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Chinese Medicine for Coronavirus Disease 2019 (COVID-19): A GRADE-Assessed Systematic Review and Meta-Analysis

Jianbo Guo,[*] Zongshi Qin,[*] Ngai Chung Lau,[*] Tung Leong Fong,[*] Wei Meng,[*,‡,§] Zhang-Jin Zhang,[*,†] Yi Luo,[*] Vivian Chi-Woon Taam Wong,[*] Yibin Feng[*] and Haiyong Chen[*,†]

[*]*School of Chinese Medicine, LKS Faculty of Medicine*
The University of Hong Kong, 10 Sassoon Road
Pokfulam, Hong Kong SAR, P. R. China

[†]*Department of Chinese Medicine, The University of Hong Kong-Shenzhen Hospital*
Futian District, Shenzhen, Guangdong 518053, P. R. China

[‡]*Hong Kong Branch of Workstation of Distinguished Professor Yu Jin for Training and Research in Integrative Gynaecology*
Hong Kong SAR, P. R. China

[§]*Hong Kong Branch of Workstation of National Master Zhu Nansun for Chinese Medicine Gynaecology*
Hong Kong SAR, P. R. China

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Abstract: Coronavirus disease 2019 (COVID-19) has caused enormous public health and socioeconomic burden globally. This study aims to evaluate the efficacy and safety of Chinese medicine (CM) against COVID-19. Eleven databases were searched on April 30, 2021, and 52 studies were included. The RoB 2.0, ROBINS-I, and GRADE tools were employed to assess the risks and evidence grades. The findings with moderate certainty in GRADE showed that compared with routine treatment (RT), Lianhua Qingwen granules (LHQW) adjunctive to RT showed significantly improved efficacy rate (relative risk (RR) = 1.19, 95% confidence interval (CI): [1.09, 1.31]), febrile score (standard mean difference (SMD) = −1.21, 95% CI: [−1.43, −0.99]), and computerized tomography (CT) lung images (RR = 1.23, 95% CI: [1.10, 1.38]); Qingfei Paidu decoction (QFPD) plus RT significantly shortened the length of hospital stay (SMD = −1.83, 95% CI: [−2.18, −1.48]); Feiyan Yihao formula (FYYH) plus RT significantly improved the clinical efficacy rate (RR = 1.07, 95% CI: [1, 1.15]), febrile time (SMD = −0.02, 95% CI: [−0.23, 0.19]), and time to negative PCR test for COVID-19 (SMD = −0.72, 95% CI: [−0.94, −0.51]). Adjunctive effects of CM with

Correspondence to: Dr. Haiyong Chen, School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong SAR, P. R. China. Tel: (+852) 3917–6413, Fax: (+852) 2872–5476, E-mail: haiyong@hku.hk

lower certainty of evidence were found, including the improvements of symptoms, laboratory findings, and mortality. No or mild adverse events were observed in most of the studies. In conclusion, the current evidence indicates that CM formulae, particularly LHQW, QFPD, and FYYH, have adjunctive effects on the standard treatment of COVID-19.

Keywords: COVID-19; Chinese Medicine; Lianhua Qingwen; Feiyan Yihao; Qingfei Paidu; Controlled Trials; Meta-Analysis; Review.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has considerably affected the world (Lu *et al*., 2020; Wang *et al*., 2020a), with over 149 million infected globally, resulting in more than 2.6 million deaths according to the data reported by WHO on April 28, 2020. Chinese medicine (CM) has played a crucial role in treatments during several pandemics throughout history (Duan *et al*., 2011; Wang *et al*., 2011; Liu *et al*., 2012, 2014; Wu *et al*., 2021). During the previous outbreaks, the CM formulae, notably Maxingshigan–Yinqiaosan, could reduce febrile time in patients with influenza A (H1N1) virus infection (Wang *et al*., 2011); several other CMs also contributed to improving the lung infiltration and quality of life of severe acute respiratory syndrome (SARS) patients (Liu *et al*., 2012; Li *et al*., 2020a). Since March 2020, China's National Health Commission included CM in COVID-19 management guidelines (Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia, Trial Version 3). For patients with different CM syndromic diagnoses, the guidelines made the corresponding treatment recommendations (Chan *et al*., 2020; Liang *et al*., 2020).

Previous systematic reviews indicated that CM formulae combined with Western medicine significantly improved the clinical symptoms compared with Western medicine alone (Wang *et al*., 2021a; Yin *et al*., 2021; Zhou *et al*., 2021a). However, the definitive conclusion was not reached due to the heterogeneity of pooled studies and a small number of eligible studies. As more studies are published, the systematic reviews need to be updated. Particularly, these newly published studies followed China's guidelines for treatment and diagnosis of COVID-19, which might reduce the heterogeneity among studies. Our study aimed to systematically review the current clinical studies on each CM formula for COVID-19 treatment.

Methods

Search Strategy

This review was registered in PROSPERO on March 27, 2020 (Registration No. CRD42020176347) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati *et al*., 2009). Eleven databases were searched by April 30, 2021, including PubMed, Excerpta Medica Database, Cochrane

Library, Allied and Complementary Medicine Database, Cumulative Index to Nursing & Allied Health Literature Plus, Chinese National Knowledge Infrastructure Database, China Scientific Journal Database, Wanfang Database, ClinicalTrials.gov, Chinese Clinical Trial Registry, and MedRxiv. MeSH and free search words were combined to yield the following search criteria: "COVID-19 OR SARS-COV-2" AND "traditional Chinese medicine" AND "trials".

Eligibility Criteria

The inclusion criteria for studies were as follows: (1) patients had a laboratory diagnosis of COVID-19; (2) either retrospective nonrandomized studies or RCTs; (3) the observation group was treated using CM plus routine treatment (RT) or CM alone; (4) inclusion of all forms of CM; and (5) treatment of the control group using RT (e.g., Western medicine, usual care). The exclusion criteria were as follows: (1) case control and cohort studies; (2) case reports, protocols, reviews, comments, clinical experiences, guidelines, expert consensus, animal or cell experiments; (3) duplicate studies; (4) the control group receiving CM, acupuncture, or moxibustion; and (5) literature without specific essential data after contacting authors.

Literature Quality Assessment

Two researchers (JG and ZQ) independently assessed the quality of the included studies, with discrepancies being resolved by a third researcher (HC). Version 2 of the Cochrane risk-of-bias tool (RoB 2.0) and the risk of bias in nonrandomized studies of interventions (ROBINS-I) were used for bias assessment of RCTs (Sterne *et al.*, 2019) and retrospective nonrandomized studies (Sterne *et al.*, 2016), respectively. The RoB 2.0 assesses the following biases: randomization process, deviations from the intended interventions, missing outcome data, outcome measurements, selection of the reported results, and overall bias. The ROBINS-I assesses the following biases: confounding, classification of intervention, deviations from intended interventions, missing data, outcome measurements, selection of the reported result, and overall bias. The meta-analysis results were graded using grades of recommendation, assessment, development, and evaluation (GRADE).

Data Extraction and Analyses

The EndNote software (version X9.3.3) was employed to remove duplication and manage the literature. Two authors (NCL and TLF) extracted data independently, and a third author (HC) supervised the process and solved the discrepancies. The following data were extracted from the included studies: (1) basic information, including the first author name, year of publication, sample size, age, routine treatment protocol, intervention group, control group, duration, and frequency of interventions; (2) primary outcome being the clinical efficacy according to the Criteria of Diagnosis and Therapeutic Effect

of Diseases and Syndromes in Traditional Chinese Medicine as represented by reduction of the main symptom scores of fever, cough, fatigue and dyspnea by ≥30%; (3) secondary outcomes including improvements in fever time, score and level; computerized tomography of lungs, length of hospital stay and death (4) minor outcomes include cough and fatigue recovery time, score and improvement rate; laboratory tests (COVID-19 PCR test, C-reactive protein, leukocytes, and lymphocytes) and adverse events. Additionally, the authors of the included studies were contacted for further clarification in case of incomplete published data.

Statistical analyses were performed using the Stata 17.0 software (Stata Corp., College Station, TX, USA). A random-effect model was used in case of significant heterogeneity of the pooled studies; otherwise, the fixed-effect model was employed. Cohen's d and relative risk (RR) were used for continuous and categorical variables, respectively, at 95% confidence interval (CI). Study heterogeneity was determined using Q statistics and I^2, with a *p*-value in Q statistics of <0.1 or $I^2 \geq 50\%$, indicating significant among-study heterogeneity. The L'Abbe plot was used to test heterogeneity among categorical variables. Publication bias was evaluated using funnel plot and Egger test. Sensitivity analysis was conducted for studies with significant heterogeneity, and subgroup analysis was performed based on the outcome measures. The mean and standard deviation were estimated based on the reformative methods (Wan *et al.*, 2014; Luo *et al.*, 2018) for studies that reported the median and interquartile range.

Results

Literature Selection and Characteristics

The initial search yielded 3,858 studies, with 2,448 studies remaining after removing duplications. After screening titles, abstracts, and full texts, 52 studies were included. The flow chart of the screening and exclusion reasons were shown in Fig. 1. During the full-text assessments, specific reasons for exclusion were as follows: lack of matched control group (24 studies), lack of comparison of CM efficacy (20 studies), CM appearing in the control group (3 studies), and the retraction of the publication (1 study).

This study included 52 studies (12 (Guo *et al.*, 2020; Liu *et al.*, 2020b; Wang *et al.*, 2020c; Xiao *et al.*, 2020a; Xiong *et al.*, 2020; Zhang *et al.*, 2020b; Feng *et al.*, 2021; Hu *et al.*, 2021; Huang, 2021; Li *et al.*, 2021; Ni *et al.*, 2021; Xu *et al.*, 2021) and 40 published in English and Chinese, respectively, containing the details of 5,634 patients. A total of 3,389 patients received CM or CM adjunctive to RT in the treatment group, while 2,245 patients received RT in the control group. Thirty-six studies reported that both groups received interventions for 3 to 28 days, while the remaining 16 studies did not report such details. The sample sizes of the included studies ranged from 22 to 563.

Individualized CM formulae were administered in 15 studies (Jin *et al.*, 2020; Lian *et al.*, 2020; Liao, 2020; Liu, 2020; Pan *et al.*, 2020; Shi *et al.*, 2020a; Song, 2020; Wang *et al.*, 2020d; Yang *et al.*, 2020c; Zhang *et al.*, 2020b; Zhang *et al.*, 2020c;

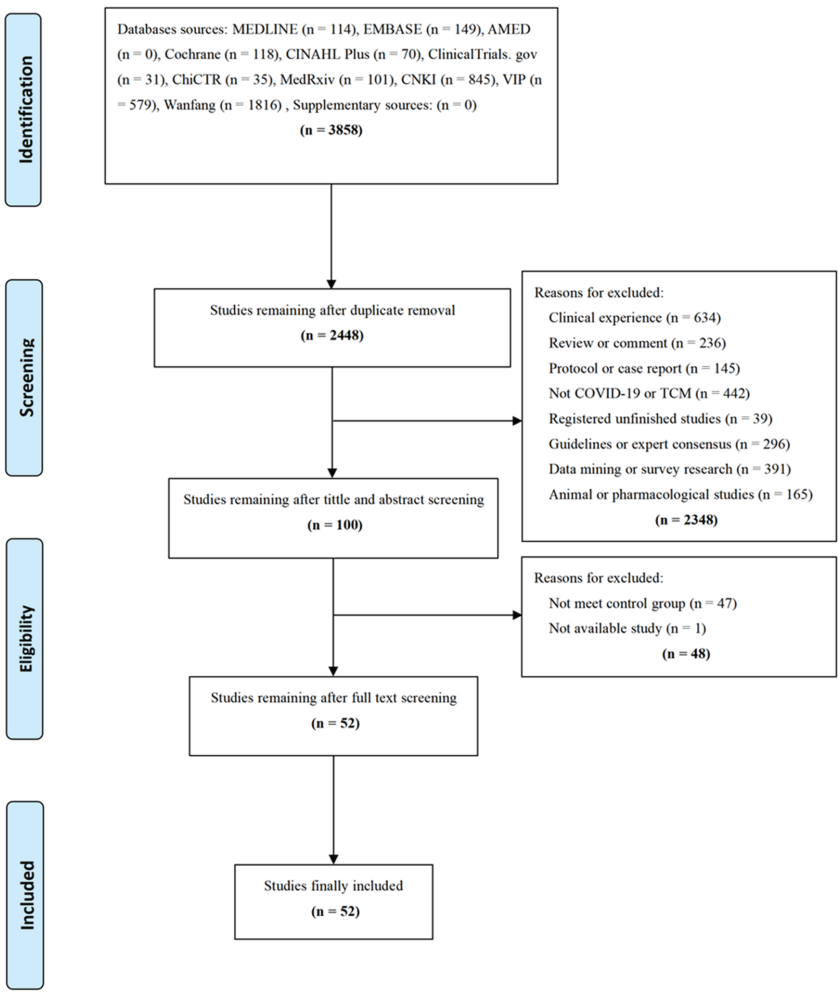

Figure 1. Flow chart for literature search (modified from PRISMA flow diagram).

Zheng *et al.*, 2020; Li *et al.*, 2021; Qin *et al.*, 2021; Zhou *et al.*, 2021b). Moreover, 37 studies used the CM formulae described in China's guidelines for COVID-19 and CM classic formulae, including Lianhua Qingwen granules (LHQW), Jinhua Qinggan granules (JHQG), Feiyan Yihao formula (FYYH), Reyanning granules (RYN), Reduning injection (RDN), Shenmai injection (SM), Buzhong Yiqi decoction (BZYQ), Shuanghuanglian oral liquids (SHL), Huashi Baidu decoction (HSBD), Keguan-1 formula (KG-1), Huoxiang Zhengqi granules (HXZQ), Xuanfei Baidu decoction (XFBD), Xiyanping injection (XYP), Xuebijing injection (XBJ), Shufeng Jiedu formula (SFJD), Qingfei Paidu decoction (QFPD), and Jinye Baidu formula (JYBD). The characteristics of the included studies were shown in Table S1.

Risk of Bias and Certainty of Evidence

The risk of bias of 21 RCTs (Ai *et al.*, 2020; Chen *et al.*, 2020a; Chen *et al.*, 2020c; Duan *et al.*, 2020; Jin *et al.*, 2020; Liao, 2020; Wang *et al.*, 2020c; Wang *et al.*, 2020d; Wen *et al.*, 2020; Xiao *et al.*, 2020a; Xiao *et al.*, 2020b; Xiong *et al.*, 2020; Yu *et al.*, 2020b; Zheng *et al.*, 2020; Chen *et al.*, 2021; He *et al.*, 2021; Hu *et al.*, 2021; Liu, 2021; Ni *et al.*, 2021; Wang *et al.*, 2021c; Xu *et al.*, 2021) was evaluated using the RoB 2.0 tool. Among them, four RCTs (Liao, 2020; Xiao *et al.*, 2020b; Zheng *et al.*, 2020; Liu, 2021) presented risk concerns regarding the randomization process because of unclear randomization methods. Almost all RCTs showed "low" risk regarding "deviations from intended intervention" except for one study that reported inconsistent intervention medicines (Xiao *et al.*, 2020b). Three RCTs (Chen *et al.*, 2020c; Liao, 2020; Zheng *et al.*, 2020) were ranked as having a "high" risk for failing to report essential items and were ranked as "high" risk in the overall bias.

The risk of bias of 31 retrospective nonrandomized studies (Chen *et al.*, 2020b; Cheng *et al.*, 2020; Guo *et al.*, 2020; Hu *et al.*, 2020; Huang *et al.*, 2020; Li *et al.*, 2020b; Lian *et al.*, 2020; Liu, 2020; Liu *et al.*, 2020b; Pan *et al.*, 2020; Qu *et al.*, 2020; Shi *et al.*, 2020a; Song, 2020; Wang *et al.*, 2020e; Yang *et al.*, 2020a; Yang *et al.*, 2020b; Yang *et al.*, 2020c; Yao *et al.*, 2020; Yu *et al.*, 2020a; Yu *et al.*, 2020c; Zeng *et al.*, 2020; Zhang *et al.*, 2020a; Zhang *et al.*, 2020b; Zhang *et al.*, 2020c; Feng *et al.*, 2021; Huang, 2021; Li *et al.*, 2021; Qin *et al.*, 2021; Wang *et al.*, 2021b; Zhang and Pan, 2021; Zhou *et al.*, 2021b) was assessed using the ROBINS-I tool. All these nonrandomized studies were ranked as having "serious" risk in terms of "selection of participants into the study" and "classification of interventions" items. Moreover, 11 nonrandomized studies (Li *et al.*, 2020b; Liu, 2020; Liu *et al.*, 2020b; Qu *et al.*, 2020; Yang *et al.*, 2020a; Yang *et al.*, 2020c; Yao *et al.*, 2020; Yu *et al.*, 2020a; Zhang *et al.*, 2020a; Zhang *et al.*, 2020b; Wang *et al.*, 2021b) missed essential data, and four nonrandomized studies (Yang *et al.*, 2020b; Zhang *et al.*, 2020c; Li *et al.*, 2021; Qin *et al.*, 2021) had confounding elements, which resulted in "serious" risks in terms of the overall bias. The certainty of the evidence for meta-analysis results was shown in Table 1.

Primary Outcomes

Clinical Efficacy

Ten studies (Ai *et al.*, 2020; Chen *et al.*, 2020a; Chen *et al.*, 2020b; Cheng *et al.*, 2020; Li *et al.*, 2020b; Xiao *et al.*, 2020b; Yu *et al.*, 2020b; Hu *et al.*, 2021; Wang *et al.*, 2021b; Wang *et al.*, 2021c) (Egger test: $p = 0{,}03$, revealed publication biases) reported the clinical efficacy rate involving four CM formulae. Subgroup analysis revealed that compared with the RT groups, the CM adjunctive to RT groups showed a significantly higher clinical efficacy rate (Fig. 2A): specifically, FYYH plus RT (RR = 1.07, 95% CI [1.00, 1.15], $p < 0.05$) with low heterogeneity (Q (1) = 0.15, $p = 0.70$, $I^2 = 0.01\%$; GRADE, moderate); LHQW plus RT (RR = 1.19, 95% CI [1.09, 1.31], $p < 0.05$) with low heterogeneity

Table 1. GRADE Summary

Outcomes	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Certainty of the Evidence (GRADE)
	Assumed Risk: Routine Treatment	Corresponding Risk: Chinese Medicine			
Clinical efficacy rate in Feiyan Yihao group	878 per 1000	940 per 1000 (878 to 1000)	RR 1.07 (1.00 to 1.15)	376 (2 studies)	⊕⊕⊕○ MODERATE
Clinical efficacy rate in Lianhua Qingwen group	716 per 1000	852 per 1000 (780 to 938)	RR 1.19 (1.09 to 1.31)	745 (4 studies)	⊕⊕⊕○ MODERATE
Clinical efficacy rate in Qingfei Paidu group	880 per 1000	959 per 1000 (739 to 922)	RR 1.09 (1.01 to 1.18)	200 (2 studies)	⊕⊕○○ LOW
Clinical efficacy rate in Shufeng Jiedu group	739 per 1000	887 per 1000 (791 to 997)	RR 1.20 (1.07 to 1.35)	268 (2 studies)	⊕⊕○○ LOW
Improvement rate of fever in Lianhua Qingwen group	597 per 1000	841 per 1000 (668 to 1000)	RR 1.41 (1.12 to 1.78)	126 (2 studies)	⊕⊕○○ LOW
Febrile time in Feiyan Yihao group	The mean anti-febrile time in the control groups was 3.35	The mean –0.02-fold lower (–0.23- 0.19-fold higher)	—	365 (2 studies)	⊕⊕⊕○ MODERATE
Febrile time in Lianhua Qingwen group	The mean anti-febrile time in the control groups was 3.30	The mean 2.67-fold lower (–1.57- 0.25-fold higher)	—	394 (3 studies)	⊕⊕○○ LOW
Febrile time in Qingfei Paidu group	The mean anti-febrile time in the control groups was 3.55	The mean 2.3-fold lower (–2.47- –0.07-fold higher)	—	100 (2 studies)	⊕⊕○○ LOW
Febrile time in Shufeng Jiedu group	The mean anti-febrile time in the control groups was 4.63	The mean 3.2-fold lower (–1.65- –0.32-fold higher)	—	307 (3 studies)	⊕⊕○○ LOW
Febrile score in Lianhua Qingwen group	The mean anti-febrile score in the control groups was –1.45	The mean –1.21-fold higher (–1.43- –0.99-fold higher)	—	365 (2 studies)	⊕⊕⊕○ MODERATE
Improvement rate of cough in Lianhua Qingwen group	505 per 1000	809 per 1000 (318 to 1000)	RR 1.60 (0.63 to 4.09)	175 (3 studies)	⊕⊕○○ LOW
Cough recovery time in Lianhua Qingwen group	The mean cough recovery time in the control groups was 6.43	The mean 4.63-fold lower (–2.89- –0.62-fold higher)	—	372 (3 studies)	⊕⊕○○ LOW

(*Continued*)

Table 1. (*Continued*)

Outcomes	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	No. of Participants (studies)	Certainty of the Evidence (GRADE)
	Assumed Risk: Routine Treatment	Corresponding Risk: Chinese Medicine			
Cough recovery time in Qingfei Paidu group	The mean cough recovery time in the control groups was 6.3	The mean 5-fold lower (–4.74- 1.04-fold higher)	—	100 (2 studies)	⊕⊕○○ LOW
Cough score in Lianhua Qingwen group	The mean cough score in the control groups was –1.6	The mean –2.85-fold lower (–3.83- –0.86-fold higher)	—	365 (2 studies)	⊕⊕○○ LOW
Improvement rate of fatigue in Lianhua Qingwen group	513 per 1000	656 per 1000 (441 to 974)	RR 1.28 (0.86 to 1.90)	153 (3 studies)	⊕⊕○○ LOW
Fatigue recovery time in Lianhua Qingwen group	The mean cough score in the control groups was 5.4	The mean 3.6-fold lower (–2.03- –0.58-fold higher)	—	366 (3 studies)	⊕⊕○○ LOW
Improvement rate of dyspnea in Lianhua Qingwen group	105 per 1000	526 per 1000 (158 to 1000)	RR 5.00 (1.50 to 16.74)	41 (2 studies)	⊕⊕○○ LOW
Improvement rate of appetite in Lianhua Qingwen group	105 per 1000	531 per 1000 (158 to 1000)	RR 5.04 (1.12 to 22.73)	57 (2 studies)	⊕⊕○○ LOW
Improvement rate of chest tightness in Lianhua Qingwen group	179 per 1000	598 per 1000 (250 to 1000)	RR 3.35 (1.40 to 8.01)	46 (2 studies)	⊕⊕○○ LOW
Improvement rate of expectoration in Lianhua Qingwen group	133 per 1000	556 per 1000 (212 to 1000)	RR 4.17 (1.59 to 10.89)	64 (2 studies)	⊕⊕○○ LOW
Improvement rate of muscle pain in Lianhua Qingwen group	222 per 1000	647 per 1000 (212 to 1000)	RR 2.91 (1.14 to 7.38)	33 (2 studies)	⊕⊕○○ LOW
Improvement rate of nausea in Lianhua Qingwen group	500 per 1000	520 per 1000 (215 to 1000)	RR 1.04 (0.43 to 2.53)	19 (2 studies)	⊕⊕○○ LOW
Rate of negative nucleic acid test in Xuebijing 50 ml group	690 per 1000	649 per 1000 (490 to 856)	RR 0.94 (0.71 to 1.24)	84 (2 studies)	⊕⊕○○ LOW

Time of negative nucleic acid test in Feiyan Yihao group	The mean time negative nucleic acid test in the control groups was 11.05	The mean 7.85-fold lower (–0.94- –0.51-fold higher)	—	365 (2 studies)	⊕⊕⊕○ MODERATE
Time of negative nucleic acid test in Lianhua Qingwen group	The mean time of negative nucleic acid test in the control groups was 17.35	The mean 16.6-fold lower (–0.74- 0.02-fold higher)	—	335 (2 studies)	⊕⊕○○ LOW
CRP in Lianhua Qingwen group	The mean CRP in the control groups was –5.25	The mean -9-fold lower (–3.40- 0.65-fold higher)	—	352 (2 studies)	⊕⊕○○ LOW
CRP in Qingfei Paidu group	The mean CRP in the control groups was –36.1	The mean –31.95-fold lower (–0.45- 0.29-fold higher)	—	113 (2 studies)	⊕⊕○○ LOW
CRP in Xuebijing 100 ml group	The mean CRP in the control groups was –13.15	The mean –36.3-fold lower (–2.98- –1.36-fold higher)	—	70 (2 studies)	⊕⊕○○ LOW
CRP in Xuebijing 50 ml group	The mean CRP in the control groups was –3.4	The mean –10.3-fold lower (–1.99- 0.12-fold higher)	—	84 (2 studies)	⊕⊕○○ LOW
WBC in Qingfei Paidu group	The mean WBC in the control groups was 1	The mean 1.7-fold higher (–0.19- 1.07-fold higher)	—	64 (2 studies)	⊕⊕○○ LOW
WBC in Shufeng Jiedu group	The mean WBC in the control groups was 0.95	The mean 1.4-fold higher (–0.33- 0.94-fold higher)	—	268 (2 studies)	⊕⊕○○ LOW
WBC in Xuebijing 100 ml group	The mean WBC in the control groups was 0.9	The mean 2.3-fold higher (–0.56- 3.52-fold higher)	—	72 (2 studies)	⊕⊕○○ LOW
WBC in Xuebijing 50 ml group	The mean WBC in the control groups was 0.95	The mean 1.45-fold higher (0.01- 0.88-fold higher)	—	84 (2 studies)	⊕⊕○○ LOW
Neutrophil in Qingfei Paidu group	The mean NEUT in the control groups was 4	The mean 3.7-fold higher (–1.13- 0.62-fold higher)	—	113 (2 studies)	⊕⊕○○ LOW
Lymphocyte counts in Feiyan Yihao group	The mean LYMPH# in the control groups was 0.1	The mean 0.25-fold higher (0.09- 0.58-fold higher)	—	376 (2 studies)	⊕⊕⊕○ MODERATE

(*Continued*)

Table 1. (*Continued*)

Outcomes	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	No. of Participants (studies)	Certainty of the Evidence (GRADE)
	Assumed Risk: Routine Treatment	Corresponding Risk: Chinese Medicine			
Lymphocyte proportion in Qingfei Paidu group	The mean LYMPH% in the control groups was 3.6	The mean 5.3-fold higher (0.02- 0.79-fold higher)	—	129 (2 studies)	⊕⊕○○ LOW
CT scan in Lianhua Qingwen group	611 per 1000	752 per 1000 (672 to 844)	RR 1.23 (1.10 to 1.38)	745 (4 studies)	⊕⊕⊕○ MODERATE
CT scan in Qingfei Paidu group	701 per 1000	883 per 1000 (778 to 1000)	RR 1.26 (1.11 to 1.43)	253 (2 studies)	⊕⊕○○ LOW
Length of hospital stay in Qingfei Paidu group	The mean length of hospital stay in the control groups was 19.75	The mean 15.8-fold lower (–2.18- –1.48-fold higher)	—	369 (2 studies)	⊕⊕⊕○ MODERATE
Adverse events incidence in Lianhua Qingwen group	506 per 1000	440 per 1000 (349 to 546)	RR 0.87 (0.69 to 1.08)	335 (2 studies)	⊕⊕○○ LOW

Notes: LOW (Low certainty): Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; MODERATE (Moderate certainty): We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

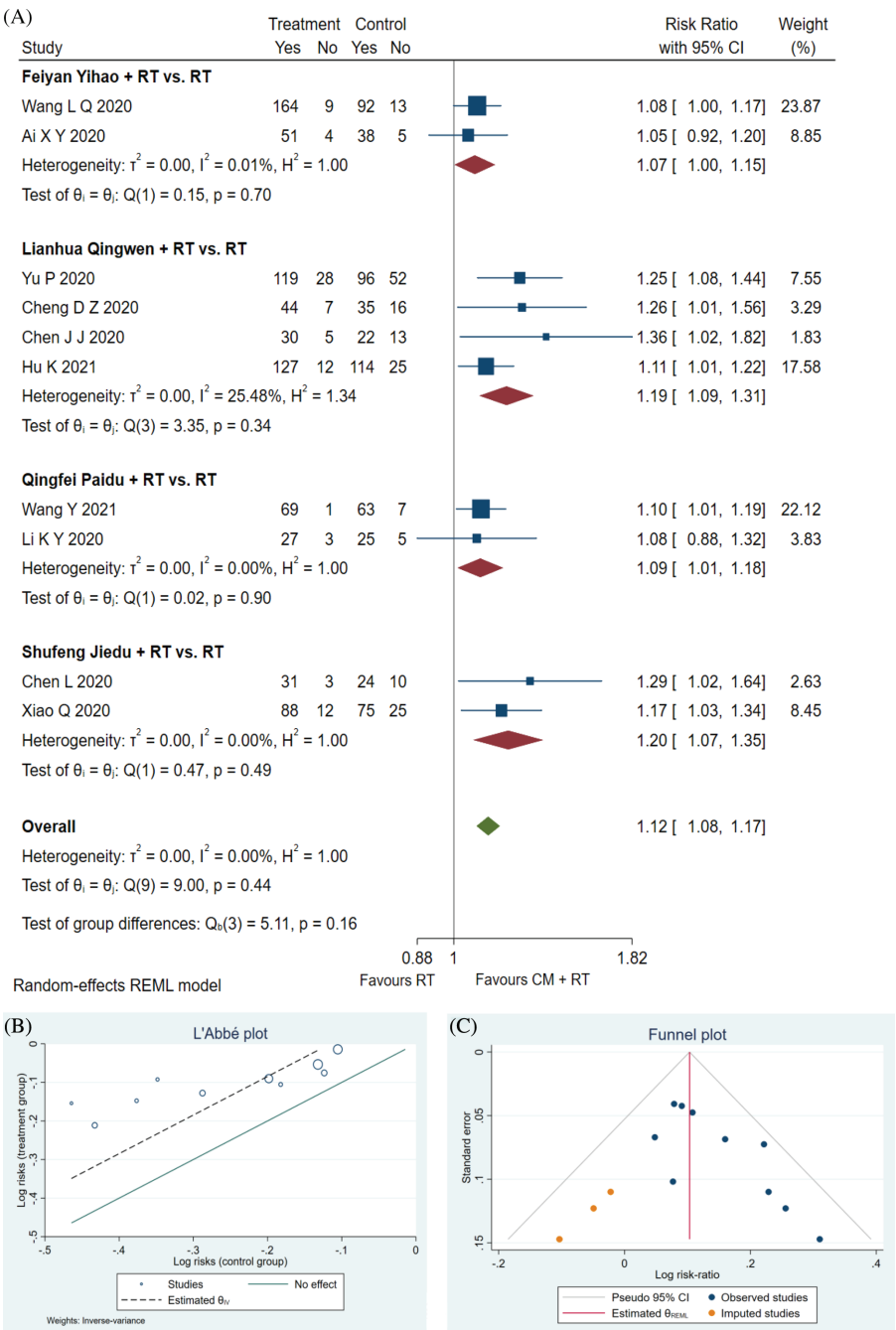

Figure 2. Clinical efficacy rate. (A) Forest plot of subgroup analysis on the clinical efficacy rate. (B) L'Abbe and (C) funnel plots of the clinical effectiveness rate. RT, routine treatment.

(Q (3) = 3.35, $p = 0.34$, $I^2 = 25.48\%$; GRADE, moderate); QFPD plus RT (RR = 1.09, 95% CI [1.01, 1.18], $p < 0.05$) without heterogeneity (Q (1) = 0.02, $p = 0.90$, $I^2 = 0$; GRADE, low); and SFJD plus RT (RR = 1.20, 95% CI [1.07, 1.35], $p < 0.05$) without heterogeneity (Q (1) = 0.47, $p = 0.49$, $I^2 = 0$; GRADE, low) (Figs. 2B–2C).

Febrile Time, Score and Level

Ten studies (Chen *et al.*, 2020b; Cheng *et al.*, 2020; Li *et al.*, 2020b; Qu *et al.*, 2020; Wang *et al.*, 2020e; Xiao *et al.*, 2020b; Yang *et al.*, 2020a; Chen *et al.*, 2021; Hu *et al.*, 2021; Wang *et al.*, 2021b) reported the febrile time with four CM formulae; namely, FYYH, LHQW, QFPD, and SFJD.

Subgroup analysis revealed that compared with RT alone, both the FYYH plus RT (SMD = –0.02, 95% CI [–0.23, 0.19], $p > 0.05$; Q (1) = 0.07, $p = 0.79$, $I^2 = 0$; GRADE, moderate) and LHQW plus RT (SMD = –0.66, 95% CI [–1.57, 0.25], $p > 0.05$; Q (2) = 31.11, $p < 0.01$, $I^2 = 92.66\%$; GRADE, low) did not significantly shorten the febrile time. Compared with RT, QFPD (SMD = –1.27, 95% CI [–2.47, –0.07], $p < 0.05$; Q (1) = 7.42, $p = 0.01$, $I^2 = 86.54\%$; GRADE, low) and SFJD (SMD = –0.99, 95% CI [–1.65, –0.32], $p < 0.05$; Q (1) = 11.86, $p < 0.01$, $I^2 = 81.99\%$; GRADE, low) adjunctive to RT significantly shortened the febrile time (Fig. 3A). Sensitivity analysis revealed that all pooled studies contributed to heterogeneity, and no study could be removed.

Two studies (Chen *et al.*, 2020a; Yu *et al.*, 2020b) indicated a significant improvement in the febrile score of LHQW plus RT compared with RT without significant heterogeneity (SMD = –1.21, 95% CI [–1.43, –0.99], $p < 0.05$; Q (1) = 0.47, $p = 0.49$, $I^2 = 0$; GRADE, moderate) (Fig. 3B).

Three studies (Cheng *et al.*, 2020; Xiao *et al.*, 2020a; Yao *et al.*, 2020) reported that LHQW plus RT lowered fever; however, there was high among-study heterogeneity ($I^2 = 69.78\%$). Sensitivity analysis revealed the time point of one study (Xiao *et al.*, 2020a). After removing the study, LHQW plus RT (RR = 1.41, 95% CI [1.12, 1.78], $p < 0.05$) significantly lowered fever without heterogeneity between the remaining studies (Q (1) = 0.12, $p = 0.73$, $I^2 = 0$; GRADE, low) (Table 2).

Secondary Outcomes

CT Scan Image

Six studies (Chen *et al.*, 2020a; Cheng *et al.*, 2020; Yu *et al.*, 2020b; Zeng *et al.*, 2020; Hu *et al.*, 2021; Zhang and Pan, 2021) reported improvements in CT scans. Subgroup analysis of the improvement rate in CT scans revealed that compared with RT, LHQW plus RT (RR = 1.23, 95% CI [1.10, 1.38], $p < 0.05$; GRADE, moderate) and QFPD plus RT (RR = 1.26, 95% CI [1.11, 1.43], $p < 0.05$; GRADE, low) significantly improved the lung images, with low (Q (3) = 2.74, $p = 0.43$, $I^2 = 17.43\%$) and no heterogeneity (Q (1) = 0.21, $p = 0.65$, $I^2 = 0$), respectively (Fig. 4).

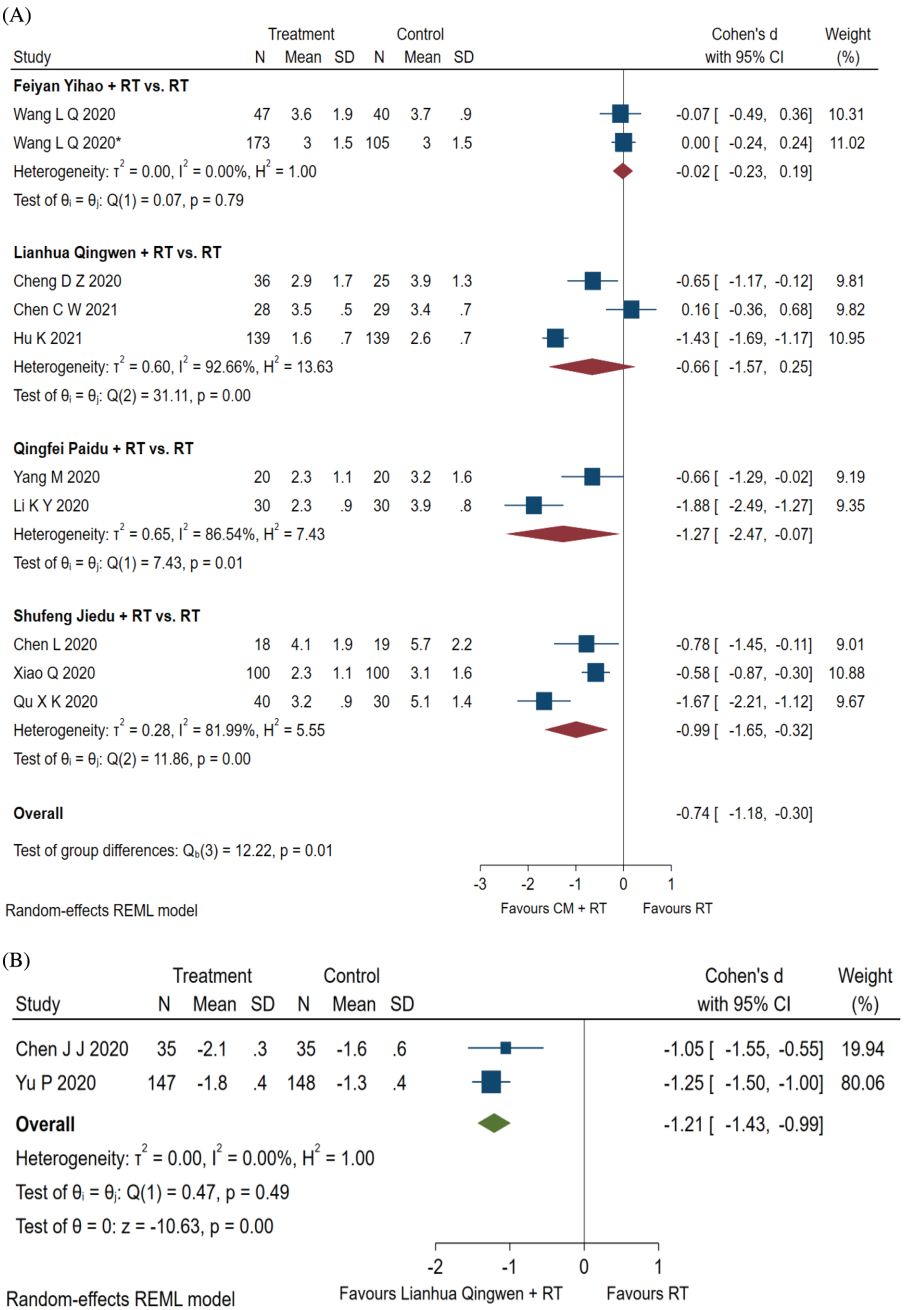

Figure 3. Improvement in fever. (A) Febrile time. (B) Febrile score. RT, routine treatment.

Table 2. Other Outcomes

Outcome Indicator	CM Formula	Pooled Studies	Pooled Sample Size (T/C)	I^2	RR with 95% CI
Improvement rate of fever	LHQW	Cheng D Z; Yao K T	126 (64/52)	0	1.41 [1.12, 1.78]
Cough recovery time	LHQW	Chen C W; Chen D Z; Hu K	372 (190/182)	92.13%	–1.75 [–2.89, –0.62]
	QFPD	Yang M; Li K Y	100 (50/50)	97.00%	–1.85 [–4.74, 1.04]
Cough score	LHQW	Chen J J; Yu P	365 (182/183)	95.47%	–2.35 [–3.83, –0.86]
Improvement rate of cough	LHQW	Xiao M Z; Cheng D Z; Yao K T	175 (84/91)	87.83%	1.60 [0.63, 4.09]
Improvement rate of fatigue	LHQW	Xiao M Z; Yao K T; Cheng D Z	153 (75/78)	44.54%	1.28 [0.86, 1.90]
Fatigue recovery time	LHQW	Cheng D Z; Chen C W; Hu K	366 (186/180)	81.62%	–1.31 [–2.03, –0.58]
Chest tightness	LHQW	Cheng D Z; Yao K T	46 (18/28)	0	3.35 [1.40, 8.01]
Dyspnea	LHQW	Cheng D Z; Yao K T	41 (22/19)	0	5.00 [1.50, 16.74]
Expectoration	LHQW	Cheng D Z; Yao K T	64 (34/30)	0	4.17 [1.59, 10.89]
Muscle pain	LHQW	Cheng D Z; Yao K T	33 (15/18)	0	2.91 [1.14, 7.38]
Appetite	LHQW	Cheng D Z; Yao K T	57 (19/38)	60.26%	5.04 [1.12, 22.73]
Nausea	LHQW	Cheng D Z; Yao K T	19 (11/8)	0	1.04 [0.43, 2.53]
Rate of negative PCR test	XBJ 50 ml	Wen L; Zhang C Y	84 (42/42)	0	0.94 [0.71, 1.24]
Time to negative PCR test	FYYH	Wang L Q; Wang L Q*	365 (220/145)	0	–0.72 [–0.94, –0.51]
	LHQW	Chen C W; Hu K	335 (167/168)	49.17%	–0.36 [–0.74, 0.02]
C-reactive protein	LHQW	Chen C W; Yu P	352 (175/177)	96.81%	–1.38 [–3.40, 0.65]
	QFPD	Yu X Y; Zhang P	113 (55/58)	0	–0.08 [–0.45, 0.29]
	XBJ 100 ml	Wen L; Chen L Z	70 (35/35)	46.23%	–2.17 [–2.98, –1.36]
	XBJ 50 ml	Wen L; Zhang C Y	84 (42/42)	81.05%	–0.93 [–1.99, 0.12]
White blood cell count	QFPD	Yang M; Zhang P	64 (32/32)	35.25%	0.44 [–0.19, 1.07]
	SFJD	Chen L; Xiao Q	268 (134/134)	81.05%	0.30 [–0.33, 0.94]
	XBJ 100 ml	Guo H; Wen L	72 (36/36)	92.89%	1.48 [–0.56, 3.52]
	XBJ 50 ml	Wen L; Zhang C Y	84 (42/42)	0	0.44 [0.01, 0.88]
Neutrophils	QFPD	Yu X Y; Zhang P	113 (55/58)	73.42%	–0.26 [–1.13, 0.62]
Lymphocyte#	FYYH	Ai X Y; Wang L Q	376 (228/148)	21.81%	0.34 [0.09, 0.58]
Lymphocyte%	QFPD	Yang M; Yu X Y	129 (63/66)	13.54%	0.41 [0.02, 0.79]
Adverse events incidence	LHQW	Hu K; Chen C W	335 (167/168)	0	0.87 [0.69, 1.08]

Notes: CM: Chinese medicine; LHQW: Lianhua Qingwen; QFPD: Qingfei Paidu decoction; XBJ: Xuebijing injection; T: Treatment group; C: Control group; RR: Relative risk; CI: confidence interval.

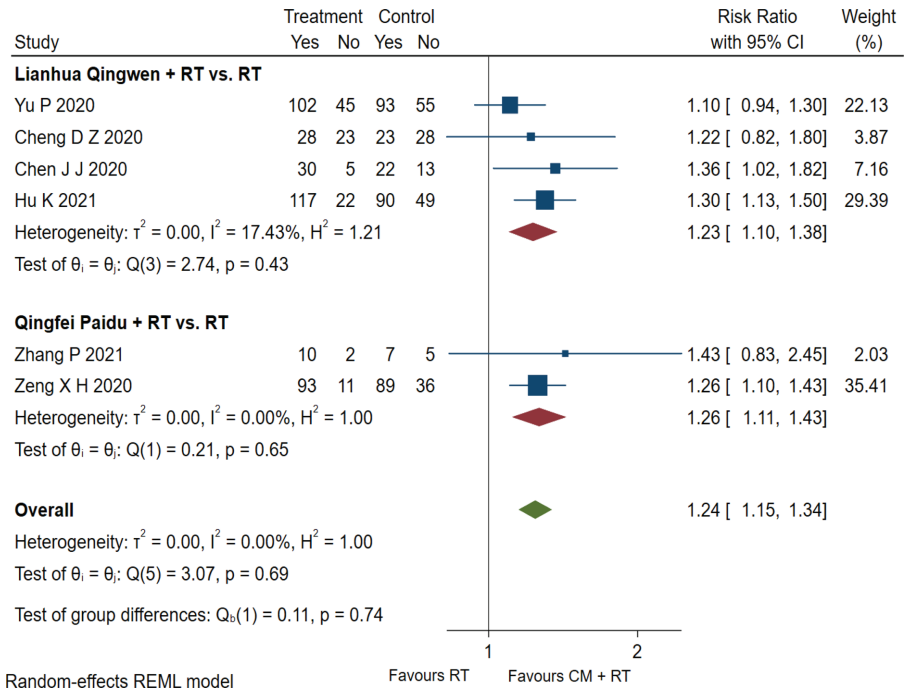

Figure 4. Chest improvement in CT scan image.

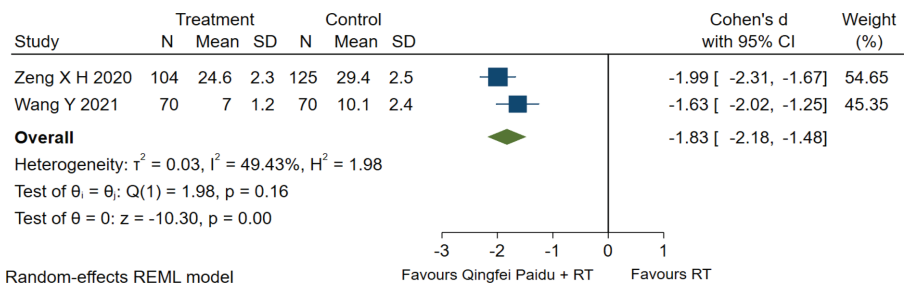

Figure 5. Length of hospital stay in patients receiving QFPD and RT or RT alone. QFPD, Qing Fei Pai Du decoction; RT, routine treatment.

Length of Hospital Stay

Three studies (Li *et al.*, 2020b; Zeng *et al.*, 2020; Wang *et al.*, 2021c) reported the length of hospital stay, with high among-study heterogeneity (Q (2) = 62.98, $p < 0.01$, $I^2 = 99.50\%$). One study (Li *et al.*, 2020) lacking measurement criteria was removed through sensitivity analysis. Compared with RT, QFPD plus RT significantly shortened hospital stay (SMD = –1.83, 95% CI [–2.18, –1.48], $p < 0.01$; Q (1) = 1.98, $p = 0.16$, $I^2 = 49.43\%$; GRADE, moderate) with moderate heterogeneity (Fig. 5).

Mortality

Seven studies (Hu *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020c; Yang *et al.*, 2020c; Qin *et al.*, 2021; Wang *et al.*, 2021b; Zhang and Pan, 2021) reported lower mortality in patients treated with CM plus RT than in those treated with RT alone. Among them, three studies (Hu *et al.*, 2020; Wang *et al.*, 2020c; Zhang and Pan, 2021) indicated that KG-1 and QFPD led to zero deaths compared with four deaths in the RT group.

Minor Outcomes

Cough Recovery Time, Score and Improvement Rate

Five studies (Cheng *et al.*, 2020; Li *et al.*, 2020b; Yang *et al.*, 2020a; Chen *et al.*, 2021; Hu *et al.*, 2021) reported that the time of cough recovery in LHQW plus RT was significantly shorter than that in RT (SMD = –1.75, 95% CI [–2.89, –0.62], $p < 0.05$; GRADE, low) with significant among-study heterogeneity (Q (2) = 17.15, $p < 0.01$, $I^2 = 92.13\%$). Compared with RT, QFPD plus RT did not significantly shorten the recovery time (SMD = –1.85, 95% CI [–4.74, 1.04], $p > 0.05$; GRADE, low) with significant heterogeneity (Q (1) = 33.35, $p < 0.01$, $I^2 = 97.00\%$) (Table 2). Inconsistent evaluation methods led to high heterogeneity in both groups.

Two studies (Chen *et al.*, 2020a; Yu *et al.*, 2020b) reported a significant improvement in the cough score of LHQW plus RT compared with RT (SMD = –2.35, 95% CI [–3.83, –0.86], $p < 0.01$; GRADE, low) with significant between-study heterogeneity (Q (1) = 22.09, $p < 0.01$, $I^2 = 95.47\%$) (Table 2). This heterogeneity might be attributed to the different scoring criteria.

Three studies (Cheng *et al.*, 2020; Xiao *et al.*, 2020a; Yao *et al.*, 2020) reported the cough improvement rate. Pooled analysis revealed that LHQW plus RT were not superior to RT alone (RR = 1.60, 95% CI [0.63, 4.09], $p > 0.05$; GRADE, low); moreover, these studies showed significant heterogeneity (Q (2) = 11.28, $p < 0.01$, $I^2 = 87.83\%$). Sensitivity analysis suggested different evaluation criteria in the three studies; therefore, the removal method could not be applied (Table 2).

Fatigue Recovery Time and Improvement Rate

Three studies (Cheng *et al.*, 2020; Xiao *et al.*, 2020a; Yao *et al.*, 2020) reported the fatigue improvement rates. Three studies (Cheng *et al.*, 2020; Chen *et al.*, 2021; Hu *et al.*, 2021) reported the fatigue recovery time, which had moderate (Q (2) = 3.21, $p = 0.20$, $I^2 = 44.54\%$) and high heterogeneity (Q (2) = 9.88, $p = 0.01$, $I^2 = 81.62\%$). Sensitivity analysis revealed that the difference in criteria for evaluating the weakness improvement led to high heterogeneity.

Pooled analysis showed that compared with RT, LHQW plus RT did not significantly improve the rate of fatigue (SMD = 1.28, 95% CI [0.86, 1.90], $p = 0.22$; GRADE, low);

however, it had a significantly shorter fatigue recovery time (SMD = –1.31, 95% CI [–2.03, –0.58], $p = 0.01$; GRADE, low) (Table 2).

Other Clinical Symptoms

Two studies (Cheng *et al.*, 2020; Yao *et al.*, 2020) reported the effect of LHQW on other clinical symptoms. The meta-analysis showed that compared with RT, LHQW plus RT significantly improved dyspnea, appetite, chest tightness, expectoration, and muscle pain, but not nausea (overall RR = 3.10, 95% CI [2.03, 4.74], $p < 0.05$; Q (11) = 12.23, $p = 0.35$, $I^2 = 15.37\%$; each GRADE, low) (Table 2).

Laboratory Findings

Covid-19 PCR Test

Two trials (Wen *et al.*, 2020; Zhang *et al.*, 2020a) reported the rate of Covid-19 Polymerase Chain Reaction (PCR) negative conversion for XBJ (50 ml per pax, bid) (Q (1) = 0.41, $p = 0.52$, $I^2 = 0$). Four studies (Wang *et al.*, 2020e; Chen *et al.*, 2021; Hu *et al.*, 2021; Wang *et al.*, 2021b) reported the time to negative PCR tests for patients receiving the FYYH (Q (1) = 0.24, $p = 0.63$, $I^2 = 0$) and LHQW (Q (1) = 1.97, $p = 0.16$, $I^2 = 49.17\%$). Pooled analysis revealed no significant difference between XBJ (50 ml/pax, bid) plus RT and RT (RR = 0.94, 95% CI [0.71, 1.24], $p = 0.66$; GRADE, low) (Table 2). Compared with RT alone, FYYH plus RT (RR = –0.72, 95% CI [–0.94, –0.51], $p < 0.05$; GRADE, moderate), but not LHQW plus RT (RR = –0.36, 95% CI [–0.74, 0.02], $p > 0.05$; GRADE, low), had a shorter time to negative nucleic acid (Table 2).

C-Reactive Protein

Nine studies (Chen *et al.*, 2020c; Guo *et al.*, 2020; Wen *et al.*, 2020; Yu *et al.*, 2020b; Yu *et al.*, 2020c; Zhang *et al.*, 2020a; Chen *et al.*, 2021; Wang *et al.*, 2021c; Zhang and Pan, 2021) reported the C-reactive protein (CRP) levels. There was high among-study heterogeneity, including LHQW ($I^2 = 96.81\%$), QFPD ($I^2 = 80.29\%$), XBJ (100 ml/pax, bid) ($I^2 = 85.08\%$), and XBJ (50 ml/pax, bid) ($I^2 = 81.05\%$). Sensitivity analysis revealed that the heterogeneity of one study (Guo *et al.*, 2020) and another study (Wang *et al.*, 2021c) attributed to the disease severity and unreliable results, respectively.

After removing both studies, subgroup analysis showed the CRP levels in LHQW plus RT were not significantly higher than those in RT (SMD = –1.38, 95% CI [–3.40, 0.65], $p > 0.05$), QFPD plus RT (SMD = –0.08, 95% CI [–0.45, 0.29], $p > 0.05$; Q (1) = 0.58, $p = 0.45$, $I^2 = 0$), and XBJ 50 ml plus RT (SMD = –0.93, 95% CI [–1.99, 0.12], $p > 0.05$). However, pooled analysis revealed that XBJ 100 ml plus RT led to significantly lower CRP levels compared with RT (SMD = –2.17, 95% CI [–2.98, –1.36], $p < 0.05$; Q (1) = 1.86, $p = 0.17$, $I^2 = 46.23\%$) (Table 2). The GRADE evidence levels were low for the above CM formulae.

White Blood Cells

The white blood cell (WBC) levels were reported in seven studies (Chen *et al.*, 2020b; Guo *et al.*, 2020; Wen *et al.*, 2020; Xiao *et al.*, 2020b; Yang *et al.*, 2020a; Zhang *et al.*, 2020a; Zhang and Pan, 2021) which assessed four CM formulae; namely, QFPD, SFJD, XBJ injection. Subgroup analysis revealed that compared with RT, XBJ 50 ml plus RT significantly increased the WBC (SMD = 0.44, 95% CI [0.01, 0.88], $p < 0.05$; Q (1) = 0.04, $p = 0.85$, $I^2 = 0$). However, there was a certain degree of among-subgroup heterogeneity due to differences in treatment duration. Compared with RT (each GRADE, low), QFPD plus RT (SMD = 0.44, 95% CI [–0.19, 1.07], $p > 0.05$; Q (1) = 1.54, $p = 0.21$, $I^2 = 35.25\%$), SFJD plus RT (SMD = 0.30, 95% CI [–0.33, 0.94], $p > 0.05$; Q (1) = 5.28, $p = 0.02$, $I^2 = 81.05\%$), and XBJ 100 ml plus RT (SMD = 1.48, 95% CI [–0.56, 3.52], $p > 0.05$; Q (1) = 14.07, $p < 0.01$, $I^2 = 92.89\%$) did not significantly increase WBC levels (Table 2).

Neutrophil and Lymphocytes

Two studies (Yu *et al.*, 2020c; Zhang and Pan, 2021) reported significantly increased neutrophil counts in QFPD plus RT than those in RT (SMD = –0.26, 95% CI [–1.13, 0.62], $p = 0.56$; GRADE, low). The different times assessed resulted in high heterogeneity (Q (1) = 3.76, $p = 0.05$, $I^2 = 73.42\%$) (Table 2).

Four studies reported the absolute number and proportion of lymphocytes (Ai *et al.*, 2020; Yang *et al.*, 2020a; Yu *et al.*, 2020c; Wang *et al.*, 2021b) including those in the FYYH (Q (1) = 1.28, $p = 0.26$, $I^2 = 21.81\%$) and QFPD (Q (1) = 1.16, $p = 0.28$, $I^2 = 13.54\%$). Subgroup analysis revealed a significantly higher lymphocyte count in the FYYH plus RT than in RT alone (SMD = 0.34, 95% CI [0.09, 0.58], $p < 0.05$; GRADE, moderate). Moreover, the proportion of lymphocytes in QFPD plus RT was significantly higher than in RT (SMD = 0.41, 95% CI [0.02, 0.79], $p < 0.05$; GRADE, low) (Table 2).

Adverse Events

Adverse events were reported in 24 studies (Ai *et al.*, 2020; Chen *et al.*, 2020c; Duan *et al.*, 2020; Li *et al*., 2020b; Lian *et al.*, 2020; Liao, 2020; Liu, 2020; Liu *et al.*, 2020b; Song, 2020; Wang *et al.*, 2020c; Wang *et al.*, 2020d; Xiao *et al.*, 2020b; Xiong *et al.*, 2020; Yang *et al.*, 2020b; Yang *et al.*, 2020c; Yu *et al.*, 2020b; Zhang *et al.*, 2020a; Zhang *et al.*, 2020b; Chen *et al.*, 2021; Hu *et al.*, 2021; Huang, 2021; Qin *et al.*, 2021; Wang *et al.*, 2021b; Wang *et al.*, 2021c). Among them, two studies (Tan *et al.*, 2020; Xiao *et al.*, 2020b) on LHQW (Q (1) = 0.58, $p = 0.20$, $I^2 = 0$) could be pooled for meta-analysis. Compared with RT alone, the LHQW plus RT had no significant adverse events (RR = 0.87, 95% CI [0.69, 1.08], $p = 0.20$; GRADE, low) (Table 2). Specifically, nine studies (Ai *et al.*, 2020; Liu, 2020; Liu *et al.*, 2020b; Song, 2020; Xiong *et al.*, 2020; Yang *et al.*, 2020b; Yu *et al.*, 2020b; Zhang *et al.*, 2020b; Wang *et al.*, 2021b) reported that none of the patients experienced treatment-induced discomfort.

Fifteen studies (Chen *et al.*, 2020c; Duan *et al.*, 2020; Li *et al*., 2020b; Lian *et al.*, 2020; Liao, 2020; Wang *et al.*, 2020c; Wang *et al.*, 2020d; Xiao *et al.*, 2020b; Yang *et al.*, 2020c; Zhang *et al.*, 2020a; Chen *et al.*, 2021; Hu *et al.*, 2021; Huang, 2021; Qin *et al.*, 2021; Wang *et al.*, 2021c) reported that patients experienced different degrees of adverse events. Among them, five studies (Wang *et al.*, 2020c; Xiao *et al.*, 2020b; Chen *et al.*, 2021; Hu *et al.*, 2021; Qin *et al.*, 2021) reported that patients suffered from diarrhea in both the treatment and control groups. One study (Duan *et al.*, 2020) reported that 27 patients experienced diarrhea in the JHQG plus RT group; among them, eight patients with moderate diarrhea resulted in cessation of treatment. Nausea was reported in both groups of five studies (Li *et al*., 2020b; Wang *et al.*, 2020c; Chen *et al.*, 2021; Hu *et al.*, 2021; Wang *et al.*, 2021c). Furthermore, two studies reported minor levels of dizziness and fatigue (Chen *et al.*, 2021; Wang *et al.*, 2021c). Laboratory findings revealed abnormal liver function in both groups of four studies (Lian *et al.*, 2020; Chen *et al.*, 2021; Hu *et al.*, 2021; Huang, 2021), without a significant between-group difference.

Recommendations

The national guidelines for COVID-19 diagnosis and treatment by China's National Health Commission, recommend the use of CM according to disease phases (mild, ordinary, severe, and critical) and symptom differentiation of patients. In line with the guidelines and symptom differentiation, recommendations of CM formulae were made for four phases of COVID-19 (Table 3).

Discussion

Previous systematic reviews (Liu *et al.*, 2020a; Sun *et al.*, 2020) have shown that CM has an advantage in COVID-19 treatment. Oral CM combined with RT improved overall efficacy and did not increase adverse events. As an adjunctive treatment, one review

Table 3. Recommendations of Included CM Formulae for Different Forms in COVID-19 Patients

Recommendation Grade	Mild	Ordinary	Severe	Critical
Moderate evidence	FYYH, LHQW, QFPD	FYYH, LHQW, QFPD	FYYH, QFPD	QFPD
Low evidence	SFJD	SFJD	XBJ	XBJ
No evidence	JHQG, BZYQ, SHL, HSBD, KG-1, HXZQ, XFBD, JYBD	JHQG, RYN, SHL, HSBD, KG-1, HXZQ, XFBD, JYBD	RDN, HSBD, XYP	RDN, SM

Notes: LHQW: Lianhua Qingwen; JHQG: Jinhua Qinggan granules; FYYH: Feiyan Yihao formula; RYN: Reyanning granules; RDN: Reduning injection; BZYQ: Buzhong Yiqi decoction; SHL: Shuanghuanglian oral liquids; HSBD: Huashi Baidu decoction; KG-1: Keguan-1 formula; HXZQ: Huoxiang Zhengqi granules; XFBD: Xuanfei Baidu decoction; XYP: Xiyanping injection; XBJ: Xuebijing injection; SFJD: Shufeng Jiedu formula; QFPD: Qingfei Paidu decoction; JYBD: Jinye Baidu formula; SM: Shenmai injection

(Zhou *et al.*, 2021a) showed that CM can improve the main symptoms and reduce the progression of the disease. However, pooled analysis of different formulae did not prove which was more effective. Our systematic review included several newly published RCTs (Duan *et al.*, 2020; Jin *et al.*, 2020; Xiao *et al.*, 2020a; Hu *et al.*, 2021; Ni *et al.*, 2021; Wang *et al.*, 2021c; Xu *et al.*, 2021) with better design quality. Moreover, we employed more appropriate tools, including ROB 2.0 and ROBINS-I, to assess RCTs and retrospective nonrandomized studies, respectively. As for the extraction of continuous variables, we took the method of extracting the difference value that increased the evaluability of the results. Additionally, we included CM injections and performed subgroup analysis according to different CM types. Based on the results of each meta-analysis, we graded the evidence based on the recommended levels, which also provided more reference information for clinical practice and further studies.

Among the candidate CMs, we found that the adjunctive effects of the FYYH, LHQW, QFPD, and SFJD were significantly higher than those of RT alone in overall clinical efficacy.

(1) LHQW plus RT significantly improved febrile score, fever level and symptoms of dyspnea, appetite, chest tightness, expectoration, and muscle pain in addition to CT Scan outcome. Although it significantly improved the cough score and fatigue recovery time, high heterogeneity among the pooled studies decreased the evidence level.
(2) Compared with RT alone, the FYYH adjunctive to RT shortens the febrile duration, the time to the negative PCR test (0.72 d), and increased lymphocytes with a moderate evidence level. Lymphopenia, common in patients with COVID-19, is negatively associated with disease severity (Tan *et al.*, 2020; Wang *et al.*, 2020b).
(3) The QFPD plus RT was associated with lower CRP level, improved lymphocyte indices and CT images, significantly shortened the hospital stay, and may reduce mortality (zero vs. four deaths). In two previous large-scale studies, QFPD was observed to accelerate recovery, viral shedding and length of hospital stay during early treatment (Shi *et al.*, 2020b), and reduce mortality (Zhang *et al.*, 2021), which was consistent with our findings.
(4) Regarding the pooled analysis of CM injection, the XBJ adjunctive to RT was significantly associated with lower CRP, but the increases in WBC were complicated by the heterogeneity of differences in treatment duration.

In China's national guidelines for the diagnosis and treatment for COVID-19, there are five disease phases, mild, ordinary, severe, critical, and convalescent. The moderate evidence supports the use of LHQW for patients at the mild and ordinary phases, FYYH for patients at mild to severe phrases, and QFPD for patients at mild to critical phases according to the syndrome differentiation. There is low evidence supporting the use of SFJD at mild to ordinary phase, and XBJ at severe and critical phases. Currently, few studies are conducted to evaluate the effects of CM for patients under COVID-19 rehabilitation (convalescent phase). A few study protocols have been published recently (Gao *et al.*, 2021; Zhong *et al.*, 2021). Evidence arising from these studies could be integrated with our findings to guide the treatment for COVID-19 patients.

This study has several limitations. First, we did not specify RT treatment in the meta-analysis. All included studies were conducted in China, where patients received RTs recommended by the China National Health Commission's guidelines for COVID-19; specifically, oxygen therapy, antiviral medications, and symptomatic therapies. We unified all RTs as the control group since it did not yield significant heterogeneity. Second, this systematic review included 31 retrospective nonrandomized studies. It was difficult to conduct prospective RCTs at the early pandemic stage. These retrospective studies introduced the bias into the results. Due to flaws in study design and reporting, there was a relatively high risk of bias in most studies. Third, according to the funnel plot (Fig. 2C), there are potential publication biases in the study. Imputing at least 3 studies reporting negative results could eliminate the publication bias. Finally, we did not analyze the outcomes of the CM formula alone compared with RT since the individualized CM formula could not be pooled. We only studied the adjunctive effect of the CM formula to RT; however, the effectiveness of each CM formula on its own requires separate studies.

Conclusion

The moderate certainty level in GRADE shows that CM formulae have adjunctive effects on COVID-19, particularly clinical symptoms, clinical efficacy, severity, and duration of disease. Adjunctively to RT, the FYYH improves the clinical efficacy rate, shortens the febrile time, and time to negative PCR test; QFPD shortens the hospital stay, improves CT lung images and mortality; LHQW improves the clinical efficacy rate, febrile score, and severity of CT lung scan.

Acknowledgments

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Supplementary Table

Table S1. Characteristics of the Included Studies

Id	Study Type	Disease Phase	Sample Size (T/C)	Mean Age (Years)	CPGs for RTs	Intervention	Comparison	Duration of Treatment	Outcomes
Duan C 2020	RCT	Mild	123 (82/41)	T:52.0 ± 13.9 C:50.3 ± 13.2	III	JHQG plus RT	RT	5 days	②③④⑤⑧⑬⑮
Jin W 2020	RCT	Ordinary	38 (18/20)	T:43.6 ± 14.5 C:41.3 ± 9.9	II	CM plus RT	RT	NR	①③④⑤⑥⑧⑪⑫⑭⑮
Liao G R 2020	RCT	NR	70 (35/35)	T:65.3 ± 7.4 C:67.2 ± 8.6	II	CM plus RT	RT	7 days	③④⑤⑬
Wang L 2020	RCT	Ordinary	80 (40/40)	T:41.1 ± 14.5 C:40.8 ± 13.7	III	CM plus RT	RT	NR	①②③④⑤⑥⑪⑫⑬⑮
Zheng Z Z 2020	RCT	Ordinary, Severe	130 (65/65)	NR	V	CM plus RT	RT	14 days	①
Wang J B 2020	RCT	NR	48 (24/24)	T:46.8 ± 14.4 C:51.4 ± 17.6	I	KG-1 plus RT	RT	14 days	①③⑦⑧⑬⑭⑮
Xiao M Z 2020	RCT	NR	121 (58/63)	T:52.9 ± 14.0 C:53.9 ± 13.9	V	LHQW plus RT	RT	14 days	③④⑤⑧⑮
Xiao M Z 2020*	RCT	NR	124 (61/63)	T:56.1 ± 12.1 C:53.9 ± 13.9	V	LHQW plus HXZQ plus RT	RT	14 days	③④⑤⑧⑮
Xiong W Z 2020	RCT	Mild, Ordinary, Severe	42 (22/20)	T:57.1 ± 14.0 C:62.4 ± 12.3	II	XFBD plus RT	RT	7 days	③④⑤⑪⑫⑬
Yu P 2020	RCT	Mild, Ordinary	295 (147/148)	T: 47.3 ± 8.7 C: 48.3 ± 9.6	III	LHQW plus RT	RT	7 days	①②⑥⑧⑪⑫⑬
Wen L 2020	RCT	Ordinary, Severe, Critical	40 (20/20)	T: 49.1 ± 4.8 C: 47.7 ± 5.7	I	XBJ 50 ml plus RT	RT	7 days	⑦⑧⑪⑫⑮

(*Continued*)

Table S1. (*Continued*)

Id	Study Type	Disease Phase	Sample Size (T/C)	Mean Age (Years)	CPGs for RTs	Intervention	Comparison	Duration of Treatment	Outcomes
Wen L 2020*	RCT	Ordinary, Severe, Critical	40 (20/20)	T: 47.1 ± 5.2 C: 47.7 ± 5.7	I	XBJ 100 ml plus RT	RT	7 days	⑦ ⑧ ⑪ ⑫ ⑮
Ai X Y 2020	RCT	Mild, Ordinary, Severe	98 (55/43)	T: 44.0 ± 12.6 C: 46.0 ± 18.3	IV	FYYH plus RT	RT	3 days	① ② ⑫ ⑬ ⑮
Chen C W 2021	RCT	Mild, Ordinary	60 (30/30)	T: 50.2 ± 5.1 C: 49.5 ± 5.1	I	LHQW plus RT	RT	NR	③ ④ ⑤ ⑦ ⑬ ⑮
Chen J J 2020	RCT	Convalescent	70 (35/35)	T: 44.8 ± 4.9 C: 45.2 ± 4.7	V	LHQW plus RT	RT	15 days	① ② ③ ④ ⑤ ⑥
Chen L Z 2020	RCT	NR	30 (15/15)	T: 42.6 ± 3.5 C: 43.1 ± 3.2	V	XBJ 100 ml plus RT	RT	14 days	① ⑬ ⑮
Xu X L 2020	RCT	Mild, Ordinary, Severe	157 (77/80)	T: 49.1 ± 15.7 C: 50.4 ± 16.0	III	RDN plus RT	RT	14 days	① ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑬ ⑮
Xiao Q 2020	RCT	Mild, Ordinary	200 (100/100)	T: 60.9 ± 8.7 C: 62.2 ± 7.5	II	SFJD plus RT	RT	14 days	⑥ ⑪ ⑫ ⑬ ⑮
Wang Y 2021	RCT	Ordinary	140 (70/70)	T: 48.0 ± 13.2 C: 49.4 ± 13.3	IV	QFPD plus RT	RT	10 days	① ② ⑨ ⑪ ⑫ ⑬ ⑮
Hu K 2020	RCT	NR	284 (142/142)	T: 50.4 ± 15.2 C: 51.8 ± 14.8	II	LHQW plus RT	RT	14 days	① ③ ④ ⑤ ⑥ ⑦ ⑧ ⑬ ⑮
He Q 2021	RCT	NR	71 (36/35)	NR	V	BZYQ plus RT	RT	10 days	① ② ⑮
Ni L 2021	RCT	Mild, Ordinary, Severe	235 (176/59)	NR	III	SHL plus RT	RT	14 days	⑥ ⑦ ⑬ ⑮
Liu Y J 2021	RCT	Severe	50 (25/25)	T: 48.0 ± 1.6 C: 48.5 ± 1.3	V	HSBD plus RT	RT	NR	① ⑪ ⑫ ⑬ ⑮
Cheng D Z 2020	NS-I	Ordinary	102 (51/51)	T:55.5 ± 12.3 C:55.8 ± 11.6	III	LHQW plus RT	RT	7 days	③ ④ ⑤ ⑥ ⑧

Lian J 2020	NS-I	Mild, Ordinary, Severe, Critical, Convalescent	64 (38/26)	T:61.3 ± 14.1 C:58.1 ± 12.0	IV	CM plus RT	RT	NR	②③⑥⑧⑪⑫⑬⑮
Liu F 2020	NS-I	Ordinary, Severe, Critical	84 (42/42)	T:52.7 ± 16.8 C:49.5 ± 13.8	III	CM plus RT	RT	NR	①③⑨⑬
Pan G T 2020	NS-I	Critical	40 (26/14)	T:57.3 ± 9.8 C:64.0 ± 16.0	III IV	CM plus RT	RT	7 days	③⑥⑦⑪⑫
Qin L X 2021	NS-I	Severe, Critical	82 (42/40)	NR	V	CM plus RT	RT	NR	①③⑥⑦⑧⑪⑫⑭⑮
Qin L X 2021*	NS-I	Severe, Critical	563 (523/40)	NR	V	CM	RT	NR	①③⑥⑦⑧⑪⑫⑭⑮
Shi J 2020	NS-I	Mild, Ordinary, Severe	67 (49/18)	T: 47.9 ± 14.5 C:46.7 ± 17.4	III	CM plus RT	RT	6 days	①②③⑥⑧⑨
Song X Y 2020	NS-I	Mild, Ordinary	60 (30/30)	NR	III	CM plus RT	RT	3 days	①③⑦⑨⑬⑮
Hu Y Q 2020	NS-I	Ordinary, Severe, Critical	52 (31/21)	T:48.3 ± 16.6 C:49.8 ± 17.2	II III IV	CM plus RT	RT	NR	①②③⑤⑥⑦⑧⑨⑪⑫
Yang M B 2020	NS-I	Ordinary	49 (26/23)	T:50.4 ± 13.4 C:47.2 ± 16.6	V	RYN plus RT	RT	7 days	②⑥⑦⑫⑬⑮
Yang Q 2020	NS-I	Severe, Critical	103 (51/52)	T:61.6 ± 1.8 C:66.4 ± 1.8	III	CM plus RT	RT	NR	①⑥⑫⑬⑭⑮
Yao K T 2020	NS-I	Ordinary	42 (21/21)	T:57.1 ± 14.0 C:62.4 ± 12.3	III	LHQW plus RT	RT	NR	③④⑤
Zhang N 2020	NS-I	Ordinary	120 (90/30)	T:51.7 ± 12.5 C:49.2 ± 13.6	II	CM plus RT	RT	5 days	③④⑤⑦⑧⑨⑮
Huang H 2020	NS-I	NR	45 (30/15)	T:58.4 ± 15.5 C:66.3 ± 14.1	V	CM Yihao plus RT	RT	3 days	③④⑤⑥⑧⑨⑪⑫⑭⑮

(*Continued*)

Table S1. (*Continued*)

Id	Study Type	Disease Phase	Sample Size (T/C)	Mean Age (years)	CPGs for RTs	Intervention	Comparison	Duration of Treatment	Outcomes
Huang H 2020*	NS-I	NR	43 (28/15)	T:61.9 ± 12.2 C:66.3 ± 14.1	V	CM Erhao plus RT	RT	3 days	③④⑤⑥⑧⑨⑪⑫⑭⑮
Zhang H T 2020	NS-I	Severe, Critical	22 (11/11)	T: 43.4 ± 15.9 C: 40.7 ± 13.3	II	CM plus RT	RT	NR	⑥⑦⑬⑮
Li L 2020	NS-I	Ordinary, Severe, Critical	96 (64/32)	T: 49.9 ± 15.5 C: 47.5 ± 14.1	V	CM	RT	28 days	①③④⑤⑥⑮
Huang L Q 2020	NS-I	Severe	55 (23/32)	T: 56.0 ± 5.3 C: 61.5 ± 5.6	II	HSBD plus XYP plus XBJ plus SM	RT	16 days	⑥⑦⑪⑫⑬
Wang L Q 2021	NS-I	Ordinary, Severe	87 (47/40)	T: 44.7 ± 11.4 C: 49.7 ± 13.1	III	FYYH plus RT	RT	NR	②③⑦⑧⑭
Wang L Q 2020*	NS-I	Mild, Ordinary, Severe, Critical	278 (173/105)	T:60.0 ± 4.8 C:62.0 ± 5.1	V	FYYH plus RT	RT	NR	①②③④⑤⑥⑧⑪⑫⑬⑭⑮
Guo H 2020	NS-I	Mild, Severe	32 (16/16)	T: 52.0 ± 2.8 C: 54.0 ± 6.8	V	XBJ 100 ml plus RT	RT	7 days	③④⑤⑥⑦⑧⑨⑪⑫⑮
Zeng X H 2020	NS-I	Ordinary	229 (104/125)	T: 46.7 ± 6.2 C: 46.2 ± 5.6	V	QFPD plus RT	RT	NR	⑥⑦⑨⑮
Chen L 2020	NS-I	Ordinary	68 (34/34)	T: 65.1 ± 10.6 C: 64.4 ± 10.3	V	SFJD plus RT	RT	7 days	③④⑤⑥⑨⑪⑫⑮
Li K Y 2020	NS-I	NR	60 (30/30)	T: 53.6 ± 0.3 C: 50.4 ± 0.3	I	QFPD plus RT	RT	3 days	①③④⑤⑥⑧⑨⑬⑮
Qu X K 2020	NS-I	Mild, Ordinary	70 (40/30)	T: 40.7 ± 8.2 C: 39.8 ± 6.4	II III	SFJD plus RT	RT	10 days	③④⑤⑦⑮

Yang M 2020	NS-I	Mild	40 (20/20)	T: 49.6 ± 5.5 C: 50.2 ± 5.8	III	QFPD plus RT	RT	7 days	③④⑤⑪⑫
Yu H Y 2020	NS-I	Mild, Ordinary	102 (64/38)	NR	V	QFPD	RT	NR	①⑧⑨
Yu H Y 2020*	NS-I	Mild, Ordinary	123 (85/38)	NR	V	LHQW	RT	NR	①⑧⑨
Yu H Y 2020**	NS-I	Mild, Ordinary	65 (27/38)	NR	V	JYBD	RT	NR	①⑧⑨
Yu X Y 2020	NS-I	Ordinary, Severe, Critical	89 (43/46)	T: 64.2 ± 2.5 C: 60.5 ± 2.1	IV	QFPD plus RT	RT	14 days	⑦⑨⑫⑮
Zhang C Y 2020	NS-I	Ordinary	44 (22/22)	NR	IV	XBJ 50 ml plus RT	RT	7 days	①⑥⑪⑫⑬⑮
Zhang P 2021	NS-I	Severe, Critical	24 (12/12)	T: 61.4 ± 13.2 C: 62.3 ± 14.7	V	QFPD plus RT	RT	7 days	③⑥⑪⑫⑭⑮
Liu Z L 2020	NS-I	Ordinary, Severe	80 (44/36)	T: 50.7 C: 51.8	II	JHQG plus RT	RT	7 days	⑥⑦⑪⑫⑬⑮
Zhou Y H 2021	NS-I	Severe	104 (66/38)	T: 58.3 ± 15.1 C: 58.8 ± 14.1	V	CM plus RT	RT	NR	①④⑤⑥⑧⑨⑮
Feng J 2021	NS-I	Severe	118 (33/85)	NR	V	CM plus RT	RT	9 days	⑨⑭⑮

Notes: RCT: randomized controlled trial; NS-I: nonrandomized study of intervention; NR: not reported; T: treatment group; C: control group; CM: Chinese medicine; LHQW: Lianhua Qingwen; JHQG: Jinhua Qinggan granules; FYYH: Feiyan Yihao formula; RYN: Reyanning granules; RDN: Reduning injection; BZYQ: Buzhong Yiqi decoction; SHL: Shuanghuanglian oral liquids; HSBD: Huashi Baidu decoction; KG-1: Keguan-1 formula; HXZQ: Huoxiang Zhengqi granules; XFBD: Xuanfei Baidu decoction; XYP: Xiyanping injection; XBJ: Xuebijing injection; SFJD: Shufeng Jiedu formula; QFPD: Qingfei Paidu decoction; JYBD: Jinye Baidu formula; SM: Shenmai injection; RT: routine treatment (including oxygen therapy, antiviral medications and symptomatic therapies); CPGs: clinical practice guidelines; ①: effective clinical rate; ②: clinical symptom score; ③: improvement of fever; ④: improvement of fatigue; ⑤: improvement of cough; ⑥: improvement of CT; ⑦: negative nucleic acid conversion rate; ⑧: severe conversion rate; ⑨: length of hospital stay; ⑩: amount of virus; ⑪: white blood cell; ⑫: lymphocyte; ⑬: adverse events; ⑭: mortality; ⑮: other results; */**: different groups in the same study or different studies; I: diagnosis and treatment program for novel coronavirus pneumonia (the 3rd trial version from National Health Commission of the People's Republic of China); II: diagnosis and treatment program for novel coronavirus pneumonia (the 4th trial version from National Health Commission of the People's Republic of China); III: diagnosis and treatment program for novel coronavirus pneumonia (the 5th trial version from National Health Commission of the People's Republic of China); IV: diagnosis and treatment program for novel coronavirus pneumonia (the 6th trial version from National Health Commission of the People's Republic of China); V: adiagnosis and treatment program for novel coronavirus pneumonia (the 7th trial version from National Health Commission of the People's Republic of China)