Improvement rate of chest CT (b). Severe conversion rate of mild/moderate patients (c). Mortality rate of severe/critical patients (d). Negativity time of nucleic acid.

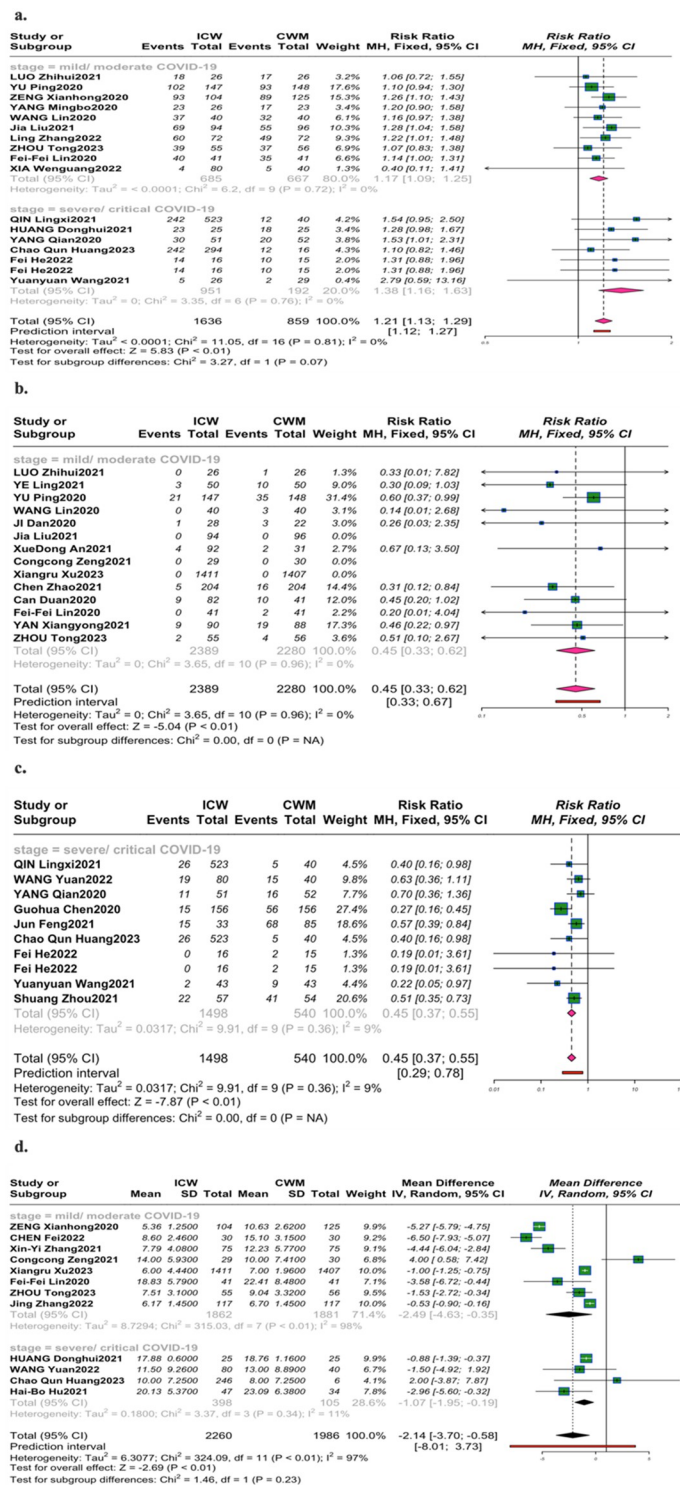https://doi.org/10.1371/journal.pone.0318892.g002

Severe conversion rate of mild/moderate patients. Severe conversion rate revealed in 14 trials [24–26, 29, 33, 37, 38, 40, 44, 46, 50, 51, 55, 57], CHM add-on effectively prevented disease progressed into severe/critical status (RR = 0.45, 95% CI [0.33,0.62]; $P < 0.01$; $I^2 = 0\%$) (Fig 2b). 2% of cases reported disease progression (95%CI [0.01,0.05]) in the ICW group, less than 7% in the CWM group (95%CI [0.03,0.13]).

Mortality rate of severe/critical patients. Significant reduction of mortality with severe/critical COVID-19 was revealed in 10 trials [22, 30, 32, 39, 41, 52, 62, 63, 64] (RR = 0.45, 95% CI [0.37,0.55]; $P < 0.01$; $I^2 = 9\%$) (Fig 2c). The pooled mortality was 12% (95%CI [0.04,0.23]) in the ICW group versus 33% in the CWM group (95%CI [0.18,0.5]).

Negativity time of nucleic acid. 12 trials [23, 27, 30, 31, 38, 39, 44, 48, 51, 55, 65, 67] evaluated the negativity time of nucleic acid (Fig 2d) (MD = -2.14,95% CI [-3.70, -0.58]; $P < 0.01$; $I^2 = 97\%$). Compared to CWM therapy (11.11 days, 95%CI [8.1;14.11]), both mild/ moderate COVID-19 and severe/ critical COVID-19 treated with ICW combination (l2.95 days, 95%CI [9.73; 16.17]) demonstrated the statistical differences in shortening time to negative conversion (MD = -2.49, 95% CI [-4.63, -0.35]; $P < 0.01$; $I^2 = 98\%$), (MD = -1.07, 95% CI [-1.95, -0.19]; $P < 0.01$; $I^2 = 11\%$). Additionally, the pooled mean negativity time of nucleic acid with added CHM was 9.21 days (95%CI [6,12.42]) in the mild/ moderate patients versus 14.89 days (95%CI [10.1,19.69]) in the severe/critical cases.

Secondary endpoints

Rate of fever reduction, time to reduction of fever. No statistical differences were observed in the rate of fever reduction from 1 trial [22] (Fig 3a) for severe/critical COVID-19 (RR = 1.06, 95% CI [0.93,1.20]; $P = 0.4$), while for mild/moderate cases in 7 trials [33, 34, 36, 40, 49, 50, 65], ICW therapy illustrated significantly clinical difference, compared with CWM therapy (RR = 1.18, 95%CI [1.09, 1.29]; $P < 0.01$; $I^2 = 27\%$). A similar trend was found in time to the reduction of fever, ICW therapy led marginal differences for severe/ critical COVID-19 in 3 trials [22, 58, 67] (MD = -0.92, 95% CI [-1.88,0.04]; $P = 0.06$, $I^2 = 60\%$), while more mild/ moderate COVID-19 participants in 8 trials [24, 29, 34, 42, 43, 46, 48, 59] received added CHM had a clinically meaningful benefit (Fig 3b) (MD = -1.14, 95% CI [-1.31, -0.97]; $P < 0.01$; $I^2 = 36\%$).

Improvement rate of cough, time to improvement of cough. Improvement rate of cough was reported only with mild/ moderate COVID-19 (Fig 3c). Compared with the CWM group, this review showed a significant improvement in the number of cough reduction cases by added CHM in 7 trials [24, 33, 35, 36, 37, 40, 49] (RR = 1.52,95% CI [1.31,1.76]; $P < 0.01$; $I^2 = 43\%$). According to the recovery time of cough (Fig 3d), different trends were observed at early stage of COVID-19 in 5 trials [24, 29, 35, 43, 59] (MD = -2.06, 95% CI [-2.49, -1.63]; $P < 0.01$; $I^2 = 3\%$), and the later stage in 3 trials [54, 64, 67] (MD = -1.96, 95% CI [-2.96, -0.96]; P = 0.05; $I^2 = 56\%$).

Improvement rate of fatigue, improvement rate of breathlessness. Regarding the symptom of fatigue or breathless (Fig 3e and 3f), a significant improvement on number of fatigue and breathless reduction cases by ICW was documented in 7 studies [34, 35, 37, 40, 50, 57, 66] /5 studies [24, 33, 34, 36, 49], at early stage of COVID-19(RR = 1.07, 95% CI [1.01,1.13]; $P < 0.01$; $I^2 = 20\%$), (RR = 2.07, 95% CI [1.47,2.93]; $P < 0.01$; $I^2 = 0\%$).

Improvement rate of symptom, time to improvement of symptom. According to the recovery rate of clinical symptoms (fever, cough, fatigue, breathlessness), compared with later stage, mild/moderate cases proved to be more effective by adding CHM (RR = 1.06, 95%CI [0.93,1.20]; RR = 1.23, 95%CI [1.17,1.29], respectively). Likewise, the time to the reduction of clinical symptoms (fever, cough) showed the same trend (MD = -1.42,95% CI [-2.11, -0.73];
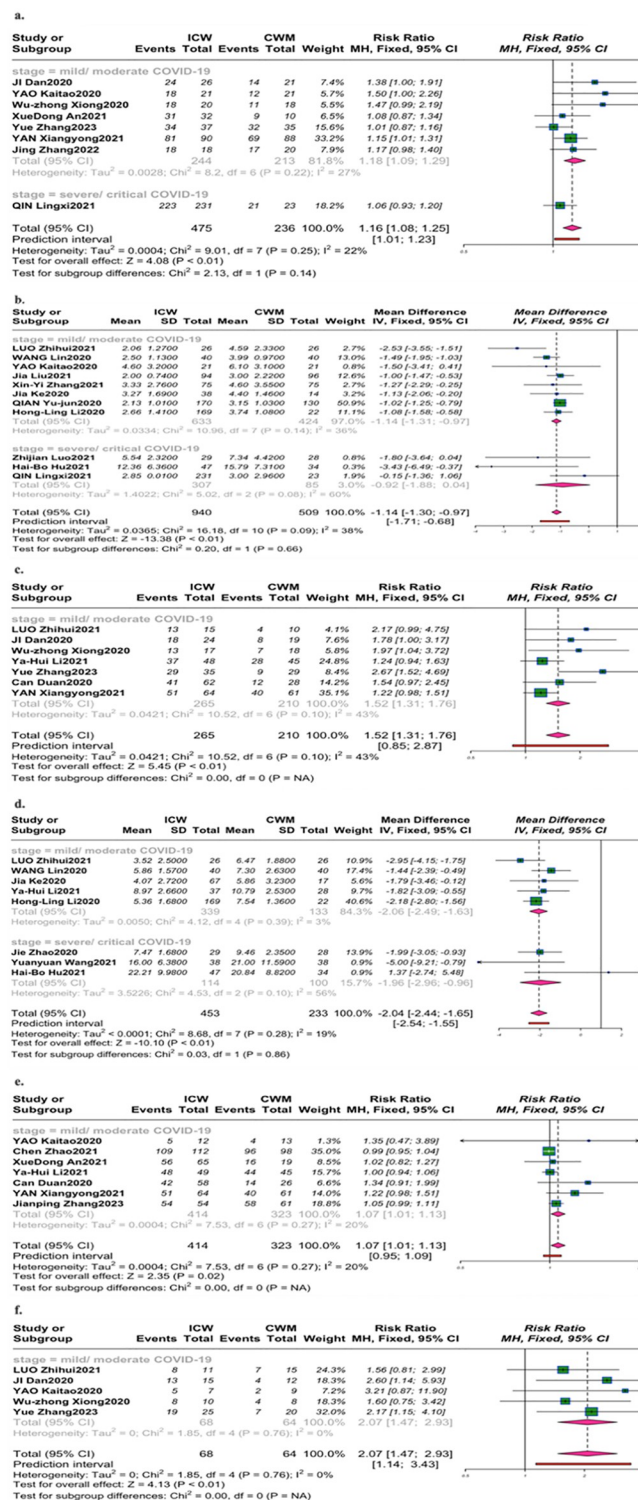
Fig 3. Forest plot of the second endpoint of the clinical symptom improvement. (a). Rate of fever reduction; (b). Time to the reduction of fever; (c). Improvement rate of cough; (d). Time to improvement of cough; (e). Improvement rate of breathless; (f). Improvement rate of fatigue.

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MD = -1.26,95% CI [-1.42, -1.11], respectively). Additionally, the pooled mean recovery time to symptom with adding CHM was 3.85 days (95%CI [2.78,4.92]) in the mild/moderate patients versus 11 days (95%CI [5.24,16.72]) in the severe/critical cases. For distinct stages of COVID-19, the pooled recovery rate was 65% (95%CI [0.55; 0.75]) with western medicine monotherapy versus 86.7% (95%CI [0.81; 0.91]) with added CHM. Likewise, the pooled mean time to recovery was 7.69 days (95%CI [5.31,10.08]) in CWM versus 6.06 days (95%CI [3.72,8.39]) with adding CHM.

White blood cell count. 13 studies [24, 25, 29, 30, 36, 42–44, 47, 53, 54, 59, 67] (Fig 4a) evaluated level of WBC($\times 10^9$L), no statistical difference was observed in both groups of COVID-19 (MD = 0.18, 95%CI [-0.02, 0.38]; $P = 0.08$; $I^2 = 0\%$), (MD = -0.27, 95%CI [-0.54, 0.00]; $P = 0.05$; $I^2 = 48\%$).

Lymphocyte count. For the level of LYM($\times 10^9$L) in 9 trials [24, 26, 30, 32, 36, 59, 43, 44, 53], a similar trend was found in distinct stages of COVID-19(Fig 4b), ICW increased the level of LYM, compared with monotherapy. (MD = -0.12, 95%CI [-0.15, -0.08]; $P < 0.01$; $I^2 = 0\%$), (MD = -0.19,95%CI [-0.22, -0.16]; $P < 0.01$; $I^2 = 0\%$).

Neutrophils count. Effects of ICW on the level of NEU($\times 10^9$L) were measured in 6 trials [23, 44, 47, 60, 66, 67], showing no trend over influencing the level of NEU with mild/ moderate COVID-19(MD = -0.47, 95%CI [-1.09,0.14]; $P = 0.13$; $I^2 = 73\%$), and severe/critical COVID-19(MD = 0.91, 95%CI [-0.55,2.38]; $P = 0.22$, $I^2 = 86\%$) (Fig 4c).

C-reactive protein. The CRP (mg/L) level was documented in 11 trials [24, 26, 28, 30, 31, 43, 44, 47, 53, 60, 67]. A different trend was found in distinct stages of COVID-19(Fig 4d). The level of CRP was significantly reduced by adding CHM in the early stage of COVID-19 (MD = 2.56, 95%CI [1.28,3.83]; $P < 0.01$; $I^2 = 14\%$), while no statistical differences were identified at the later stage (MD = 0.90, 95%CI [-6.28, 8.08]; $P = 0.81$; $I^2 = 83\%$).

Length of hospital stays. Fifteen studies evaluated hospitalizations (Fig 5), different trend was observed compared to CWM therapy at distinct stages of COVID-19(MD = -1.97, 95% CI [-3.85, -0.08]; $P = 0.04$; $I^2 = 98\%$), (MD = -7.47, 95% CI [-23.95,9.02]; $P = 0.37$; $I^2 = 96\%$) [23, 24, 27, 32, 38, 42, 43, 45, 47, 51, 54, 55, 57, 63]. Compared with the CWM group (21.23 days,95%CI [13.02; 29.45]), patients who received ICW therapy (16.9 days,95%CI [13.73;20.08]) had a shorter length of hospital stays. Further, the pooled mean length of hospital stays of mild/moderate patients treated with ICW therapy was 15.9 days (95%CI [11.92; 19.89]) days, which was shorter than 19.1 days (95%CI [13.66; 24.49]) in severe/critical patients.

Sensitivity analysis

Sensitivity analyses were conducted to investigate sources of heterogeneity by excluding each study; there was no significant change in effects during this exercise, indicating that no individual study had undue influence on the results.

Subgroup analysis

The negativity time of nucleic acid ($I^2 = 97\%$), neutrophils count ($I^2 = 93\%$), C-reactive protein count ($I^2 = 59\%$), and length of hospital stays ($I^2 = 99\%$) meta-analysis exhibited considerable heterogeneity. Selected subgroup analysis resulted in a reduction of heterogeneity (Table 1). The results suggested that study course and distinct stages of COVID-19 may be the source of heterogeneity for negativity time of nucleic acid; sex(male%) may cause the heterogeneity for the level of neutrophils count; dosage formulations and usage may be the source of heterogeneity for the level of C-reactive protein count; and age group may be the cause of heterogeneity for the length of hospital stays. Moreover, subgroup and sensitivity analyses for the other
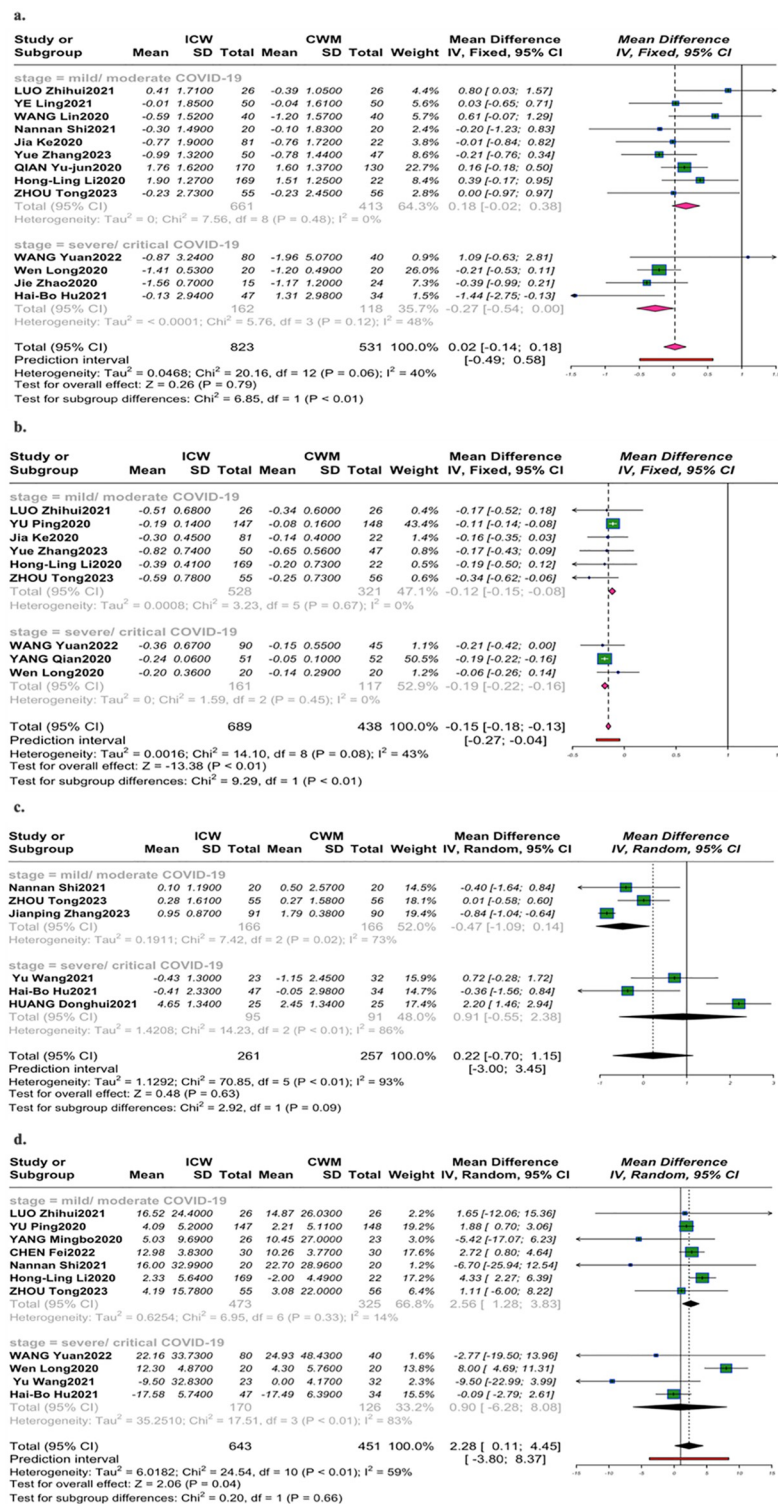
Fig 4. Forest plot of inflammatory markers. (a). White blood cell count; (b). Lymphocyte count; (c). Neutrophils count; (d). C-reactive protein level.
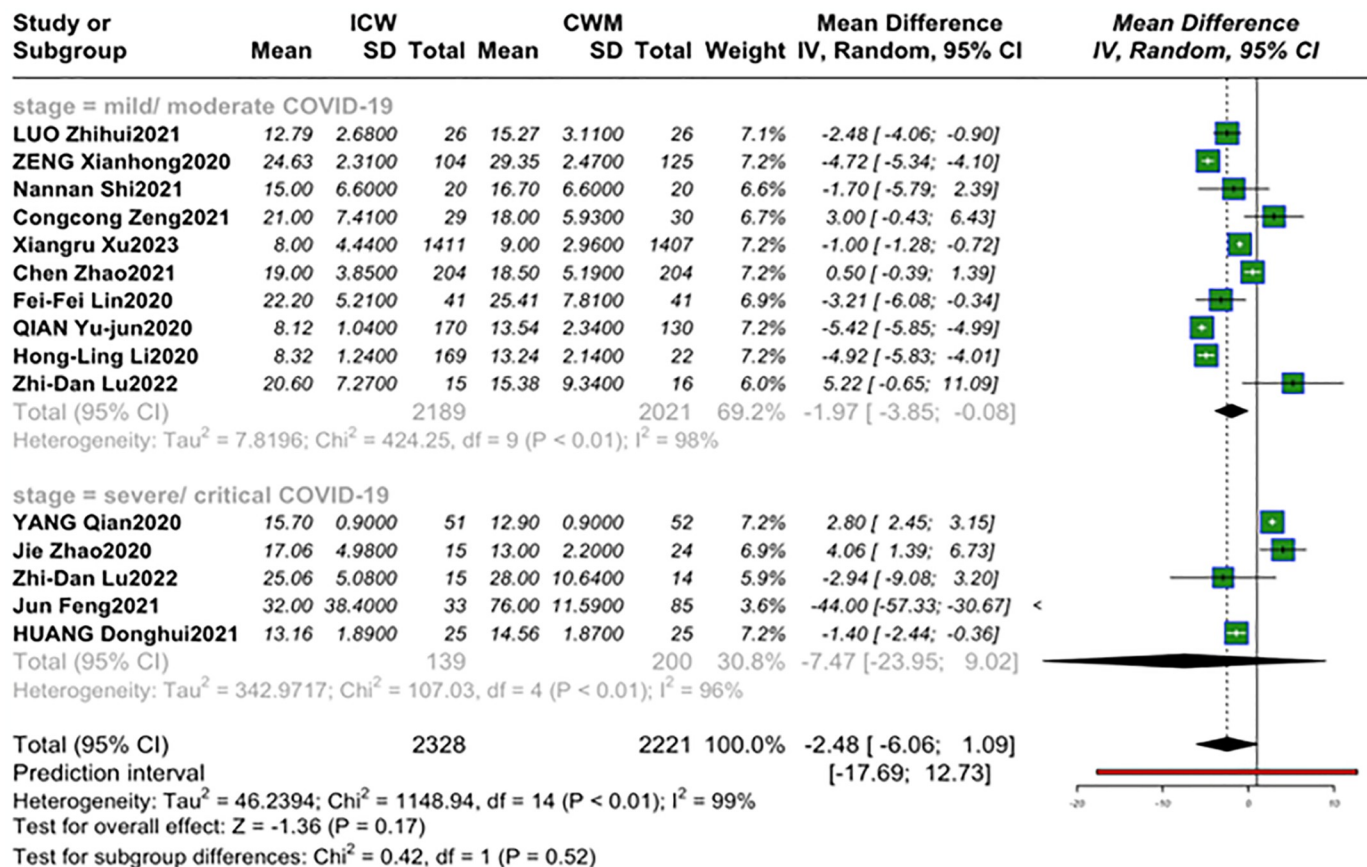
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Study or Subgroup	ICW Mean	SD	Total	CWM Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
stage = mild/ moderate COVID-19								
LUO Zhihui2021	12.79	2.6800	26	15.27	3.1100	26	7.1%	-2.48 [-4.06; -0.90]
ZENG Xianhong2020	24.63	2.3100	104	29.35	2.4700	125	7.2%	-4.72 [-5.34; -4.10]
Nannan Shi2021	15.00	6.6000	20	16.70	6.6000	20	6.6%	-1.70 [-5.79; 2.39]
Congcong Zeng2021	21.00	7.4100	29	18.00	5.9300	30	6.7%	3.00 [-0.43; 6.43]
Xiangru Xu2023	8.00	4.4400	1411	9.00	2.9600	1407	7.2%	-1.00 [-1.28; -0.72]
Chen Zhao2021	19.00	3.8500	204	18.50	5.1900	204	7.2%	0.50 [-0.39; 1.39]
Fei-Fei Lin2020	22.20	5.2100	41	25.41	7.8100	41	6.9%	-3.21 [-6.08; -0.34]
QIAN Yu-jun2020	8.12	1.0400	170	13.54	2.3400	130	7.2%	-5.42 [-5.85; -4.99]
Hong-Ling Li2020	8.32	1.2400	169	13.24	2.1400	22	7.2%	-4.92 [-5.83; -4.01]
Zhi-Dan Lu2022	20.60	7.2700	15	15.38	9.3400	16	6.0%	5.22 [-0.65; 11.09]
Total (95% CI)			2189			2021	69.2%	-1.97 [-3.85; -0.08]
Heterogeneity: Tau^2 = 7.8196; Chi^2 = 424.25, df = 9 (P < 0.01); I^2 = 98%								
stage = severe/ critical COVID-19								
YANG Qian2020	15.70	0.9000	51	12.90	0.9000	52	7.2%	2.80 [2.45; 3.15]
Jie Zhao2020	17.06	4.9800	15	13.00	2.2000	24	6.9%	4.06 [1.39; 6.73]
Zhi-Dan Lu2022	25.06	5.0800	15	28.00	10.6400	14	5.9%	-2.94 [-9.08; 3.20]
Jun Feng2021	32.00	38.4000	33	76.00	11.5900	85	3.6%	-44.00 [-57.33; -30.67]
HUANG Donghui2021	13.16	1.8900	25	14.56	1.8700	25	7.2%	-1.40 [-2.44; -0.36]
Total (95% CI)			139			200	30.8%	-7.47 [-23.95; 9.02]
Heterogeneity: Tau^2 = 342.9717; Chi^2 = 107.03, df = 4 (P < 0.01); I^2 = 96%								
Total (95% CI)			2328			2221	100.0%	-2.48 [-6.06; 1.09]
Prediction interval								[-17.69; 12.73]

Heterogeneity: Tau^2 = 46.2394; Chi^2 = 1148.94, df = 14 (P < 0.01); I^2 = 99%
Test for overall effect: Z = -1.36 (P = 0.17)
Test for subgroup differences: Chi^2 = 0.42, df = 1 (P = 0.52)

Fig 5. Forest plot of the hospital stay length in distinct stages of patients.

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primary outcomes were documented in S7 Table. There was a significant trend towards an older group who exhibited less effectiveness by added CHM in negativity time of nucleic acid, the improvement rate of cough, level of NEU, and CRP ($P_{subgroup}$<0.01, $P_{subgroup}$ <0.01, $P_{subgroup}$ = 0.02, respectively). Stratifying studies by design did not produce statistically significant differences in effect sizes ($P_{subgroup}$ >0.05; each outcome).

Bias and quality of evidence

No publication bias was suggested for the improvement rate of chest CT, which was confirmed by dispersion produced by visual analysis of funnel plots (S3 Fig), and neither was the Egger regression intercept test (P = 0.23) statistically significant. The GRADE analysis reported moderate-to-high-quality evidence on the effect of ICW combination versus CWM monotherapy on the primary endpoints. Fifty trials obtained a total of 155 outcome indicators, of which 15 had high-grade scores, accounting for 9.68%; moderate GRADE scores in 102 items, accounting for 65.81%, and 38 (24.5%) low GRADE scores. Details are provided in S8 Table.

Discussion

Considerable systematic reviews were performed to evaluate the clinical efficiency of adding CHM to the treatment of COVID-19 [13, 67–69]. For uninfected and suspected COVID-19 patients, Siying Hu found CHM could reduce the risk of infection [70]. For confirmed

Table 1. Subgroup and sensitivity analyses for the primary outcomes.

		No. of Studies	MD/RR, 95%CI	I^2	Q	$P_{subgroup}$
Negativity time of nucleic acid, mean ± SD						
Age Group [a]	≤50years	5	-4.04(-6.18,-1.9)	98.40%	7.61	0.006*
	>50years	7	0.49(-1.91,2.9)	93.10%		
Study Design	RCT	6	-0.86(-1.33,-0.38)	69.10%	0.54	0.46
	RCS	7	-2.05(-5.17,1.08)	98.10%		
Dosage Formulations	decoction/capsule/granule/injection	1	-1.5(-4.9,1.9)	NA	25.86	< 0.0001*
	decoction	7	-0.92(-4.39,2.55)	98.20%		
	injection	1	-4.44(-6.04,-2.84)	NA		
	capsule	1	-0.53(-0.9,-0.16)	NA		
	liquid	2	-1.02(-5.6,-3.23)	NA		
	granule	1	-2.96(-5.6,-0.32)	NA		
Usage	once daily	1	-4.44(-6.04,-2.84)	NA	18.07	0.0004*
	2 times daily	7	-0.32(-3.55,2.91)	96.10%		
	3 times daily	1	-1.53(-2.72,-0.34)	NA		
	4 times daily	1	-1(-1.25,-0.75)	NA		
Study Course	<14d	3	-0.86(-1.29,-0.44)	63.00%	0.04	0.84
	≥14d	3	-0.39(-4.82,4.04)	81.30%		
Sex(male%)	<50%	6	-1.01(-4.1,2.07)	95.30%	0.17	0.68
	≥50%	7	-1.84(-4.26,0.58)	98.00%		
Stage of COVID-19	mild/moderate COVID-19	8	-2.49(-4.63,-0.35)	98.00%	1.46	0.23
	severe/critical COVID-19	4	-1.07(-1.95,-0.19)	11%		
Neutrophils, mean ± SD						
Age Group [a]	≤50years	1	-0.84(-1,-0.64)	NA	6.73	0.001*
	>50years	5	0.49(-0.5,1.47)	85.00%		
Study Design	RCT	2	-0.46(-1.29,0.36)	86.00%	2.7	0.26
	PCS	1	-0.40(-1.64,0.84)	NA		
	RCS	3	0.91(-0.55,2.38)	86.00%		
Dosage Formulations	granule/injection	1	0.72(-0.28,1.72)	NA	17.11	0.002*
	decoction/tablet	1	-0.84(-1.04,-0.64)	NA		
	decoction	2	0.95(-1.6,3.5)	91.90%		
	granule	1	-0.36(-1.56,0.84)	NA		
	liquid	1	0.01(-0.58,0.6)	NA		
Usage	2 times daily	2	0.95(-1.6,3.5)	91.90%	1.07	0.3
	3 times daily	2	-0.46(-1.29,0.36)	85.90%		
Study Course	<14d	2	-0.46(-1.28,0.36)	85.90%	0.01	0.93
	≥14d	1	-0.4(-1.64,0.84)	NA		
Sex(male%)	<50%	3	-0.47(-1.08,0.15)	73.40%	2.8	0.09
	≥50%	3	0.9(-0.58,2.39)	85.80%		
Stage of COVID-19	mild/moderate COVID-19	3	-0.47(-1.09,0.14)	73%	2.92	0.09
	severe/critical COVID-19	3	0.91(-0.55,2.38)	86%		
C-reactive protein, mean ± SD						
Age Group [a]	≤50years	6	3.53(1.26,5.81)	68.60%	5.4	0.02*
	>50years	5	-0.42(-2.86,2.02)	0%		
Study Design	RCT	5	2.60(-1.70,6.91)	71%	0.86	0.65
	PCS	1	-6.70(-25.94,12.54)	NA		
	RCS	5	2.06(-0.36,4.49)	58%		

(Continued)

Table 1. (Continued)

		No. of Studies	MD/RR, 95%CI	I^2	Q	$P_{subgroup}$
Dosage Formulations	decoction/capsule/granule/injection	1	-2.77(-19.5,13.96)	NA	17.74	0.003*
	granule/injection	1	-9.5(-23,4)	NA		
	decoction	4	3.39(1.86,4.92)	0.00%		
	granule	2	1.29(-0.49,3.06)	41.70%		
	liquid	2	-0.66(-6.73,5.41)	0.00%		
	injection	1	8(4.69,11.31)	NA		
Usage	2 times daily	6	4.26(1.68,6.84)	46.50%	4.42	0.11
	3 times daily	2	1.86(0.7,3.02)	0.00%		
	2~4 times daily	1	-5.42(-17.07,6.23)	NA		
Study Course	<14d	4	2.9(-1.61,7.4)	78.00%	1.16	0.28
	≥14d	2	-4.46(-17.09,8.16)	0.00%		
Sex(male%)	<50%	5	3.15(0.35,5.96)	78.20%	1.91	0.17
	≥50%	6	-0.99(-6.13,4.16)	16.30%		
Stage of COVID-19	mild/moderate COVID-19	7	2.56(1.28,3.83)	14%	0.2	0.66
	severe/critical COVID-19	4	0.90(-6.28,8.08)	83%		
Length of hospital stays, mean ± SD						
Age Group [a]	≤50years	4	4.1(-5.27,-2.93)	64.10%	0	0.96
	>50years	9	-3.91(-12.06,4.23)	99.10%		
Study Design	RCT	4	-0.30(-2.26,1.66)	83.00%	1.44	0.49
	PCS	1	-1.70(-5.79,2.39)	NA		
	RCS	10	-4.37(-11.34,2.59)	99.00%		
Dosage Formulations	capsule/granule/injection	2	1.19(-6.81,9.19)	71.80%	1.33	0.72
	decoction	10	-1.53(-3.72,0.67)	99.20%		
	granule	2	-21.23(-65.83,22.37)	97.70%		
	liquid	1	-1(-1.28,-0.72)	NA		
Usage	2 times daily	10	-4.52(-11,1.98)	99.10%	1.12	0.29
	4 times daily	1	-1(-1.28,-0.72)	NA		
Study Course	<14d	2	-0.31(-1.78,1.15)	90.00%	0.03	0.86
	≥14d	3	-0.68(-4.45,3.1)	73.70%		
Sex(male%)	<50%	5	-3.98(-10.75,2.79)	99.20%	0.42	0.52
	≥50%	10	-3.98(-10.75,2.79)	99.20%		
Stage of COVID-19	mild/moderate COVID-19	10	-1.97(-3.85,-0.08)	90%	0.42	0.52
	severe/critical COVID-19	5	-7.47(-23.95,9.02)	96%		

*Statistically significant subgroup effect sizes, ascertained as $P_{subgroup}$ (χ2 test) <0.05.

[a] Studies categorized by age group depending on the mean.

Abbreviation: MD: difference in mean; RR: ratio risk; CI: confidence interval; SD: standard deviation

COVID-19 patients (regardless of stage), previous literature indicates that the combination of Chinese and Western medicine treatment has shown significant improvement in overall efficiency, chest CT improvement rate, disease progression rate, as well as fever, malaise, and cough [12, 71]. For COVID-19 patients in the recovery stage, adding CHM could facilitate the improvement of clinical symptoms and lung function and the achievement of a balanced body constitution in these patients recovering from COVID-19 [72]. In line with them, we also found a significantly positive effect that adding Chinese medicine strengthened the therapeutic effect of Western monotherapy in confirmed COVID-19 patients at all distinct stages.

Compared with the western monotherapy, the ICW group showed a higher recovery rate of chest CT, shortened negativity time of nucleic acid, reduced number of mild/moderate patients developing into severe conditions, and decreased mortality rate. In contrast to previous meta-analyses that focused only on a certain stage of COVID-19 or did not strictly restrict the enrollment of patient (probably because most early trials did not divide the patients into distinct clinical stages specifically) [12, 70, 71]. In this study, COVID-19 patients were strictly categorized into different stages and the therapeutic effects of herbal medicine on co patients in different stages were explored. For mild/moderate COVID-19 patients, compared with Western medicine monotherapy, the ICW group showed a clinically meaningful difference in improving chest CT by 11%, relieving symptoms by 23%, shortening time to recovery and negative conversion, decreasing the rate of patients developing into severe conditions by 5%. We did not observe the statistical difference in clinical symptom improvements and time to reduction of clinical symptoms in the severe/critical stages. This phenomenon may be in the early stage of COVID-19 when patients manifest fever, cough, breathlessness, and fatigue, which belong to the category of typical external syndrome from the perspective of CHM [73]. With timely intervention of CHM at this stage, COVID-19 disease progression can be effectively blocked from mild to critical stages, thus shortening the course of the disease, improving the cure rate, and preventing deterioration. In the plaque reduction experiment, Merarchi M found that LQHW could inhibit the proliferation of influenza virus, and the remarkable decrease of virus titer occurred mainly in 0–2 hours, suggesting that the early intervention of CHM as adjuvant drugs may inhibit the early replication of influenza virus [74]. However, some symptoms, including fatigue and breathlessness in this stage, were not documented, which required more carefully performed trials to support this evidence further.

Laboratory tests are crucial for precisely predicting the prognosis and therapeutic effect in COVID-19 cases. We typically added laboratory test results as observational indicators, while previous studies only included clinical indicators (11–130). Interestingly, we found that the level of LYM was significantly elevated by ICW therapy, which might suggest that patients in the later stage suffer from severe immune imbalance. Thus, improving the level of immune cells was helpful to improve the prognosis. We also found that although a three-armed trial of 60 severe COVID-19 patients conducted by Wen Long et al. [52], compared with the low dose group of 50 mL XBJ injection, the CRP of the high dose group of 100 mL XBJ injection was significantly decreased, no remarkable superiority was observed according to the level of CRP in this study.

Additionally, due to the limited number of clinical trials, most previous research only focused on the single prescription [67, 68], so we systematically summarized and presented the potential drug candidates of CHM remedy recommended at distinct stages for COVID-19 in this meta-analysis. For mild to moderate COVID-19 cases, Lianhua Qingwen (LHQW) granules, Jinhua Qinggan (JQ) granules, and Qingfei Paidu Decoction (QPD) were most frequently used. In line with the 8thVersion of Diagnosis and Treatment Protocol for COVID-19(8) and previous studies [69, 75, 76], LHQW, a Chinese patent medicine composed of 13 herbs, has been used to treat the early stage of COVID-19. It could significantly inhibit SARS-CoV-2 replication, alter the viral morphology, reduce the cytokine release from host cells, and confer anti-inflammatory activity in vitro [77]. In our study, two studies including the RCT and RCS, provided evidence for the advantage of treating in mild/moderate patients with LHQW (26,34). Also, Fan AY found that JQ was developed for mild cases during the pandemic of COVID-19 [12]. While Qingfei Paidu Decoction (QPD) recommended by the 8th Version of Diagnosis and Treatment Protocol for COVID-19 and the previous reviews (8, 12,72), and was used to treat COVID-19 patients with mild, moderate, severe cases. QPD was also used reasonably with the consideration of the actual conditions of critically ill patients. In this meta-

analysis, only one RCS was performed with moderate COVID-19 cases, indicating a better therapeutic effect of QPD than CWM(27). Jian Chen divided QPD into five functional units (FUs) and measured by drug perturbation of COVID-19 network robustness, showing that all five FUs may protect COVID-19 independently, and targeting 8 specifically expressed drug-attacked nodes which were related to the bacterial and viral responses, immune system, signaling transduction, etc [78]. When it comes to severe and critical cases, Shengfu injection, Xuebijing injection, and Tanreqing injection were most frequently used. In accordance with previous meta-analysis [75], Xuebijing injection plus routine treatment could reduce the development of ARDS and the use of mechanical ventilation. Wen-Jiang Zheng [79] used the Swiss Target Prediction database to predict XBJ's effector targets and mapped them to the abovementioned COVID-19 disease targets, indicating the pharmacological mechanisms of XBJ in the treatment of COVID-19, which could be explained by the effector mechanism of sepsis and severe pneumonia treatment. However, the potential mechanisms of other CHM in this study are still unclear. In the future, more research on clinical evidence and molecular mechanisms by Chinese herbal formulas are warranted.

Besides, most previous studies did not perform the subgroup analysis based on methodology and clinical factors [11–13, 67, 68, 71]. Thus, extensive literature searching of relevant clinical trials published in both Chinese and English databases concerning all-cross recipes was conducted, and up to 46 studies were enrolled in this review, including RCTs and, PCSs and RCSs. The use of a comprehensive search strategy to identify and select studies for review could minimize selection bias, and with sufficient trials to support subgroup analysis on methodology and clinical factors, leading to a more persuasive and feasible conclusion, which is essential for confirming the effectiveness of CHM for COVID-19 from different angles and levels. We also evaluated the effectiveness of adding CHM by clinical heterogeneity, methodological limitations, and subgroup analysis. Our results indicated that course, sex, dosage formulations, usage, and age may cause heterogeneity. There was a significant trend towards that older patients were less effective by adding CHM in negativity time of nucleic acid, the improvement rate of cough, level of NEU, and CRP, probably due to the older age in later stage COVID-19 included in this study.

Limitation

Firstly, the exact efficacy of long-term symptoms of COVID-19 of CHM deserves continuous attention and medical observation, especially for patients in the critical stage. However, the duration of all the studies is shorter than one month, which may cause the missed. Secondly, we included RCTs, PCSs, and RCSs with different underlying target variables, with relatively small sample size in some RCTs. Although no significant heterogeneity was detected between these three types of the study, the potential selection bias still exists due to the different research types. Besides, the quality of the included studies is not in the same accordance. Issues regarding sequence generation of randomization, concealment of allocation, reporting on blinding, dropouts, and pre-estimation of sample size should not be neglected in the further studies. Thirdly, 16 literatures did not document the exact dose size of single-flavor drugs in each recipe, and 10 literatures used Chinese medicine differentiation treatment according to the signal patient, which caused difficulty in summarizing the dose size of single-flavor drugs in this meta-analysis. Besides, a customized medication may have a better effect than fixed formulas for reaching a better therapeutic effect in COVID-19 patients. However, the dose and composition of formula ingredients may be the source of heterogeneity which may disturbs the final conclusions. Thirdly, our study population is based on the Chinese populations, which may lead to the bias from ethnicity. So, we typically limited our conclusions and

recommendations on Chinese COVID-19 patients. Moreover, although we conducted subgroup analysis according to diversity in CHM syndrome differentiation treatment and standard Western medicine treatment in each study, figuring out the source of heterogeneity, more trials developed strictly according to the CONSORT statement [80] for CHM were necessary to confirm the conclusion. Finally, the number of included studies focused on severe/critical COVID-19 was still relatively small, and only one study reported a rate of fever reduction, which may lead to the possibility that the efficacy was not statistically significant. More large-scale clinical trials, which are performed at later stages, are needed in the future to obtain unbiased results.

Conclusions

ICW had a significantly better effect than Western medicine monotherapy in all distinct stages of Chinese COVID-19 patients. Adding CHM could decrease chest radiograph abnormalities, alleviate clinical symptoms, promote rehabilitation, reduce disease progression, and prolong the therapeutic window for Chinese COVID-19 patients. Besides, earlier intervention of CHM may contribute to a better therapeutic effect in Chinese populations. However, considering the intrinsic heterogeneity of CHM and some qualities of included studies were poor, which may affect conclusions of the meta-analysis. In the future, more large-scale clinical trials, which are performed with fixed formulas, are needed for obtaining unbiased results.

Supporting information

S1 Fig. Risk of bias assessment.
(DOCX)

S2 Fig. The recommended Chinese herds/prescriptions for different clinical types of COVID-19.
(DOCX)

S3 Fig. Funnel plot of improvement rate of chest CT.
(DOCX)

S1 Table. Details of the search strategy of PubMed/ Embase/ Cochrane Library.
(DOCX)

S2 Table. Details of the search strategy of Wan fang Database / VIP Information Database/ SinoMed/ China National Knowledge Infrastructure.
(DOCX)

S3 Table. The reason for excluded studies at full-reading stage.
(DOCX)

S4 Table. General information of included studies.
(DOCX)

S5 Table. Bias risk assessment results of included retrospective studies.
(DOCX)

S6 Table. Components of TCM prescriptions in the included studies.
(DOCX)

S7 Table. Subgroup and sensitivity analyses for the other main outcomes.
(DOCX)

S8 Table. Quality evaluation of outcome indicators.
(DOCX)

S1 Checklist. PRISMA checklist COVID-19.
(DOCX)

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References

1. W.H. Organization, WHO Coronavirus Disease (COVID-19) Dashboard, 2024. Preprint at https://covid19.who.int/.

2. Jin Y.H., Zhan Q.Y., Peng Z.Y., et al., Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: An evidence-based clinical practice guideline (updated version), Mil Med Res 7 (1) (2020) https://doi.org/10.1186/s40779-020-00270-8 PMID: 32887670

3. Tsang H.F., Chan L.W.C., Cho W.C.S., et al., An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies, Expert Rev Anti Infect Ther 19(7) (2021) https://doi.org/10.1080/14787210.2021.1863146 PMID: 33306423

4. Asselah T., Durantel D., Pasmant E., et al., COVID-19: Discovery, diagnostics and drug development, J Hepatol 74(1) (2021) https://doi.org/10.1016/j.jhep.2020.09.031 PMID: 33038433

5. Saravolatz L.D., Depcinski S., Sharma M., Molnupiravir and Nirmatrelvir-Ritonavir: Oral Coronavirus Disease 2019 Antiviral Drugs, Clin Infect Dis 76(1) (2023) https://doi.org/10.1093/cid/ciac180 PMID: 35245942

6. Ji Z., Hu H., Qiang X., et al., Traditional Chinese Medicine for COVID-19: A Network Meta-Analysis and Systematic Review, Am J Chin Med 50(4) (2022) https://doi.org/10.1142/S0192415X22500379 PMID: 35729086

7. Qing G.C., Zhang H., Bai Y., et al., Traditional Chinese and Western Medicines Jointly Beat COVID-19 Pandemic, Chin J Integr Med 26(6) (2020) https://doi.org/10.1007/s11655-020-3095-6 PMID: 32361935

8. N.H.C.o.t.P.s.R.o. China, Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition). 2020. Preprint at http://en.nhc.gov.cn/2020-09/07/c_81565.

9. Huang K., Zhang P., Zhang Z., et al., Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms, Pharmacol Ther 225 (2021) https://doi.org/10.1016/j.pharmthera.2021.107843 PMID: 33811957

10. Kang X., Jin D., Jiang L., et al., Efficacy and mechanisms of traditional Chinese medicine for COVID-19: a systematic review, Chin Med 17(1) (2022) https://doi.org/10.1186/s13020-022-00587-7 PMID: 35227280

11. Zeng M., Li L., Wu Z., Traditional Chinese medicine Lianhua Qingwen treating corona virus disease 2019(COVID-19): Meta-analysis of randomized controlled trials, PLoS One 15(9) (2020) https://doi.org/10.1371/journal.pone.0238828 PMID: 32915877

12. Fan A.Y., Gu S., Alemi S.F., Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis, J Integr Med 18(5) (2020) https://doi.org/10.1016/j.joim.2020.07.008 PMID: 32792254

13. Liu M., Gao Y., Yuan Y., et al., Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Corona Virus Disease 2019 (COVID-19): a systematic review and meta-analysis, Pharmacol Res 158 (2020) https://doi.org/10.1016/j.phrs.2020.104896 PMID: 32438037

14. Page M.J., McKenzie J.E., Bossuyt P.M., et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Bmj 372 (2021) https://doi.org/10.1136/bmj.n71 PMID: 33782057

15. Stroup D.F., Berlin J.A., Morton S.C., et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group, Jama 283(15) (2000) https://doi.org/10.1001/jama.283.15.2008 PMID: 10789670

16. Schardt C., Adams M.B., Owens T., et al., Utilization of the PICO framework to improve searching PubMed for clinical questions, BMC Med Inform Decis Mak 7 (2007) https://doi.org/10.1186/1472-6947-7-16 PMID: 17573961

17. Yüce M., Filiztekin E., Özkaya K.G., COVID-19 diagnosis -A review of current methods, Biosens Bioelectron 172 (2021) https://doi.org/10.1016/j.bios.2020.112752 PMID: 33126180

18. Pedder H., Sarri G., Keeney E., et al., Data extraction for complex meta-analysis (DECiMAL) guide, Syst Rev 5(1) (2016) https://doi.org/10.1186/s13643-016-0368-4 PMID: 27964742

19. e.a. Higgins JPT, Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). 2023. Cochrane. Preprint at www.training.cochrane.org/handbook.

20. Stang A., Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur J Epidemiol 25(9) (2010) https://doi.org/10.1007/s10654-010-9491-z PMID: 20652370

21. Guyatt G., Oxman A.D., Akl E.A., et al., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, J Clin Epidemiol 64(4) (2011) https://doi.org/10.1016/j.jclinepi.2010.04.026 PMID: 21195583

22. Huang Donghui, Yuan Qingliang, T. Chunhui., Effect of Gengzi No.3 recipe on neutrophils to lymphocyte ratio of inner blocking causing collapse syndrome caused by severe COVID-19., Shanxi J Of TCM 37(07) (2021).

23. Zhihui L., Kunxiu W., Ziqin C., et al., Clinical Efficacy of Modified Sanxiaoyin in Treatment of Mild or Moderate COVID-19 Patients:Based on Retrospective Analysis., Chinese Journal of Experimental Traditional Medical Formulae 28(01) (2022) https://doi.org/10.13422/j.cnki.syfjx.20212497

24. ling Y., Hongjia Z., Shungui X., et al., Clinical Study of Modified Shengjiang Powder in the Treatment of Ordinary COVID-19, Chinese and Foreign Medical Research. Chinese and Foreign Medical Research 19(28) (2021) https://doi.org/10.14033/j.cnki.cfmr.2021.28.003

25. Ping Y., Yezi L., Shaobing W., et al., Effects of Lianhua Qingwen Granules Plus Arbidol on Treatment of Mild Corona Virus Disease-19., Chinese Pharmaceutical Journal. 55(12) (2020).

26. Xianhong Z., Wenhui M., jie W., Effect of Qingfei Paidu decoction on clinical efficacyy of COVID-19 pneumonia with Phlegm heat blocking lung., Medical Journal of West China 32(12) (2020).

27. Mingbo Y., Shuangsuo D., Sheng H., et al., Multi-center Clinical Observation of Reyanning Mixture in Treatment of COVID-19., Chinese Journal of Experimental Traditional Medical Formulae 26(14) (2020) https://doi.org/10.13422/j.cnki.syfjx.20201321

28. Lin W., Meng X., Yu W., et al., Clinical study on Shengmai Powder combined with Shenling Baizhu Powder in the treatment of common Corona Virus Disease 2019., China Journal of Traditional Chinese Medicine 35(08) (2020).

29. Yuan W., Donghui H., Huixian W., et al., Curative effect of integrated Chinese and Western medicine on 80 severe and critical COVID-19 patients., Journal of Beijing University of Traditional Chinese Medicine 45(06) (2022).

30. Fei C., Bo F., Yuanming B., Clinical Curative Effect Observation of Combining Traditional Chinese and Western Medicine on Common New Coronavirus Pneumonia in Xiaogan Area, Journal of Sichuan of Traditional Chinese Medicine 40(07) (2022).

31. Qian Y., Qinguo S., Bo J., et al., Retrospective clinical study on treatment of COVID-19 patients with integrated traditional Chinese and western medicine., Chinese Traditional and Herbal Drugs 51(08) (2020).

32. Dan J., Ping F., Xinying F., Retrospective Study of Clinical Efficacy of Integrated Chinese and Western Medicine in Treatment of COVID-19., Shandong Journal of Traditional Chinese 39(07) (2020) https://doi.org/10.16295/j.cnki.0257-358x.2020.07.001

33. Kaitao Y., Mingyu L., Xin L., et al., Retrospective Clinical Analysis on Treatment of Coronavirus Disease 2019 with Traditional Chinese Medicine Lianhua Qingwen., Chinese Journal of Experimental Traditional Medical Formulae 26(11) (2020) https://doi.org/10.13422/j.cnki.syfjx.20201099

34. Yahui L., Aijun Z., Junkai W., et al., Clinical Efficacy of Jinbei Oral Liquid in the Treatment of COVID-19 by Retrospective Analysis., Pharmacology and Clinics of Chinese Materia Medica 37(05) (2021) https://doi.org/10.13412/j.cnki.zyyl.20210608.002

35. Yue Z., Genping L., Ting W., et al., Clinical Efficacy of Jiangxia Mobile Cabin Hospital Decoction Series for the Treatment of Mild COVID- 2019., Journal of Emergency in Traditional Chinese 32(06) (2023).

36. Can D., Wenguang X., Chanjuan Z., et al., Clinical Observation on Jinhua Qinggan Granule Combined with Conventional Western Medi- cine Therapy in Treating Mild Cases of Coronavirus Disease 2019, Journal of Traditional Chinese Medicine 61(17) (2020) https://doi.org/10.13288/j.11-2166/r.2020.17.001

37. Feifei L., Jianping H., Jun Y., et al., Clinical study on the adjuvant treatment of common novel coronavirus pneumonia with Xuanfei Qingre prescription., Zhejiang Journal of Integrated Traditional Chinese and Western Medicine 30(12) (2020).

38. Chaoqun H., Wenliang L., Hao L., et al., 2132 cases of Corna Virus Disease 2019 in Hubei province: A real-world study., China Journal of Traditional Chinese Medicine and Pharmacy 38(02) (2023).

39. Xiangyong Y., Zhongsheng Y., Jun L., et al., Clinical Observation of Integrative Medicine Therapy of COVID-19., Western Journal of Traditional Chinese Medicine 34(09) (2021).

40. Fei H., Qin H., Zhihui L., et al., Retrospective study on the treatment of severe novel coronavirus pneumonia by TCM syndrome differentiation and protocol., Zhejiang Journal of Integrated Traditional Chinese and Western Medicine 32(06) (2022).

41. Yujun Q., Yanju W., Bo Y., et al., Clinical Efficacy of Mild Type of Novel Coronavirus Pneumonia Treated with Integrated Traditional Chinese and Western Medicine., Smart Healthcare 6(22) (2020) https://doi.org/10.19335/j.cnki.2096-1219.2020.22.028

42. Li H.-l., Clinical effect analysis of integrated traditional Chinese and Western medicine in treating patients with novel coronavirus pneumonia., World Latest Medicine Information. (2020) 20,187–188. https://doi.org/10.3969/j.issn.1671-3141.2020.91.102

43. Tong Z., Xi'an Z., Yuli T., et al., Clinical Efficacy of Chonglian Oral Liquid on COVID-19 Patients, Chinese Journal of Experimental Traditional Medical Formulae 29(17) (2023) https://doi.org/10.13422/j.cnki.syfjx.20240295

44. Lu Zhidan F.Z., Congxin Li, Chenxi Liu, Dong Shang, Nan Li, Effectiveness evaluation of integrative medicine in treatment of 60 patients with coronavirus disease 2019 pneumonia in Wuhan Leishenshan Hospital, Chin J TCM WM Crit Care Vol. 29, No.5 (2022) https://doi.org/10.3969/j.issn.1008-9691.2022.05.007

45. Liu J., Yang W., Liu Y., et al., Combination of Hua Shi Bai Du granule (Q-14) and standard care in the treatment of patients with coronavirus disease 2019 (COVID-19): A single-center, open-label, randomized controlled trial, Phytomedicine 91 (2021) https://doi.org/10.1016/j.phymed.2021.153671 PMID: 34425471

46. Shi N., Guo L., Liu B., et al., Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: A non-randomized controlled trial, Phytomedicine 81 (2021) https://doi.org/10.1016/j.phymed.2020.153367 PMID: 33260064

47. Zhang X.Y., Lv L., Zhou Y.L., et al., Efficacy and safety of Xiyanping injection in the treatment of COVID-19: A multicenter, prospective, open-label and randomized controlled trial, Phytother Res 35(8) (2021) https://doi.org/10.1002/ptr.7141 PMID: 33979464

48. Xiong W.Z., Wang G., Du J., et al., Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19:A pilot randomized clinical trial, Integr Med Res 9(3) (2020) https://doi.org/10.1016/j.imr.2020.100489 PMID: 32874913

49. An X., Xu X., Xiao M., et al., Efficacy of Jinhua Qinggan Granules Combined With Western Medicine in the Treatment of Confirmed and Suspected COVID-19: A Randomized Controlled Trial, Front Med (Lausanne) 8 (2021) https://doi.org/10.3389/fmed.2021.728055 PMID: 34712679

50. Zeng C., Yuan Z., Zhu J., et al., Therapeutic effects of traditional Chinese medicine (Maxingshigan-Weijing Decoction) on COVID-19: An open-label randomized controlled trial, Integr Med Res 10(Suppl) (2021) https://doi.org/10.1016/j.imr.2021.100782 PMID: 34660195

51. Zhou S., Feng J., Xie Q., et al., Traditional Chinese medicine shenhuang granule in patients with severe/critical COVID-19: A randomized controlled multicenter trial, Phytomedicine 89 (2021) https://doi.org/10.1016/j.phymed.2021.153612 PMID: 34126419

52. Weng Long Z.Z., Dixuan Jiang, Kang Huang, Effect of Xuebijing injection on inflammatory markers and disease outcome of coronavirus disease 2019, Chinese Critical Care Medicine 32,426–429 (2020) https://doi.org/10.3760/cma.j.cn121430-20200406-00386 PMID: 32527346

53. Zhao J., Yang X., Wang C., et al., Yidu-toxicity blocking lung decoction ameliorates inflammation in severe pneumonia of SARS-COV-2 patients with Yidu-toxicity blocking lung syndrome by eliminating IL-6 and TNF-a, Biomed Pharmacother 129 (2020) https://doi.org/10.1016/j.biopha.2020.110436 PMID: 32768938

54. Xu X., Zhou S., Chen C., et al., Efficacy and safety of Reyanning mixture in patients infected with SARS-CoV-2 Omicron variant: A prospective, open-label, randomized controlled trial, Phytomedicine 108 (2023) https://doi.org/10.1016/j.phymed.2022.154514 PMID: 36334390

55. e.a. Zhang L, Efficacy and Safety of Lianhua Qingke Tablets in the Treatment of Mild and Common-Type COVID-19: A Randomized, Controlled, Multicenter Clinical Study. Evid Based Complement, Alternat Med. (2022) 2022,8733598. https://doi.org/10.1155/2022/8733598 PMID: 35186107

56. Zhao C., Li L., Yang W., et al., Chinese Medicine Formula Huashibaidu Granule Early Treatment for Mild COVID-19 Patients: An Unblinded, Cluster-Randomized Clinical Trial, Front Med (Lausanne) 8 (2021) https://doi.org/10.3389/fmed.2021.696976 PMID: 34604251

57. Luo Z., Chen W., Xiang M., et al., The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: A prospective randomized controlled trial, Eur J Integr Med 42 (2021) https://doi.org/10.1016/j.eujim.2021.101305 PMID: 33552315

58. Ke J., Tian F., Hongju L., Analysis of curative effect of integrated traditional Chinese and Western medicine on novel coronavirus pneumonia., World Latest Medicine Information. (2020) 20,256–257. https://doi.org/10.3969/j.issn.1671-3141.2020.78.112 (2020).

59. Wang Y., Lu C., Li H., et al., Efficacy and safety assessment of severe COVID-19 patients with Chinese medicine: A retrospective case series study at early stage of the COVID-19 epidemic in Wuhan, China, J Ethnopharmacol 277 (2021) https://doi.org/10.1016/j.jep.2021.113888 PMID: 33529638

60. Wenguang X., Chanjuan Z., Jixian Z., et al., Randomized controlled study of a diagnosis and treatment plan for moderate coronavirus disease 2019 that integrates Traditional Chinese and Western Medicine, J Tradit Chin Med 42(2) (2022) https://doi.org/10.19852/j.cnki.jtcm.20210220.001 PMID: 35473344

61. Chen G., Su W., Yang J., et al., Chinese herbal medicine reduces mortality in patients with severe and critical Coronavirus disease 2019: a retrospective cohort study, Front Med 14(6) (2020) https://doi.org/10.1007/s11684-020-0813-6 PMID: 32926320

62. Feng J., Fang B., Zhou D., et al., Clinical Effect of Traditional Chinese Medicine Shenhuang Granule in Critically Ill Patients with COVID-19: A Single-Centered, Retrospective, Observational Study, J Microbiol Biotechnol 31(3) (2021) https://doi.org/10.4014/jmb.2009.09029 PMID: 33746189

63. Wang Y., Liu Y., Lv Q., et al., Effect and safety of Chinese herbal medicine granules in patients with severe coronavirus disease 2019 in Wuhan, China: a retrospective, single-center study with propensity score matching, Phytomedicine 85 (2021) https://doi.org/10.1016/j.phymed.2020.153404 PMID: 33637412

64. Zhang J., Liu L., Zhang G., et al., Treating patients infected with the SARS-CoV-2 Omicron variant with a traditional Chinese medicine, Shufeng Jiedu capsule, Biosci Trends 16(3) (2022) https://doi.org/10.5582/bst.2022.01220 PMID: 35732417

65. e.a. Zhang J, Oral Liushen pill for patients with COVID-19: A prospective randomized controlled trial., Pulm Circ. (2023) 1, e12187. https://doi.org/10.1002/pul2.12187 PMID: 36733313

66. Hu H., Wang K., Wang L., et al., He-Jie-Shen-Shi Decoction as an Adjuvant Therapy on Severe Coronavirus Disease 2019: A Retrospective Cohort and Potential Mechanistic Study, Front Pharmacol 12 (2021) https://doi.org/10.3389/fphar.2021.700498 PMID: 34220524

67. Lei Y., Guan H., Xin W., et al., A Meta-Analysis of 13 Randomized Trials on Traditional Chinese Medicine as Adjunctive Therapy for COVID-19: Novel Insights into Lianhua Qingwen, Biomed Res Int 2022 (2022) https://doi.org/10.1155/2022/4133610 PMID: 36349317

68. Wang X., Ma T., Zhang W., et al., Effectiveness and safety research of Qingfei Paidu (QFPD) in treatment of COVID-19: an up-to-date systematic review and meta-analysis, Chin Med 17(1) (2022) https://doi.org/10.1186/s13020-022-00675-8 PMID: 36307813

69. You L.Z., Dai Q.Q., Zhong X.Y., et al., Clinical evidence of three traditional Chinese medicine drugs and three herbal formulas for COVID-19: A systematic review and meta-analysis of the Chinese population, J Integr Med 21(5) (2023) https://doi.org/10.1016/j.joim.2023.08.001 PMID: 37596131

70. Hu S., Luo D., Zhu Q., et al., An updated meta-analysis of Chinese herbal medicine for the prevention of COVID-19 based on Western-Eastern medicine, Front Pharmacol 14 (2023) https://doi.org/10.3389/fphar.2023.1257345 PMID: 38044944

71. Jiang F., Xu N., Zhou Y., et al., Contribution of traditional Chinese medicine combined with conventional western medicine treatment for the novel coronavirus disease (COVID-19), current evidence with systematic review and meta-analysis, Phytother Res 35(11) (2021) https://doi.org/10.1002/ptr.7209 PMID: 34256418

72. Zhang W., Ma L., Xie W., et al., Advances in the application of traditional Chinese medicine during the COVID-19 recovery period: A review, Medicine (Baltimore) 103(14) (2024) https://doi.org/10.1097/MD.0000000000037683 PMID: 38579075

73. Li S., Liu C., Guo F., et al., Traditional Chinese Medicine as Potential Therapy for COVID-19, Am J Chin Med 48(6) (2020) https://doi.org/10.1142/s0192415x20500627 PMID: 32907358

74. Merarchi M., Dudha N., Das B.C., et al., Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs, Phytother Res 35(10) (2021) https://doi.org/10.1002/ptr.7151 PMID: 34132421

75. Wang H., Xu B., Zhang Y., et al., Efficacy and Safety of Traditional Chinese Medicine in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis, Front Pharmacol 12 (2021) https://doi.org/10.3389/fphar.2021.609213 PMID: 34421581

76. Guan W., Lan W., Zhang J., et al., COVID-19: Antiviral Agents, Antibody Development and Traditional Chinese Medicine, Virol Sin 35(6) (2020) https://doi.org/10.1007/s12250-020-00297-0 PMID: 32997322

77. Runfeng L., Yunlong H., Jicheng H., et al., Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2), Pharmacol Res 156 (2020) https://doi.org/10.1016/j.phrs.2020.104761 PMID: 32205232

78. Chen J., Wang Y.K., Gao Y., et al., Protection against COVID-19 injury by qingfei paidu decoction via anti-viral, anti-inflammatory activity and metabolic programming, Biomed Pharmacother 129 (2020) https://doi.org/10.1016/j.biopha.2020.110281 PMID: 32554251

79. Zheng W.J., Yan Q., Ni Y.S., et al., Examining the effector mechanisms of Xuebijing injection on COVID-19 based on network pharmacology, BioData Min 13 (2020) https://doi.org/10.1186/s13040-020-00227-6 PMID: 33082858

80. Gagnier J.J., Boon H., Rochon P., et al., Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement, Ann Intern Med 144(5) (2006) https://doi.org/10.7326/0003-4819-144-5-200603070-00013 PMID: 16520478