Received: 7 February 2021 | Revised: 12 May 2021 | Accepted: 2 June 2021

DOI: 10.1002/ptr.7209

REVIEW

WILEY

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

Fei Jiang[1,2] | Nana Xu[1,3] | Yanxi Zhou[4] | Jinxing Song[1] | Jinjuan Liu[1] | Hong Zhu[5] | Jihong Jiang[1] | Yonghong Xu[1] | Rongpeng Li[1]

[1]The Key Laboratory of Biotechnology for Medicinal Plants of Jiangsu Province and School of Life Sciences, Jiangsu Normal University, Xuzhou, China

[2]Department of Laboratory Medicine, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

[3]Department of Morphology, Xuzhou Medical University, Xuzhou, China

[4]School of Medical Technology, Xuzhou Medical University, Xuzhou, China

[5]Institute of Botany, Jiangsu Province and Chinese Academy of Sciences, Nanjing, China

Correspondence
Rongpeng Li and Yonghong Xu, The Key Laboratory of Biotechnology for Medicinal Plants of Jiangsu Province and School of Life Sciences, Jiangsu Normal University, No. 101, Shanghai Road, Tongshan New District, Xuzhou 221116, China.
Email: lirongpeng@jsnu.edu.cn (R. L.), 6020150060@jsnu.edu.cn (Y. X.)

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81870005; Natural Science Foundation of the Jiangsu Higher Education Institutions of China, Grant/Award Number: 18KJA180003; Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD); Project of Xuzhou Applied and Basic Research, Grant/Award Numbers: KC20102, KC18009

This study provides current evidence for efficacy and safety of treating COVID-19 with combined traditional Chinese medicine (TCM) and conventional western medicine (CWM). Six databases were searched from January 1 to December 31, 2020. Randomized controlled trials (RCTs), case–control studies (CCTs), and cohort studies on TCM or TCM combined with CWM treatment for COVID-19 were included. The quality of included RCTs was assessed by Cochrane risk of bias tool, and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies and CCTs. Review Manager 5.4 software was used to perform meta-analysis. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. A total of 35 studies (3,808 patients) composing 19 RCTs and 16 observational studies were included. The results of meta-analysis revealed that comparing with CWM alone, integrated TCM and CWM had significant improvement in total effective rate, improvement rate of chest CT, the rate of disease progression, as well as improvement of fever, fatigue and cough. The overall quality of evidence was very low to moderate. In conclusion, TCM combined with CWM was a potential treatment option for increasing clinical effective rate, improving the clinical symptoms, and preventing disease progression in COVID-19 patients. High-quality clinical trials are required in the further.

KEYWORDS
COVID-19, integrative medicine, meta-analysis, systematic review, traditional Chinese medicine

Abbreviations: CCT, case–control study; CI, confidence intervals; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; CWM, conventional western medicine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LYM, lymphocyte count; MD, mean difference; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT, randomized controlled trial; RR, risk ratio; SMD, standardized mean difference; TCM, traditional Chinese medicine; WBC, white blood cell count.

Fei Jiang, Nana Xu, and Yanxi Zhou contributed equally to this work.

1 | INTRODUCTION

Since December 2019, a novel positive strand RNA coronavirus named SARS-COV-2 was confirmed to be the pathogen causing an outbreak of unexplainable pneumonia (Zhu et al., 2020). The rapid human-to-human transmission and the lack of specific antiviral drugs and vaccines have resulted in an outbreak of coronavirus disease 2019 (COVID-19) in 212 countries and regions around the world. By the end of 2020, so far, the cumulative number of confirmed cases has reached more than 70 billion, and the cumulative number of deaths has reached more than 1.6 million. Although the epidemic has subsided in China, the number of new confirmed cases overseas is on the rise. The COVID-19 remains a major threat to global public health.

In China, traditional Chinese medicine (TCM) combined with conventional western medicine (CWM) has been a great success in the treatment of COVID-19. During this COVID-19 outbreak, over 90% of total confirmed COVID-19 patients in China had been treated with TCM or TCM combined with CWM (News Conference of the State Council Information Office, 2020). Related reports including case reports, observational studies and randomized clinical trials had confirmed that integrated TCM and CWM could increase clinical effective rate, improve the clinical symptoms, shorten length of hospital stay, and reduce patient number of transferred to severe or critically ill cases (Hu et al., 2020; Tian et al., 2020; Xiao, Tian et al., 2020; Zhang, Tian et al., 2020). Moreover, a number of systematic reviews have assessed the efficacy and safety of TCM for treating COVID-19 (M. Liu et al., 2020; Luo et al., 2020; Pang et al., 2020; Xiong, Wang et al., 2020). But the previous systematic reviews included a maximum of 11 RCTs (Pang et al., 2020). The limited number of literature included in these reviews provided limited TCM treatment schemes because TCM emphasizes perspective of harmonization between environment and human body, different provinces released different treatment guidance according to the disease, local climate characteristics, and different physical conditions. A summary at a time when the epidemic in China is leveling off was performed to provide complete guidance for clinical practice.

2 | METHODS

2.1 | Study registration

This review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42020201639). This study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009).

2.2 | Inclusion criteria

2.2.1 | Type of studies

Randomized controlled trials (RCTs), cohort studies and case–controlled studies (CCTs) were included in this systematic review. Publications in English and Chinese were included.

2.2.2 | Type of participants

Participants confirmed with COVID-19 were included regardless of their age, sex, race, and nationality. Diagnostic criteria consisted of the following: (a) historical epidemiology; (b) being symptomatic (either having fever, coughing, or fatigue) plus radiologic abnormalities consistent with pneumonia; (c) positive for SARS-CoV-2 nucleic acid tests; (d) the gene sequence of the virus was highly homologous to the known novel coronavirus. Patients who simultaneously met the (a) and (b), any one of (c), and (d) following criteria were included.

2.2.3 | Type of interventions

TCM (Chinese herbal medicine and Chinese patent medicine) alone or TCM combined with CWM was included. There was no limitation on the number of herbs, administration methods, dosage, or duration of treatment for traditional Chinese medicine. Other TCM therapeutic methods including acupuncture, moxibustion, cupping, massage, qigong, Tai Chi, etc. were excluded. The control group was treated with CWM alone.

2.2.4 | Type of outcome measurements

The primary outcome was rate of disease progression (proportion of patients who have progressed from mild or ordinary types to severe or critical types after treatment), negative conversion rate of nucleic acid (proportion of patients whose nucleic acid test become negative after treatment), and improvement rate of chest CT (number of patients whose CT lesions disappeared or decreased after treatment as a percentage of all patients treated). The secondary outcomes were total effective rate (number of patients cured plus the number in remission per group divided by the total number of patients in each group), incidence of adverse events (number of patients with side effects after treatment as a percentage of all patients treated), disappearance rate of main symptoms (number of patients whose symptoms [fever, cough, and fatigue] disappeared after treatment as a percentage of all patients treated), lymphocyte count, and length of hospital stay.

2.3 | Exclusion criteria

The exclusion criteria were as follows: self-control or lack of control, case report and case series, cross-sectional study, experience summary, animal experiment research, systematic review and meta-analysis, and full texts were not available.

2.4 | Databases and search strategy

We searched 6 electronic databases as follows: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese

Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and Wanfang database (Wanfang Data). The search time was limited from the January 1 to December 31, 2020. We would apply a combination of MeSH terms and free-text to search and adjust the search strategy according to the characteristics of each database. Pubmed and Wanfang database detailed search strategy as examples were shown in Tables S1 and S2.

2.5 | Data extraction

Two independent authors (F. Jiang and N.N. Xu) performed literature selection and data extraction independently and used NoteExpress software to remove duplicate literature and then excluded irrelevant literature by reading the title and abstract. In the remaining literature, full-text assessment was carried out to determine whether to be included. Any disagreement between reviewers was resolved by discussion or consultation with a third reviewer (Y.X. Zhou).

2.6 | Assessment of risk of bias

The RoB2 assessment form (revised tool for risk of bias in randomized trials) was used for assessing RCTs in following five fields: randomisation process, deviation from intended interventions, missing outcome data，measurement of the outcome, and selection of the reported result (Sterne et al., 2019). Each field was assessed to be "low risk", "high risk", or "some concerns". The Newcastle-Ottawa Scale (NOS) assesses the quality of cohort studies and CCTs with the following three broad categories: selection, comparability and exposure, or outcome (Wells et al., 2003). The total score is 9, the higher the score, the better the quality of the study. Two reviewers (F. Jiang and N.N. Xu) independently completed the data extraction and quality assessment. Any disagreement was resolved by discussion or consultation with a third reviewer (Y.X. Zhou).

2.7 | Data analysis

Review Manager (version 5.4) was used to perform the statistical analysis. The effect measure of binary variable would be expressed as risk ratio (RR) or odds ratio (OR) and 95% confidence interval (CI). For continuous variables, 95% CI and mean difference (MD) or standardized mean difference (SMD) would be used. We assessed statistical heterogeneity in each pairwise comparison with I^2 test. If $I^2 \leq 50\%$ and $p > .05$, the heterogeneity among included studies was considered low. If $I2 > 50\%$ or $p \leq .05$, the heterogeneity among included studies was considered high. Considering the heterogeneity of TCM interventions, the random effects models would be used to calculate the effect size. If there was a significant level of heterogeneity and available data were enough, sensitivity analysis or subgroup analysis would be conducted. The publication bias was evaluated by funnel plot, and it is determined by observing whether the left and right were symmetrical. If the left and right were not symmetrical, there is a bias.

2.8 | Quality of evidence

Considering that observational studies are of low-quality evidence and that there are factors that reduce the quality of evidence, leading to a very low quality of evidence, we only evaluated the quality of evidence for RCTs. According to the GRADE approach, the quality of RCTs can be downgraded for five reasons (risk of bias, imprecision, inconsistency, indirectness, and publication bias). Summary of Findings table was created by GRADE online (https://gradepro.org/).

3 | RESULTS

3.1 | Study selection and characteristics

A total of 5,697 articles were retrieved, including 3,685 duplicates. According to the inclusion and exclusion criteria, 1967 articles were removed based on their titles and abstracts. Forty-five full-text articles were assessed for eligibility, and 10 articles were excluded due to following reasons: ① Duplicates ($n = 5$); ② Observation group did not meet the inclusion criteria ($n = 2$); ③ Including suspected case ($n = 1$); ④ Article retracted ($n = 1$); ⑤ Cross-sectional study ($n = 1$). Thirty-five clinical studies were included in this systematic review. The process of study screening is shown in Figure 1.

Basic characteristic of enrolled studies are summarized in Table 1. Five articles were published in English, and 30 studies were published in Chinese. Among the 35 clinical trials, 19 were RCTs (Ding et al., 2020; Duan et al., 2020; Fu, Lin, & Tan, 2020a, 2020b; Hu et al., 2020; Li & Zhang, 2020; Liao, 2020; Pan et al., 2020; Qiu et al., 2020; Sun et al., 2020; Wang, Wang, et al., 2020; Wang, Yang, et al., 2020; Wen, Zhou, Jiang, & Huang, 2020; Xiao, Tian et al., 2020; Xiong et al., 2020; Yu, Li, Wan, & Wang, 2020; Zhang, Lei, Xu, Wei, & Hu, 2020; Zheng et al., 2020; Zhou, Zhao, Li, & Tian, 2020), 14 were CCTs (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Huang et al., 2020; Ji, Feng, & Fei, 2020; Lian et al., 2020; F. Liu, 2020; Qu et al., 2020; Shi et al., 2020; Xiao, Jiang, et al., 2020; Yang, Dang, Huang, Li, & Guo, 2020; Yang, Sun, et al., 2020; Yao, Liu, Li, Huang, & Cai, 2020; Zhang, Huang et al., 2020) and 2 were retrospective cohort study (Tian et al., 2020; Xia et al., 2020). Totally, 3,808 patients including 2077 patients in the intervention group and 1731 patients in the control group were enrolled, with the sample size ranged from 12 to 721. In the intervention group, COVID-19 patients were all treated by integrated TCM and CWM, while patients were treated by CWM alone in the control group. TCM used in these studies including Chinese patent medicine ($n = 14$) and Chinese herbal decoction ($n = 20$) and injection ($n = 1$). The compositions of TCM were summarized in Table S3. Treatment

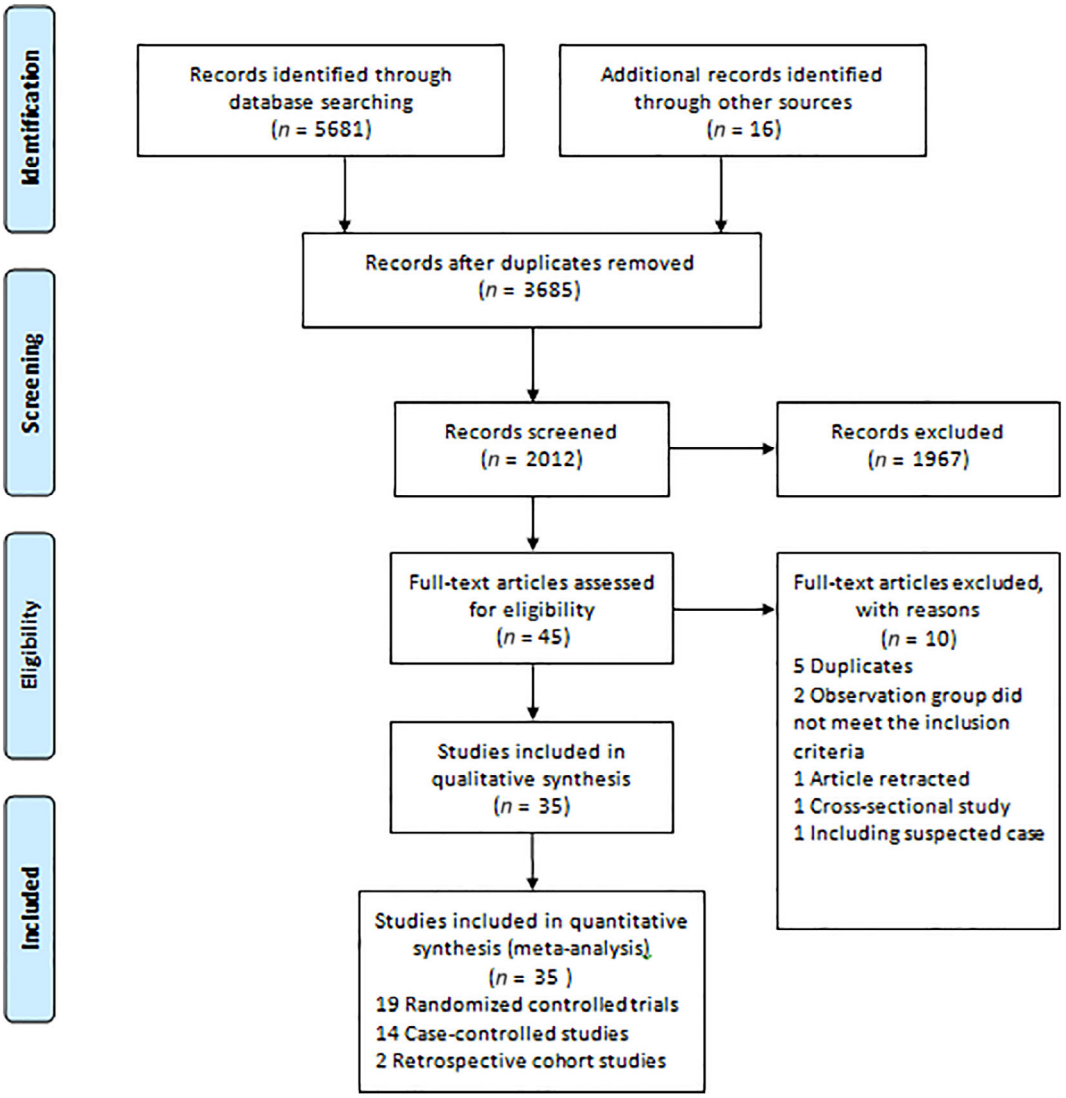

FIGURE 1 Flow diagram of study screening

duration varied from 5 to 15 days. The outcome measure of concern is total effective rate, improvement of chest CT, adverse events, negative conversion of nucleic acid, relief rate and relief time of main clinical symptom, rate of disease progression and length of stay.

3.2 | Assessment of risk of bias

The risk of bias of the included RCTs was shown in Figure 2. Among the included 19 studies, nine studies had low risk of bias, eight studies had some concerns and two studies had high risk of bias.

Sixteen observational studies including 14 CCTs and 2 retrospective cohort studies (RCSs) were assessed for quality by the NOS. The range of scores was 6 to 8. These studies showed a moderate quality sufficient to conduct a meta-analysis (Table 2).

3.3 | Meta-analysis

3.3.1 | Rate of disease progression

Rate of disease progression was reported in 21 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Duan et al., 2020; Fu et al., 2020b; Hu et al., 2020; Huang, Wang, et al., 2020; Huang, Tan, et al., 2020; Ji et al., 2020; Lian et al., 2020; F. Liu, 2020; Qiu et al., 2020; Shi et al., 2020; Sun et al., 2020; Tian et al., 2020; Wang, Wang, et al., 2020; Xia et al., 2020; Xiao, Tian, et al., 2020; Yang, Dang, et al., 2020; Yu et al., 2020; Zhang, Lei, et al., 2020). Compared with the CWM group, the TCM + CWM group significantly reduced the rate of conversion to severe cases, the difference was statistically significant (RR = 0.30, 95%CI = [0.20, 0.44], I^2 = 19%, p < .00001) (Figure 3).

TABLE 1 Basic characteristic of included literatures on the treatment of COVID-19 with integrated Traditional Chinese and Western medicine

First author	Time of publish ion	Type of study	Severity of disease (no.)	Sample size		Sex ratio (male/female)		Mean age(y)		Intervention characteristics		Duration (days)	Outcome measures[a]
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Ding XJ 2020	May, 2020	RCT	Mild (21), Ordinary (70), Severe and Critical (9)	51	49	39/12	39/10	54.7 ± 21.3	50.8 ± 23.5	Qingfei Touxie Fuzheng recipe (150 ml, bid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	10	(2)(4)(6)(9)
Duan C 2020	Mar 24, 2020	RCT	Mild (123)	82	41	39/43	23/18	51.99 ± 13.88	50.29 ± 13.17	Jinhua Qinggan granule (10 g, tid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	5	(2)(3)(4)(7)(8)
Fu XX 2020a	Jun, 2020	RCT	Mild (5), Ordinary (60)	32	33	17/15	19/14	43. 26 ± 7. 15	43. 68 ± 6. 45	Toujie Quwen granules+C	Antiviral therapy (abidol 0.2 g, tid), antibacterial therapy (Moxifloxacin hydrochloride 0.4 g, qd), supportive therapy (ambroxol hydrochloride 30 mg, tid),	10	(1)(6)(7)(8)(9)
Fu XX 2020b	May, 2020	RCT	Ordinary (73)	37	36	19/18	19/17	45.26 ± 7.25	44.68 ± 7.45	Toujie Quwen granules+C	Antiviral therapy (arbidol tablets 0.2 g, tid), supportive therapy (ambroxol tablets 30 mg, tid)	15	(1)(7)(8)(9)
Hu K 2020	May 8, 2020	RCT	-	142	142	79/63	71/71	50.4 ± 15.2	51.8 ± 14.8	Lianhua Qingwen capsule (4 capsules tid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	14	(1)(2)(3)(4)(5)(6)(7)(8)
Li YD 2020	May, 2020	RCT	Severe (12)	6	6	4/2	3/3	52. 00 ± 6. 56	50. 00 ± 10. 00	Qingfei Paidu decoction+C	Antiviral therapy, antibacterial therapy, supportive therapy.	6	(1)(5)(6)(8)(9)
Liao GR 2020	Jun, 2020	RCT	-	35	35	20/15	18/17	65.25 ± 7.42	67.16±8.64	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(2)(3)(4)(8)
Pan GT 2020	Apr, 2020	RCT	Severe and Critical (40)	26	14	14/12	8/6	57.31 ± 9.88	64.01 ± 16.00	Chinese herbal medicine+C	Antiviral therapy (abidol), antibacterial therapy (moxifloxacin, levofloxacin, cephalosporins, meropenem), supportive therapy (asmeton, ambroxol, acetyl cysteamine acid, gamma globulin, methylprednisolone)	7	(1)(5)(6)(9)
Qiu M 2020	May 7, 2020	RCT	Ordinary (50)	25	25	13/12	14/11	53.35 ± 18.35	51.32 ± 14.62	Maxing Xuanfei Jiedu decoction (150 ml, tid) + C	Antiviral therapy (α-interferon 50 μg bid, lopinavir/ritonavir 400 and 100 mg bid), supportive therapy.	10	(1)(2)(4)(6)(7)
Sun HM 2020	Jul, 2020	RCT	Ordinary (57)	32	25	17/15	11/14	45.4 ± 14.10	42.0 ± 11.70	Lianhua Qingke granule (50 mg, tid) + C	Antibacterial therapy (α-interferon 50 μg bid, lopinavir/ritonavir 400 and 100 mg bid), supportive therapy.	14	(2)(3)(4)(6)(7)
Wang JB 2020	Jun 26, 2020	RCT	-	24	23	14/10	12/11	46.8 ± 14.4	51.4 ± 17.6	Keguan-1 (19.4 g bid) + C	Antibacterial therapy (α-interferon 50 μg bid, lopinavir/ritonavir 400 and 100 mg bid).	14	(2)(5)(8)

TABLE 1 (Continued)

First author	Time of publish ion	Type of study	Severity of disease (no.)	Sample size		Sex ratio (male/female)		Mean age(y)		Intervention characteristics		Duration (days)	Outcome measures[a]
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Wang YL 2020	Mar 23, 2020	RCT	Ordinary (20)	10	10	5/5	5/5	39.24±10.01	55.90 ± 3.71	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(2)(3)(4)(5)(6)
Wen L 2020	Apr, 2020	RCT	Severe (60)	40	20	12/8	9/11	47.1 ± 5.2	47.7 ± 5.7	Xuebijing injection (50 or 100 ml, bid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(5)(7)(8)(9)
Xiao MZ 2020	Aug 3, 2020	RCT	-	61	63	33/28	35/28	56.07 ± 12.10	53.9 ± 13.92	Huoxiang Zhengqi dropping pills/ Lianhua Qingwen granules+C	Antiviral therapy (oseltamivir tablet 75 mg qd, arbidol 200 mg tid, ribavirin 150 mg tid), antibacterial therapy (penicillins, cephalosporins, ofloxacin) and macrolide, supportive therapy	14	(2)(3)(4)(8)
Xiong WZ	Jul, 2020	RCT	Mild, ordinary, severe	22	20	-	-	57.10 ± 14.00	62.40 ± 12.30	Xuanfei Baidu decoction+C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(2)(3)(4)(9)
Yu P 2020	Apr 22, 2020	RCT	Mild (295)	147	148	82/65	89/59	48.27 ± 9.56	47.25 ± 8.67	Lianhua Qingwen granule (6 g. tid) + C	Antiviral therapy (abidol hydrochloride 0.2 g tid), antibacterial therapy (moxifloxacin 0.4 g qd), supportive therapy (ambroxol hydrochloride 30 mg tid.	7	(1)(6)(7)(8)(9)
Zhang YL 2020	May 5, 2020	RCT	Ordinary (120)	80	40	30/50	23/17	53.40 ± 13.70	52.0 ± 14.10	Oral honeysuckle (60 ml, tid) + C	α-interferon (50 μg bid), lopinavir/ ritonavir (400 and 100 mg bid), supportive therapy.	10	(2)(3)(4)(5)(6)(7)(8)
Zheng ZZ 2020	Feb, 2020	RCT	Ordinary (119), Severe (11)	65	65	42/23	44/21	-	-	Chinese herbal medicine +C	Antiviral therapy (α-interferon, abidol, lopinavir/ritonavir), antibacterial therapy (moxifloxacin), supportive therapy (methylprednisolone).	14	(1)
Zhou WM 2020	Feb 28, 2020	RCT	Ordinary (104)	52	52	32/20	28/24	52.47 ± 10.99	51.11 ± 9.87	Diammonium glycyrrhizinate (150 mg,tid) + C	Antiviral therapy (lopinavir/ ritonavir 400 and 100 mg bid), supportive therapy, oxygen therapy	14	(1)(8)(9)
Chen L 2020a	Jul 23, 2020	CCT	Ordinary (230)	115	115	55/60	47/68	63.02 ± 13.61	60.17 ± 16.02	Ganlu Xiaodu decoction (100 ml, tid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(1)(2)(3)(4)(6)(7)(8)(9)(10)
Chen L 2020b	Aug, 2020	CCT	Ordinary (68)	34	34	14/20	15/19	65.06 ± 10.63	64.35 ± 10.34	Shufeng Jiedu Capsule (2.08 g, tid) + C	Antiviral therapy (abidol 0.2 g tid), antibacterial therapy (moxifloxacin 0.4 g qd), supportive therapy (ambroxol)	7	(1)(2)(3)(4)(6)(8)(9)(10)
Cheng DZ 2020	May 2020	CCT	Ordinary (102)	51	51	26/25	27/24	55.5 ± 12.3	55.8 ± 11.6	Lianhua Qingwen granule (6 g tid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	7	(1)(2)(3)(4)(6)(7)
Huang H 2020a	Aug, 2020	CCT	-	30	15	13/17	9/6	58.4 ± 15.5	66.3 ± 14.1	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy	10	(2)(3)(4)(5)(6)(7)(9)(10)

(Continues)

TABLE 1 (Continued)

First author	Time of publish ion	Type of study	Severity of disease (no.)	Sample size		Sex ratio (male/female)		Mean age(y)		Intervention characteristics		Duration (days)	Outcome measures[a]
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Huang H 2020b	Aug, 2020	CCT	-	28	15	16/12	9/6	61.9 ± 12.2	66.3 ± 14.1	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy	10	(2)(3)(4)(5)(6)(7)(9)(10)
Ji D 2020	Jul, 2020	CCT	Ordinary (50)	28	22	16/12	12/10	45.3 ± 13.7	47.6 ± 14.1	Chinese herbal medicine+C	Antiviral therapy (abidol, 0.2 g tid, ribavirin, recombinant human interferon a-2b), antibacterial therapy (moxifloxacin), supportive therapy (ambroxol tablets 30 mg tid).	10	(2)(3)(4)(7)
Lian J 2020	Jun 28, 2020	CCT	Mild, ordinary, severe and critical, recovery	38	26	15/23	10/16	61.3 ± 14.1	58.07 ± 11.9	Chinese herbal medicine+C	Antiviral therapy (arbidol tablets 0.2 g tid, recombinant human interferon a-2b, resochin), antibacterial therapy (moxifloxacin, 0.4 g qd, cefperazone-Sulbactam), supportive therapy (human immunoglobulin).	10	(2)(3)(4)(6)(7)(8)
Liu F 2020	2020	CCT	Ordinary (35), Severe (42), Critical (7)	42	42	15/27	17/25	52.7 ± 16.8	49.5 ± 13.8	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy.	-	(1)(2)(7)(8)(10)
Qu XK 2020	Mar, 2020	CCT	Ordinary (70)	40	30	25/15	16/14	40.65 ± 8.23	39.82 ± 6.40	Shufeng Jiedu capsule (2.08 g, bid) + C	Antiviral therapy (abidol hydrochloride 0.2 g tid), antibacterial therapy, supportive therapy,	10	(1)(2)(3)(4)(5)(6)(8)
Shi J 2020	Apr, 2020	CCT	Ordinary (67)	49	18	26/23	10/8	47.94 ± 14.46	46.72 ± 17.40	Chinese herbal medicine+C	Antiviral therapy (recombinant human interferon a-2b, lopinavir/ritonavir, arbidol, darunavir corbita, interferon K, hydroxychloroquine), antibacterial therapy, methylprednisolone sodium succinate, gamma globulin, and supportive therapy	-	(1)(2)(3)(4)(6)(7)(10)
Xiao Q 2020	May, 2020	CCT	Mild (200)	100	100	64/36	66/34	60.90 ± 8.70	62.20 ± 7.50	Shufeng Jiedu capsule (2.08 g, tid) + C	Antibacterial therapy (abidol 0.2 g tid)	14	(1)(2)(3)(4)(6)(8)(9)
Yang MB 2020	Jul, 2020	CCT	Ordinary (49)	26	23	16/10	9/14	50.35 ± 13. 37	47.17 ± 16. 57	Reyanning mixture (10–20 ml, 2 to 4 times daily) + C	α-interferon (50 μg bid), lopinavir/ritonavir (400 and 100 mg bid), ribavirin (0.5 g, bid), Abidol hydrochloride(0.2 g, tid)	7	(2)(3)(4)(5)(6)(8)(9)
Yang Q 2020	Apr, 2020	CCT	Severe (103)	51	52	28/23	24/28	61.57 ± 1.84	66.46 ± 2.29	Chinese herbal medicine+C	Antiviral therapy, antibacterial therapy, supportive therapy.	-	(1)(6)(8)(9)(10)
Yao KT 2020	Jun, 2020	CCT	Ordinary (42)	21	21	16/5	12/9	57.1 ± 14.0	62.4 ± 12.3	Lianhua Qingwen granules (6 g, tid) + C	Antiviral therapy, antibacterial therapy, supportive therapy.	14	(2)(3)(4)

TABLE 1 (Continued)

First author	Time of publish ion	Type of study	Severity of disease (no.)	Sample size		Sex ratio (male/female)		Mean age(y)		Intervention characteristics		Duration (days)	Outcome measures[a]
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
Zhang HT 2020	May, 2020	CCT	Ordinary (22)	11	11	4/7	4/7	43.4 ± 15.9	40.7 ± 13.3	Chinese herbal medicine+C	Antiviral therapy (α-interferon, lopinavir/ritonavir), antibacterial therapy, supportive therapy	-	(2)(5)(6)(7)(8)
Tian JX 2020	Aug, 2020	RCS	Mild (721)	430	291	201/229	146/145	43.79 ± 12.099	55.44 ± 14.641	Hanshiyi formula	Conventional treatment	-	(7)
Xia WG 2020	Mar, 2020	RCS	Ordinary (40), Severe (10), Critical (2)	34	18	17/17	6/12	54. 18 ± 13. 08	53. 67 ± 12. 70	Chinese herbal medicine+C	Antiviral therapy (abidol, ribavirin, interferon alpha, Lopinavir/ritonavir, oseltamivir), antibacterial therapy (moxifloxacin, levofloxacin, azithromycin, cephalosporins, penicillins), supportive therapy (gamma globulin, methylprednisolone),	10	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)

Abbreviations: CCT, case-control study; RCS, retrospective cohort study; RCT, randomized controlled trial; –, lack of data.

[a](1) Total effective rate; (2) Fever improvement; (3) Fatigue improvement; (4) Cough improvement; (5) negative conversion rate of nucleic acid; (6) chest CT improvement; (7) rate of conversion to severe cases; (8) Adverse events; (9) Peripheral blood index; (10) length of stay.

3.3.2 | Negative conversion rate of nucleic acid

The negative conversion rate of nucleic acid after treatment was analyzed in 6 studies (Hu et al., 2020; Pan et al., 2020; Qu et al., 2020; Wen et al., 2020; Yang, Dang, et al., 2020; Zhang, Lei, et al., 2020). Meta-analysis showed no significant difference between the TCM + CWM group and the CWM group (RR = 1.17, 95%CI = [0.99, 1.39], I2 = 57%, $p = .07$) (Figure 4).

3.3.3 | Improvement rate of chest CT

Seventeen studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Ding et al., 2020; Fu et al., 2020b; Hu et al., 2020; Huang, Wang, et al., 2020; Huang, Tan, et al., 2020; Pan et al., 2020; Shi et al., 2020; Sun et al., 2020; Wang, Wang, et al., 2020; Xia et al., 2020; Xiao,Tian et al., 2020; Yang, Dang, et al., 2020; Yang, Sun, et al., 2020; Yu et al., 2020;) evaluated improvement rate of chest CT. Compared with the CWM group, a significant difference was identified (RR = 1.21, 95%CI = [1.13, 1.29], $I^2 = 23\%$, $p < .00001$) (Figure 5).

3.3.4 | Total effective rate

Fifteen studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Fu et al., 2020a, 2020b; Hu et al., 2020; Li & Zhang, 2020; F. Liu, 2020; Pan et al., 2020; Xia et al., 2020; Xiao, Tian et al., 2020; Yang, Sun, et al., 2020; Yu et al., 2020; Zheng et al., 2020; Zhou et al., 2020) evaluated the effects of TCM + CWM on total effective rate. The intervention group exhibited a significant improvement compared with the control group (RR = 1.20, 95%CI = [1.14, 1.26], $I^2 = 12\%$, $p < .00001$) (Figure 6).

3.3.5 | Incidence of adverse events

Nineteen studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Duan et al., 2020; Hu et al., 2020; Li & Zhang, 2020; Lian et al., 2020; Liao, 2020; F. Liu, 2020; Qu et al., 2020; Wang, Wang, et al., 2020; Wen et al., 2020; Xia et al., 2020; Xiao, Tian, et al., 2020; Xiong et al., 2020; Yang, Sun, et al., 2020; Yu et al., 2020; Zhang, Huang, Tan et al., 2020; Zhang, Lei, et al., 2020; Zhou et al., 2020) evaluated incidence of adverse events. Meta-analysis revealed no significant difference between the TCM + CWM group and the CWM group (RR = 0.77, 95%CI = [0.53, 1.13], $I^2 = 28\%$, $p = .18$) (Figure 7).

3.3.6 | Major symptom (fever, fatigue and cough) relief

The main clinical symptoms are summarized in Table 3. Thirteen studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng

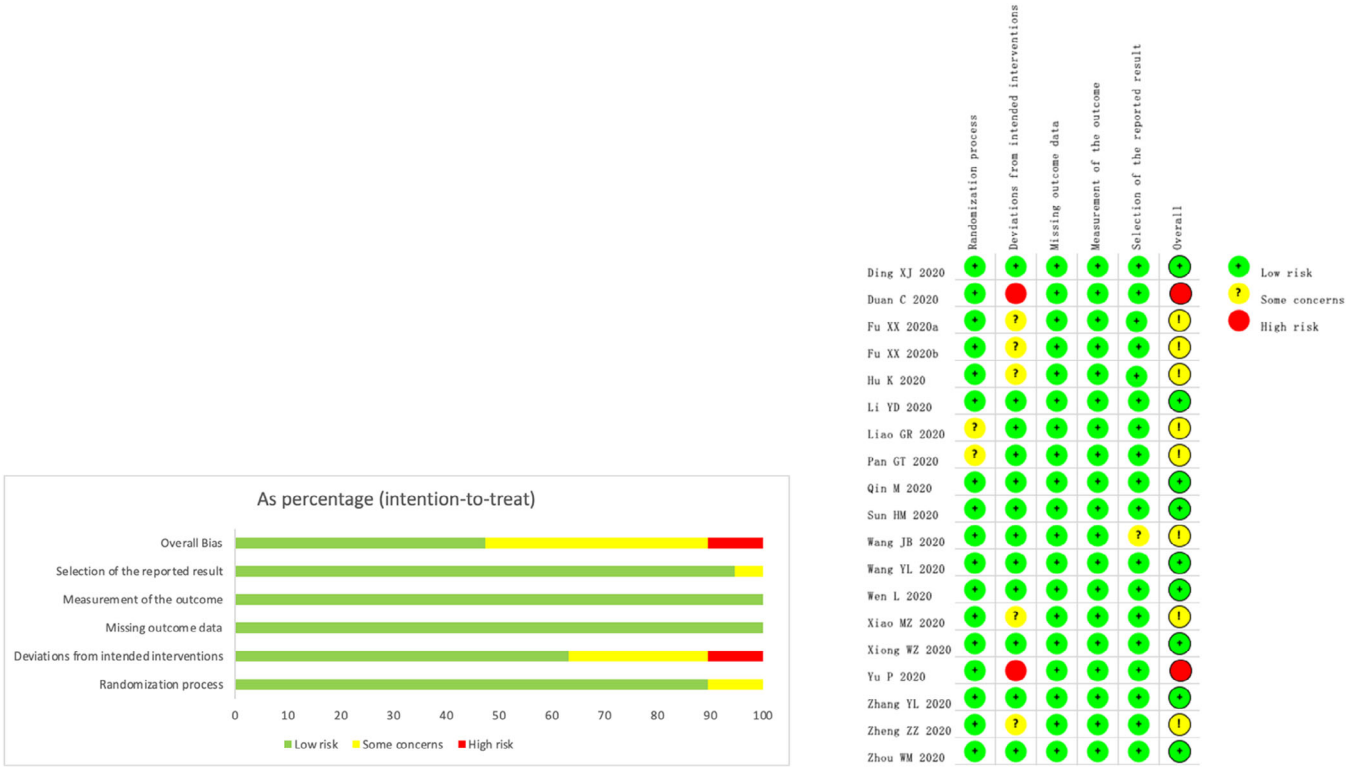

FIGURE 2 Risk of bias graph (left) and summary (right)

et al., 2020; Ding et al., 2020; Duan et al., 2020; Ji et al., 2020; Liao, 2020; Sun et al., 2020; Wang, Yang, et al., 2020; Xiao, Tian, et al., 2020; Xiong, Wang, Du, & Ai, 2020; Yao et al., 2020; Zhang, Lei, et al., 2020) reported relief rate of fever symptom, and eleven studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; F. Liu, 2020; Qiu et al., 2020; Qu et al., 2020; Xia et al., 2020; Xiao, Jiang, et al., 2020; Zhang, Huang, Tan et al., 2020) reported fever relief time. Meta-analysis revealed statistically significant between the TCM + CWM group and the CWM group in fever relief rate (RR = 1.20, 95% CI = [1.05, 1.37], I^2 = 86%, p = .008) and fever reduction time (MD = -1.54, 95%CI = [−1.91, −1.17], I^2 = 54%, p < .00001). A significant heterogeneity was identified in fever relief rate. We conducted a sensitivity analysis by removing studies and recalculated the combined estimate on remaining studies. The I^2 become 13% after removing "Zhang YL 2020" and "Xiao MZ 2020" at the same time, indicating that these two studies were the main sources of heterogeneity. For fever reduction time, the value of I^2 was 14% after removing "Xiao Q 2020", varying that this study was the source of heterogeneity.

Fatigue relief rate was reported in 11 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Duan et al., 2020; Ji et al., 2020; Liao, 2020; Sun et al., 2020; Xiao, Tian, et al., 2020; Xiong et al., 2020; Yao et al., 2020; Zhang, Lei, et al., 2020), and fatigue relief time was reported in 7 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; Qu et al., 2020; Xiao, Jiang, et al., 2020). Meta-analysis showed a significant improvement on number of fatigue relief cases (RR = 1.31, [1.13, 1.52], I^2 = 53%, p = .0004) and fatigue relief time (MD = −1.50, [−2.19, −0.81], I^2 = 81%, p = .0001). We investigated the influence of a single study on the overall risk estimate by excluding one study at a time. For fatigue relief rate and fatigue relief time, "Zhang YL 2020" and "Xiao Q 2020" were the source of heterogeneity. I^2 become 21 and 0%, respectively, after removing these two studies.

The effect of TCM on cough relief rate and cough relief time was evaluated in 11 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Ding et al., 2020; Duan et al., 2020; Ji et al., 2020; Liao, 2020; Xiao, Tian, et al., 2020; Xiong et al., 2020; Yao et al., 2020; Zhang, Lei, et al., 2020) and 8 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Cheng et al., 2020; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; Qiu et al., 2020; Qu et al., 2020; Xiao, Jiang, et al., 2020) respectively. A significant improvement on cough relief rate (RR = 1.35, [1.14, 1.59], I^2 = 59%, p = .0003) and cough relief time (MD = −1.96, [−2.88, −1.04], I^2 = 84%, p < .0001) was observed by the TCM + CWM group. Removing "Xiao MZ 2020" and "Xiao Q 2020" separately in two outcome measures above, values of I^2 were all reduced to less than 50%.

For these studies considered to be the source of heterogeneity, we found that there was not statistically significant (p < .05) in relevant outcome measurements between the TCM + CWM group and the CWM group.

TABLE 2 Quality of included observational studies

Study	Selection				Comparability	Outcome			
Case–control study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score
Chen L 2020a	★			★	★★	★	★	★	7
Chen L 2020b	★			★	★★	★	★	★	7
Cheng DZ 2020	★			★	★	★	★	★	6
Huang H 2020	★			★	★	★	★	★	6
Ji D 2020	★			★	★	★	★	★	6
Lian J 2020	★	★		★	★★	★	★	★	8
Liu F 2020	★	★		★	★	★	★	★	7
Qu XK 2020	★			★	★	★	★	★	6
Shi J 2020	★			★	★★	★	★	★	7
Xia WG 2020	★	★		★	★★	★	★	★	8
Xiao Q 2020	★			★	★	★	★	★	6
Yang MB 2020	★			★	★	★	★	★	6
Yang Q 2020	★			★	★	★	★	★	6
Yao KT 2020	★			★	★	★	★	★	6
Zhang HT 2020	★			★	★	★	★	★	6
Retrospective cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Tian JX 2020	★	★	★	★	★★	★		★	8

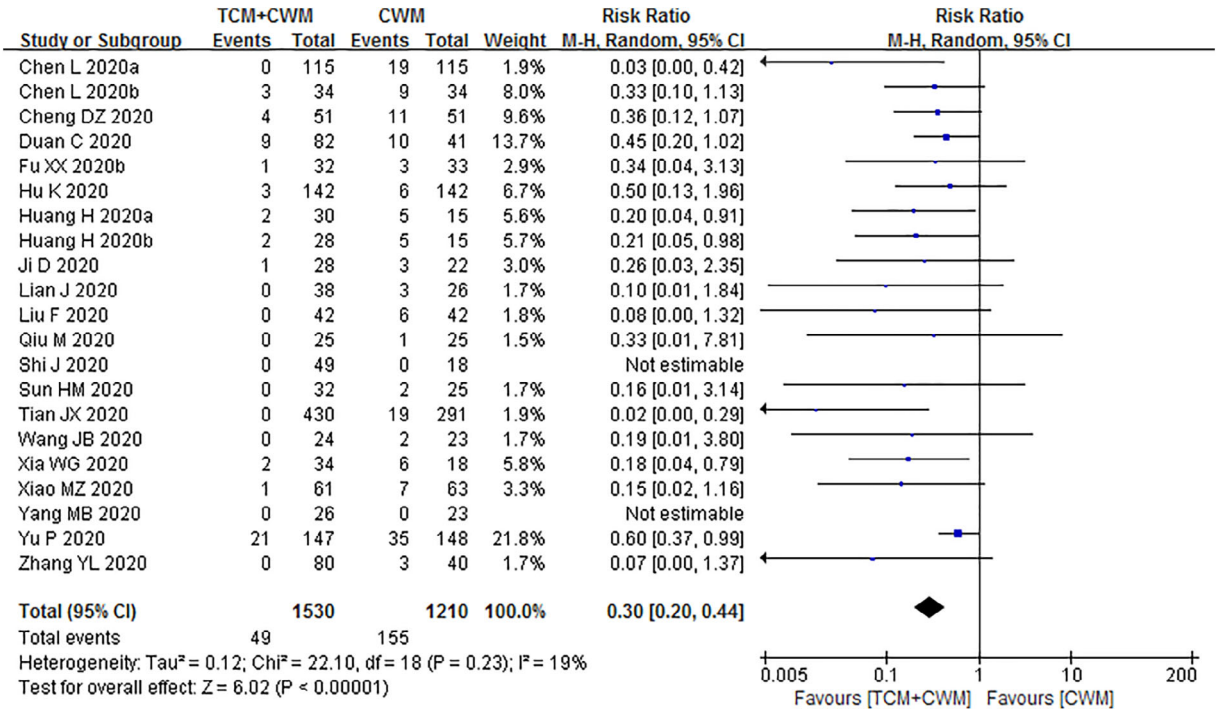

FIGURE 3 Rate of disease progression of patients with COVID-19 between TCM + CWM group and CWM group

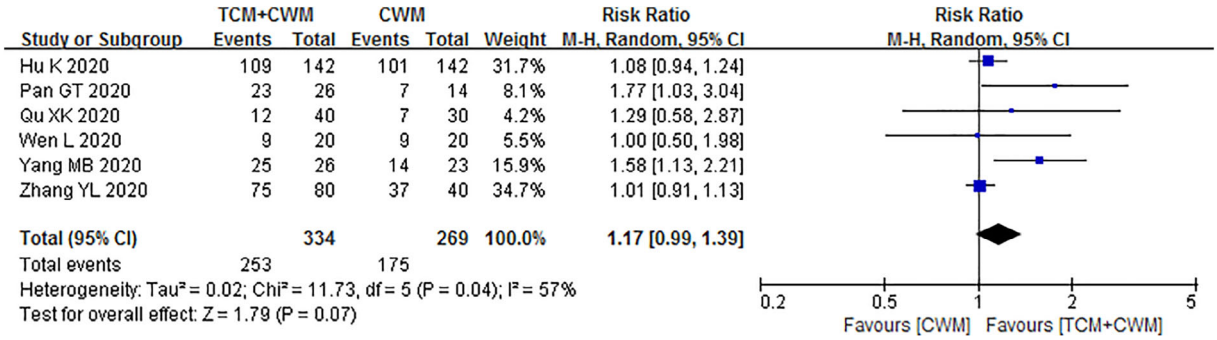

FIGURE 4 Negative conversion rate of nucleic acid of patients with COVID-19 between TCM + CWM group and CWM group

3.3.7 | Main peripheral blood indexes

The main peripheral blood indexes are summarized in Table 3. The effect of TCM on white blood cell count and lymphocyte count was evaluated in 10 (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Fu et al., 2020a, 2020b; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; Li & Zhang, 2020; Wen et al., 2020; Xiao, Jiang, et al., 2020; Yu et al., 2020) and 10 studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Fu et al., 2020a, 2020b; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; Wen et al., 2020; Xiao, Tian, et al., 2020; Yang, Sun, et al., 2020; Yu et al., 2020), respectively. Meta-analysis showed a significant improvement of WBC (MD = 0.77, 95% CI = [0.47, 1.06], I^2 = 91%, p < .0001) and LYM (MD = 0.22, 95% CI = [0.12, 0.33], I^2 = 93%, p < .0001) in TCM + CWM group. Sensitivity analysis and subgroup analysis of the main peripheral blood index based on study type and disease severity showed the stability of our results.

3.3.8 | Length of stay

Nine studies (Chen, Chen, et al., 2020; Chen, Liu, et al., 2020; Huang, Tan, et al., 2020; Huang, Wang, et al., 2020; Li & Zhang, 2020; F. Liu, 2020; Shi et al., 2020; Xia et al., 2020; Yang, Sun, et al., 2020) reported length of stay. Comparing with the CWM group, patients in the TCM + CWM group had a shorter

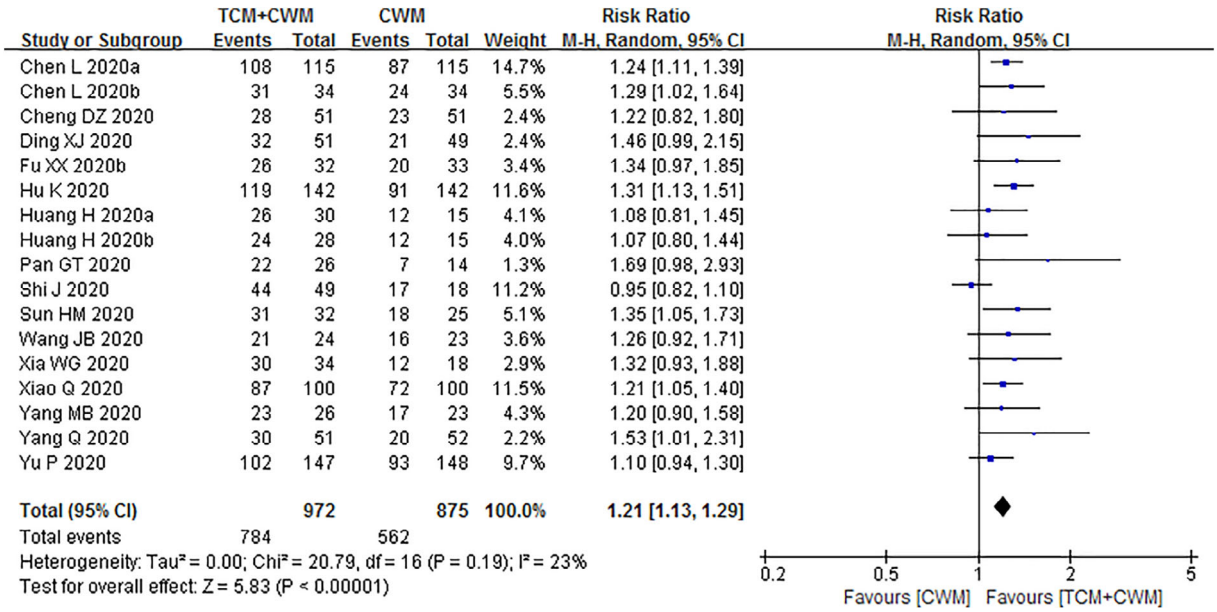

FIGURE 5 Improvement rate of chest CT of patients with COVID-19 between TCM + CWM group and CWM group

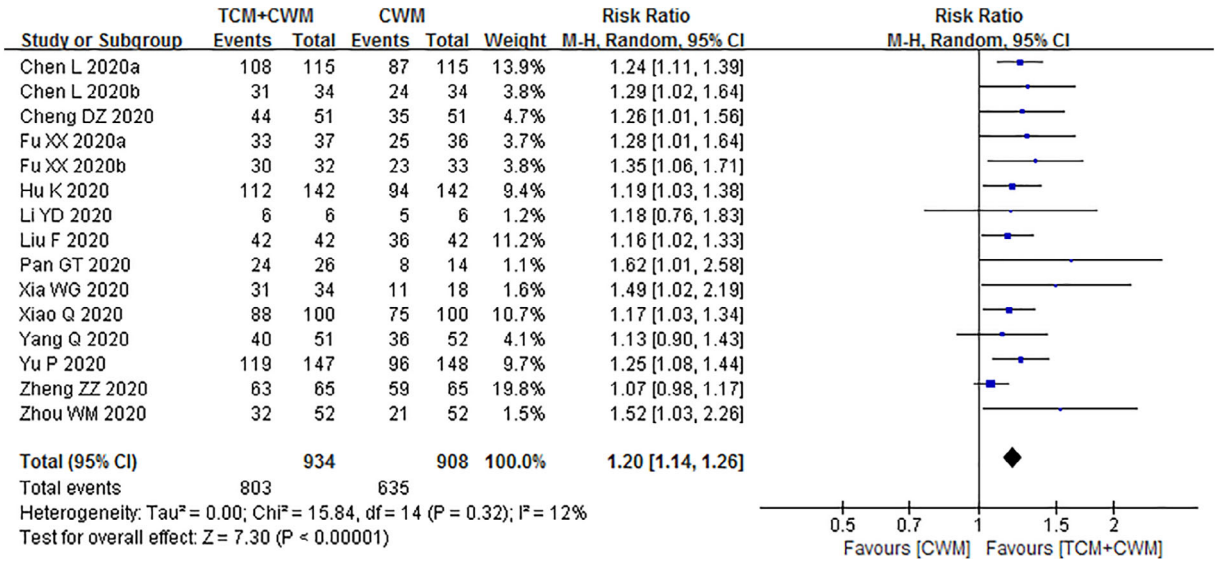

FIGURE 6 Total effective rate of patients with COVID-19 between TCM + CWM group and CWM group

hospital stay with a statistical significance (MD = -2.98, 95% CI = [−5.48, 0.48], $I^2 = 96\%$, $p = .02$). Sensitivity analysis showed the stability of our result (Table 3).

3.4 | Publication bias

We assessed publication bias for primary outcome indicators which exceeded 10 articles. These outcome measures include total effective rate, improvement rate of chest CT, rate of disease progression and adverse events. The funnel plots suggested a mild publication bias in total effective rate, improvement rate of chest CT and incidence of adverse events. A severe publication bias was observed in rate of disease progression (Figure 8).

3.5 | Subgroup analysis

We performed a subgroup analysis of the total effective rate based on study type and disease severity. The results of the subgroup

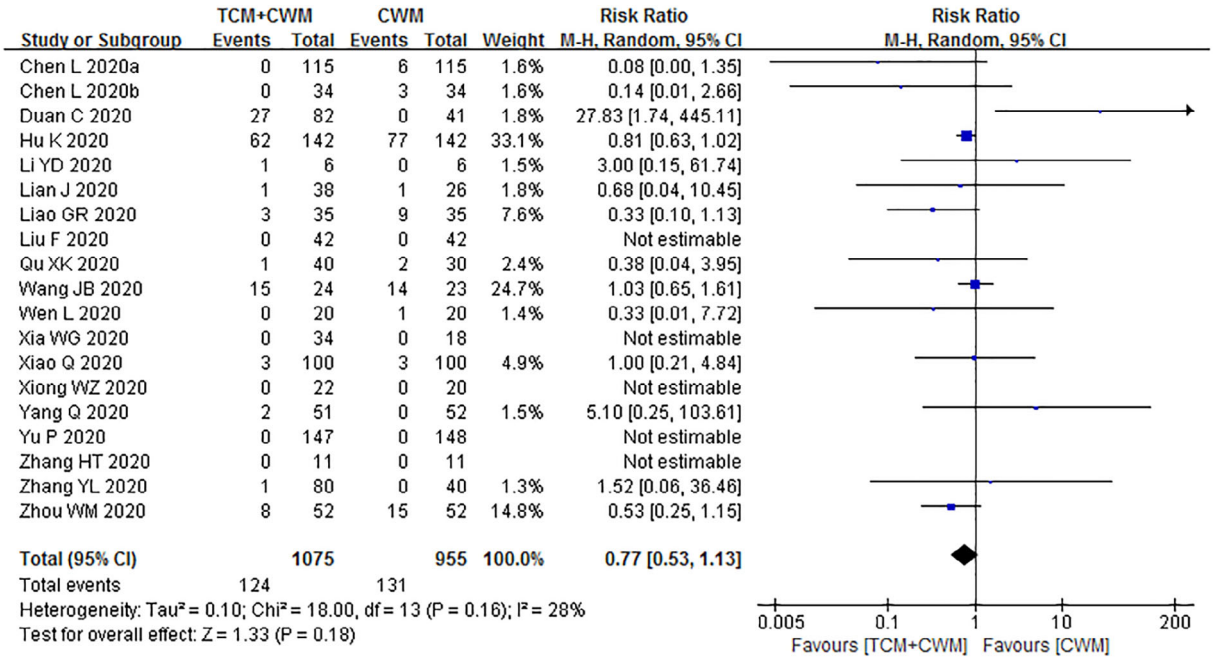

FIGURE 7 Incidence of adverse events of patients with COVID-19 between TCM + CWM group and CWM group

TABLE 3 Comparison of some second outcomes between TCM group and CWM group

Outcome measure	Number of study	Sample size		Statistical method	I^2	Effect value	*p*-value
		TCM	CWM				
Fever relief rate	13	390	259	RR, random, 95%	86%	1.20 [1.05, 1.37]	.008
Fatigue relief rate	11	323	247	RR, random, 95%	53%	1.31 [1.13, 1.52]	.0004
Cough relief rate	11	432	366	RR, random, 95%	59%	1.35 [1.14, 1.59]	.0003
Time to fever relief	11	383	343	MD, random, 95%CI	54%	−1.54 [−1.91, −1.17]	<.00001
Time to fatigue relief	8	262	219	MD, random, 95%CI	81%	−1.50 [−2.19, −0.81]	<.0001
Time to cough relief	8	354	313	MD, random, 95%CI	84%	−1.96 [−2.88, −1.04]	<.0001
WBC	10	549	522	MD, random, 95%CI	91%	0.77 [0.47, 1.06]	<.00001
LYM	10	520	491	MD, random, 95%CI	93%	0.22 [0.12, 0.33]	<.0001
Length of stay	9	389	315	MD, random, 95%CI	96%	−2.98 [−5.48, −0.48]	.02

analyses revealed more effective outcomes in the integrated medicine than the control group. Detailed results of the analyses are shown in Table 4.

3.6 | Quality of evidence

The quality of evidence from RCTs was low (total effective rate, negative conversion rate of nucleic acid, rate of disease progression, and incidence of adverse events) to moderate (improvement rate of chest CT). The quality of evidence from observational studies was very low. The overall quality of evidence was low to moderate (Table 5).

4 | DISCUSSION

TCM had been used to treat and prevent infectious diseases for thousands of years in China. Since the outbreak of COVID-19, TCM treatment has been widely used and achieved great success. RCTs and observational studies of TCM combined with CWM treatment for COVID-19 were conducted throughout the country and had shown significant clinical effectiveness. This updated systematic review and meta-analysis including 19 RCTs and 16 observational studies evaluated comprehensively the efficacy and safety of TCM combined with CWM for COVID-19 treatment. Comparing with CWM alone, integrated TCM and CWM could improve overall efficiency without increasing the incidence of adverse events.

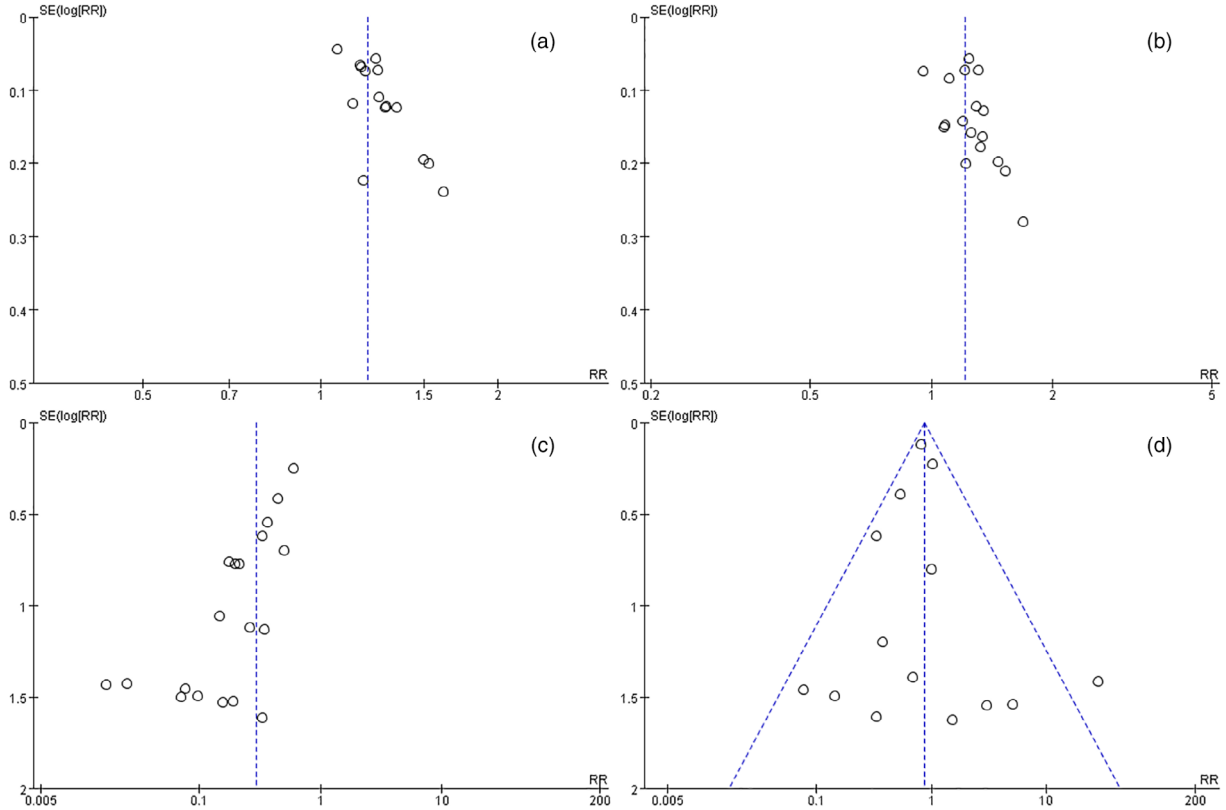

FIGURE 8 Funnel plot of total effective rate (a), improvement rate of chest CT (b), rate of disease progression (c) and incidence of adverse events (d)

TABLE 4 Subgroup analyses of the total clinical effectiveness

Subgroup	Number of study	Sample size		Statistical method	I^2	Effect value	*p*-value
		TCM	CWM				
Study type							
RCT	8	507	496	OR, random, 95%	0	2.45 [1.80, 3.34]	<.00001
CCT	7	427	412	OR, random, 95%	0	3.09 [2.08, 4.59]	<.00001
Disease severity							
Mild or ordinary case	9	710	711	OR, random, 95%	0	2.65 [2.04, 3.44]	<.00001
Severe or critical case	3	83	72	OR, random, 95%	31	2.37 [1.11, 5.04]	.03
Mixed case	3	141	125	OR, random, 95%	0	5.87 [2.08, 16.51]	.0008

The commonly used dosage formulation was Chinese patent medicine and Chinese herbal decoction derived from medical plants. The main mechanisms of medical plants or their extract treatment for COVID-19 were to inhibit viral replication and enhance the patient's immunity. For example, the aqueous extract of *Houttuynia cordata*, the major constituent of Lianhua Qingwen capsule, inhibits two key proteins of SARS-CoV, namely chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp). The extract also increased CD4+ and CD8+ cell count in test animals suggesting its immune-stimulatory effect that can be an additional advantage on top of its role in slowing down viral replication (Lau et al., 2008). The extracts of *Rheum officinale*, which is one of the main components of Lianhua Qingke Granule, were found to inhibit the interaction of SARS-CoV (S) protein and ACE2 (functional receptor to infect host cells) (Islam et al., 2020). In addition, many functional food plants with anti-viral and immunomodulatory properties against SARS-CoV-2 including garlic, ginger, and tea and so on not only could inhibit viral replication but also enhance innate and adaptive immune responses (Upadhyay et al., 2020; Yang, Zhang, Huang et al., 2020). Concerns over the use of botanical drugs and supplements were immune-stimulating herbs may initiate a cytokine storm, resulting in acute respiratory distress syndrome (ARDS), systemic coagulation and

TABLE 5 Summary of findings

Traditional Chinese medicine compared to conventional western medicine for COVID-19					
Patient or population: Patients with COVID-19; setting: Intervention: TCM; comparison: CWM					
				Anticipated absolute effects	
Outcomes	**No. of participants (studies) follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Risk with CWM**	**Risk difference with TCM**
Total effective rate	1,003 (8 RCTs)	⨁⨁◯◯ LOW[a,b]	RR 1.24 (1.15 to 1.33)	667 per 1,000	160 more per 1,000 (100 more to 220 more)
Negative conversion rate of nucleic acid	484 (4 RCTs)	⨁⨁◯◯ LOW[b,c]	RR 1.07 (0.93 to 1.24)	713 per 1,000	50 more per 1,000 (50 fewer to 171 more)
Improvement rate of chest CT	888 (7 RCTs)	⨁⨁⨁◯ MODERATE[b]	RR 1.27 (1.16 to 1.38)	613 per 1,000	165 more per 1,000 (98 more to 233 more)
Rate of disease progression	1,165 (9 RCTs)	⨁⨁◯◯ LOW[a,d]	RR 0.45 (0.31 to 0.65)	128 per 1,000	70 fewer per 1,000 (88 fewer to 45 fewer)
Incidence of adverse events	1,137 (10 RCTs)	⨁⨁◯◯ LOW[a,b]	RR 0.92 (0.75 to 1.13)	220 per 1,000	18 fewer per 1,000 (55 fewer to 29 more)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, Confidence interval; RR, Risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

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.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Lack of blinding, lack of allocation concealment, unclear reporting bias.

[b]Mild publication bias.

[c]Small sample size.

[d]Severe publication bias.

thrombus formation (coagulopathy) and sepsis-related multipleorgan failure, because patients infected with SARS-CoV-2 had higher concentrations and circulating levels of various cytokine than those in healthy adults (Huang et al., 2020). But a great number of clinical studies showed that the immunomodulatory botanicals can improve parameters of the immune response, without evidence of risk of overstimulation, and even may have the potential to decrease the risk of a cytokine storm (Brendler et al., 2020).

In this review, there are several highlights deserved our attention. First, this review included more clinical trials, especially including 19 RCTs, which greatly enhanced the credibility of the evidence. Second, new studies included in this review provided new TCM formulations for the treatment of COVID-19, including Huoxiang Zhengqi dropping pills, Xuanfei Baidu decoction, Oral honeysuckle, Diammonium glycyrrhizinate, Xuebijing injection, etc., which are not available in the previous literature. Third, though the CCTs and retrospective study may not contribute much to evidence compared with RCTs, the treatment regimen they used could provide an option for follow-up of high-quality RCTs.

Although our study can demonstrate the effectiveness of TCM combined with CWM on the treatment of COVID-19, there were several limitations of this systematic review. First, patients infected with SARS-CoV-2 had higher concentrations and circulating levels of various cytokine than those in healthy adults (Huang et al., 2020). However, only four clinical trials detected cytokine levels, including IL-6, IFN-γ (Ding et al., 2020), CD4, CD8, CD4/CD8, CD45 (Fu et al., 2020b), IL-6 (Huang et al., 2020), IL-4, TNF-α, CD3, CD4, CD8, CD4/CD8 (Zhou et al., 2020). The diversity of cytokines compromised the statistical significance of the data. Second, because of the time required to develop antibody detection kits, none of the clinical trials detected antibody levels in patients. In addition, most of the clinical trials had flaws in the methodological design, including randomization, concealment of allocation, and inadequate reports on blinding. The follow-up in included studies was insufficient. Only studies published in Chinese and English were searched, and there may be language bias. And some ongoing or unpublished trials were not included, which may lead to potential publication bias.

5 | CONCLUSIONS

In summary, the results of this review confirmed that integrated TCM and CWM was a potential treatment option to improve the clinical symptoms of COVID-19 patients without increasing the incidence of adverse events. High-quality RCTs are needed to further evaluate the effect of integrated medicine for COVID-19.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (NSFC81870005); the Natural Science Foundation of the

Jiangsu Higher Education Institutions of China (18KJA180003); the Project of Xuzhou Applied and Basic Research (KC18009, KC20102); and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). We thank Dr. Yi Guo (Department of Laboratory Medicine, the Affiliated Hospital of Xuzhou Medical University) for his constant support and advice.

CONFLICT OF INTEREST

The authors declared that there was no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

Fei Jiang: Searched the literature, conducted data analysis and drafted the manuscript. **Nana Xu**: Screened the articles and collected the data. **Yanxi Zhou**: Assessed the methodological quality of included studies. **Jinxing Song, Jinjuan Liu, and Hong Zhu**: Checked the data. **Jihong Jiang and Rongpeng Li**: Designed the study and participated in manuscript revision.

ETHICS STATEMENT

Ethical approval and patient consent are not required since this is an overview based on published studies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Fei Jiang https://orcid.org/0000-0002-4462-0549

REFERENCES

Brendler, T., Al-Harrasi, A., Bauer, R., Gafner, S., Hardy, M. L., Heinrich, M., … Williamson, E. M. (2020). Botanical drugs and supplements affecting the immune response in the time of COVID-19: Implications for research and clinical practice. *Phytotherapy Research*, *35*, 3013–3031. https://doi.org/10.1002/ptr.7008

Chen, L., Chen, Y. G., Cheng, Z. Q., Liu, F., Wu, J. H., Xia, Y., & Sheng, B. (2020). Retrospective analysis on clinical efficacy of Ganlu Xiaodu decoction combined with Western medicine in treatment of common COVID-19 patients. *Chinese Journal of Experimental Traditional Medical Formulae*, *26*(19), 60–67. https://doi.org/10.13422/j.cnki.syfjx.20202011

Chen, L., Liu, F., Wu, J. H., Song, H. Y., Xia, J. S., Sheng, B., & Chen, Y. G. (2020). Clinical efficacy of Shufeng Jiedu capsule combined with western medicine in treatment of common COVID-19 patients by retrospective analysis. *Chinese Journal of Experimental Traditional Medical Formulae*, *36*(16), 16–20. https://doi.org/10.13422/j.cnki.syfjx.20201628

Cheng, D. Z., Wang, W. J., Li, Y., Wu, X. D., Zhou, B., & Song, Q. Y. (2020). Efficacy analysis on 51 cases of COVID-19 treated with traditional Chinese medicine Lianhua Qingwen: A multi-center retrospective study. *Tianjin University of Traditional Chinese Medicine*, *37*(5), 509–516. https://doi.org/10.11656/j.issn.1672-1519.2020.05.06

Ding, X. J., Zhang, Y., He, D. C., Zhang, M. Y., Tan, Y. J., Yu, A. R., … Liu, L. (2020). Clinical effect and mechanism of Qingfei Touxie Fuzheng recipe in the treatment of Novel Coronavirus pneumonia. *Herald of Medicine*, *39*(5), 640–644. https://doi.org/10.3870/j.issn.1004-0781.2020.05.012

Duan, C., Xia, W. G., Zhen, C. J., Sun, G. B., Li, Z. L., Li, Q. L., … Liu, Q. Q. (2020). Clinical observation on the treatment of mild COVID-19 with Jinhua Qinggan Granules combined with conventional western medicine. *Journal of Traditional Chinese Medicine* *61*(17), 1473–1477. https://doi.org/10.13422/j.cnki.syfjx.20201314

Fu, X. X., Lin, L. P., & Tan, X. H. (2020a). Clinical observation on effect of Toujie Quwen granules in treatment of COVID-19. *Chinese Journal of Experimental Traditional Medical Formulae*, *26*(12), 44–48. https://doi.org/10.13422/j.cnki.syfjx.20201314

Fu, X. X., Lin, L. P., & Tan, X. H. (2020b). Clinical study on 37 case of COVID-19 treated with integrated traditional Chinese and Western Medicine. *Traditional Chinese Drug Research & Clinical Pharmacology*, *31*(5), 600–604. https://doi.org/10.19378/j.issn.1003-9783.2020.05.016

Hu, K., Guan, W. J., Bi, Y., Zhang, W., Li, L. J., Zhang, B. L., … Zhong, N. S. (2020). Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. *Phytomedicine*, *85*, 153242. https://doi.org/10.1016/j.phymed.2020.153242

Huang, C. L., Wang, Y. M., Li, X. W., Ren, L. L., Zhao, J. P., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Huang, H., Tan, S. C., Zuo, X. H., Jin, J. S., Zhao, Y., & Ding, Y. (2020). Clinical efficacy analysis and TCM syndrome characteristics of 72 patients with COVID-19. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, *29*, 2395–2483. https://doi.org/10.3969/j.issn.1008-8849.2020.22.001

Islam, M. T., Sarkar, C., El-Kersh, D. M., Jamaddar, S., Uddin, S. J., Shilpi, J. A., & Mubarak, M. S. (2020). Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. *Phytotherapy Research*, *34*(10), 2471–2492. https://doi.org/10.1002/ptr.6700

Ji, D., Feng, P., & Fei, X. Y. (2020). Retrospective study of clinical efficacy of integrated Chinese and western medicine in treatment of COVID-19. *ShanDong ZhongYi ZaZhi*, *39*(7), 645–653. https://doi.org/10.16295/j.cnki.0257-358x.2020.07.001

Lau, K. M., Lee, K. M., Koon, C. M., Cheung, C. S., Lau, C. P., Ho, H. M., & Fung, K. P. (2008). Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *Journal of Ethnopharmacology*, *118*, 79–85. https://doi.org/10.1016/j.jep.2008.03.018

Li, Y., & Zhang, W. (2020). Evaluation on the clinical effect of traditional Chinese medicine and western medicine regimens on COVID-19. *Guangming Journal of Chinese Medicine*, *35*(9), 1273–1275. https://doi.org/10.1016/j.biopha.2017.07.118

Lian, J., Zhang, S. J., Li, G. L., Shang, D., Wang, Q. Y., Xu, L. S., … Liu, X. X. (2020). Retrospective analysis of 38 cases with COVID-19 treated with integrated traditional Chinese and western medicine. *Journal of Traditional Chinese Medicine*, *61*(24), 2126–2130. https://doi.org/10.13288/j.11-2166/r.2020.24.003

Liao G. R. (2020). Study on efficacy and safety of TCM decoction in patients with COVID-19. *International Infectious Diseases*, *9*(2), 353.

Liu, F. (2020). *Clinical observation of 42 cases with COVID-19 treated with integrated traditional Chinese and western medicine*. Beijing, China: National Science and Technology Revitalization of urban Economic Research Association.

Liu, M., Gao, Y., Yuan, Y., Yang, K., Shi, S., Zhang, J., & Tian, J. (2020). Efficacy and safety of integrated traditional Chinese and Western medicine for Corona Virus Disease 2019 (COVID-19): A systematic review and meta-analysis. *Pharmacological Research*, *158*, 104896. https://doi.org/10.1016/j.phrs.2020.104896

Luo, X. F., Ni, X. J., Lin, J. H., Zhang, Y. D., Wu, L., Huang, D. H., … Lin, L. (2020). The add-on effect of Chinese herbal medicine on COVID-19: A

systematic review and meta-analysis. *Phytomedicine*, *85*, 153282. https://doi.org/10.1016/j.phymed.2020.153282

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*, 264–269.

News Conference of the State Council Information Office. (2020). *Yu Yanhong briefing the important role of TCM in COVID-19 containment and treatment*. Beijing, China: State Council Information Office.

Pan, G. T., Du, C., Liu, Y. H., Liu, Y., Cheng, Y. F., Han, F., … Yang, S. L. (2020). Integrated traditional Chinese and western medicine in the treatment of 40 cases of critical patients with COVID-19. *Acta Medicinae Universitatis Science of Technologiae Huazhong*, *49*(2), 202–207. https://doi.org/10.3870/j.issn.1672-0741.2020.02.016

Pang, W., Liu, Z., Li, N., Li, Y., Yang, F., Pang, B., … Zhang, J. (2020). Chinese medical drugs for coronavirus disease 2019: A systematic review and meta-analysis. *Integrative Medicine Research*, *9*(3), 100477. https://doi.org/10.1016/j.imr.2020.100477

Qiu, M., Li, Q. T., Zhu, D. P., Wang, C. H., Sun, Q. Z., Qian, C. F., … Li, Y. P. (2020). Efficacy observation of maxing Xuanfei Jiedu decoction on moderate COVID-19 patients. *Journal of Emergency in Traditional Chinese Medicine*, *39*(7), 1129–1132. https://doi.org/10.3969/j.issn.1004-745X.2020.07.001

Qu, X. K., Hao, S. L., Ma, J. H., Wei, G. Y., Song, K. Y., Tang, C., … Du, W. J. (2020). Observation on the clinical effect of Shufeng Jiedu capsule combined with Arbidol Hydrochloride Capsules in the treatment of COVID-19. *Zhong Cao Yao*, *51*, 1167–1170. https://doi.org/10.7501/j.issn.0253-2670.2020.05.011

Shi, J., Yang, Z. G., Ye, C., Chen, S. S., Lu, Y. F., Lv, Y., … Chen, X. R. (2020). Clinical observation of 49 cases of non-critical COVID-19 treated by integrated traditional Chinese and western medicine in Shanghai. *ShangHai ZhongYi ZaZhi*, *54*(4), 30–35. https://doi.org/10.16305/j.1007-1334.2020.04.095

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., & Boutron, I. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*, l4898. https://doi.org/10.1136/bmj.l4898

Sun, H. M., Xu, F., Zhang, L., Wei, C., Chen, J. Y., Wang, Q. X., & Jia, Z. H. (2020). Study on clinical efficacy of Lianhua Qingke granule in treatment of mild and ordinary COVID-19. *Chinese Journal of Experimental Traditional Medical Formulae*, *26*(14), 29–34. https://doi.org/10.13422/j.cnki.syfjx.20201438j

Tian, J. X., Yan, S. Y., Wang, H., Zhang, Y., Zheng, Y. J., Wu, H. R., … Tong, X. L. (2020). Hanshiyi formula, a medicine for Sars-CoV2 infection in China, reduced the proportion of mild and moderate COVID-19 patients turning to severe status: A cohort study. *Pharmacological Research*, *161*, 105127. https://doi.org/10.1016/j.phrs.2020.105127

Upadhyay, S., Tripathi, P. K., Singh, M., Raghavendhar, S., Bhardwaj, M., & Patel, A. K. (2020). Evaluation of medicinal herbs as a potential therapeutic option against SARS-CoV-2 targeting its main protease. *Phytotherapy Research*, *34*(12), 3411–3419. https://doi.org/10.1002/ptr.6802

Wang, J. B., Wang, Z. X., Jing, J., Zhao, P., Dong, J. H., Zhou, Y. F., … Xiao, X. H. (2020). Exploring an integrative therapy for treating COVID-19: A Randomized Controlled Trial. *Chinese Journal of Integrative Medicine*, *26*(9), 648–655. https://doi.org/10.1007/s11655-020-3426-7

Wang, Y. L., Yang, X. D., Liu, Y. P., Zhang, J., Feng, Y. F., Shang, L., … He, X. J. (2020). Preliminary clinical effect analysis of the treatment of novel coronavirus pneumonia by internal administration of traditional Chinese medicine plus fumigation and absorption combined with super dose of vitamin C in treating NOVID-19. *Journal of Xi'an Jiaotong University (Medical Science)*, *41*(6), 931–935. https://doi.org/10.7652/jdyxb202006023

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2003). *The Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses*. Retrieved from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Wen, L., Zhou, Z. G., Jiang, D. X., & Huang, K. (2020). Effect of Xuebijing injection on inflammatory markers and disease outcome of coronavirus disease 2019. *Chin Crit Care Med*, *32*(4), 426–429. https://doi.org/10.3760/cma.j.cn121430-20200406-00386

Xia, W. G., An, C. Q., Zhen, C. J., Zhang, J. X., Huang, M., Wang, Y., … Zhang, B. L. (2020). Clinical study on 34 case of COVID-19 treated with integrated traditional Chinese and Western Medicine. *Journal of Traditional Chinese Medicine*, *61*(5), 375–382. https://doi.org/10.13288/j.11-2166/r.2020.05.002

Xiao, M. Z., Tian, J. X., Zhou, Y. N., Xu, X., Min, X. J., Lv, Y., … Tong, X. L. (2020). Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: A randomized controlled trial. *Pharmacological Research*, *161*, 105126. https://doi.org/10.1016/j.phrs.2020.105126

Xiao, Q., Jiang, Y. J., Wu, S. S., Wang, Y., An, J., Xu, W. P., & Wu, J. J. (2020). Value analysis of Shufeng Jiedu Capsule combined with arbidol hydrochloride capsules in the treatment of mild cases of COVID-19. *Journal of Emergency in Traditional Chinese Medicine*, *29*(5), 756–758. https://doi.org/10.3969/j.issn.1004-745X.2020.05.002

Xiong, W. Z., Wang, G., Du, J., & Ai, W. (2020). Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: A pilot randomized clinical trial. *Integrative Medicine Research*, *9*(3), 100489. https://doi.org/10.1016/j.imr.2020.100489

Xiong, X., Wang, P., Su, K., Cho, W. C., & Xing, Y. (2020). Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis. *Pharmacological Research*, *160*, 105056. https://doi.org/10.1016/j.phrs.2020.105056

Yang, F., Zhang, Y., Tariq, A., Jiang, X. L., Ahmed, Z., Zhang, Z. H., … Bussmann, R. W. (2020). Food as medicine: A possible preventive measure against coronavirus disease (COVID-19). *Phytotherapy Research*, *34*(12), 3124–3136. https://doi.org/10.1002/ptr.6770

Yang, M. B., Dang, S. S., Huang, S., Li, Y. J., & Guo, Y. L. (2020). Multicenter clinical observation of Reyanning mixture in treatment of novel coronavirus pneumonia. *Chinese Journal of Experimental Traditional Medical Formulae*, *26*(14), 7–14. https://doi.org/10.13422/j.cnki.syfjx.20201321

Yang, Q., Sun, Q. G., Jiang, B., Xu, H. J., Luo, M., Xie, P., … Cong, Z. W. (2020). Retrospective clinical study on treatment of COVID-2019 patients with integrated traditional Chinese and Western medicine. *Zhong Cao Yao*, *51*(8), 2050–2054. https://doi.org/10.7501/j.issn.0253-2670.2020.08.009

Yao, K. T., Liu, M. Y., Li, X., Huang, J. H., & Cai, H. B. (2020). Retrospective clinical analysis on treatment of novel coronavirus-infected pneumonia with traditional Chinese medicine Lianhua Qingwen. *Chinese Journal of Experimental Traditional Medical Formulae*, *26*(11), 8–12. https://doi.org/10.13422/j.cnki.syfjx.20201099

Yu, P., Li, Y. Z., Wan, S. B., & Wang, Y. (2020). Clinical observation of Lianhua Qingwen granule combined with Abidor in the treatment of mild COVID-19. *Chinese Pharmaceutical Journal*, *55*(12), 1042–1045. https://doi.org/10.11669/cpj.2020.12.014

Zhang, H. T., Huang, M. X., Liu, X., Zheng, X. C., Li, X. H., Chen, G. Q., … Hong, Z. S. (2020). Evaluation of the adjuvant efficacy of natural herbal medicine on COVID-19: A retrospective matched case-control study. *The American Journal of Chinese Medicine*, *48*(4), 779–792. https://doi.org/10.1142/S0192415X20500391

Zhang, K., Tian, M. L., Zeng, Y., Wang, L. W., Luo, S., Xia, W., … Zha, Y. (2020). The combined therapy of a traditional Chinese medicine formula and Western medicine for a critically ill case infected with COVID-19. *Complementary Therapies in Medicine*, *52*, 102473. https://doi.org/10.1016/j.ctim.2020.102473

Zhang, Y. L., Lei, L., Xu, Y., Wei, D. R., & Hu, F. (2020). Clinical efficacy of Jinyinhua oral liquid in the treatment of 80 patients with coronavirus disease 2019. *China Pharmaceuticals*, *29*(9), 23–26. https://doi.org/10.3969/j.issn.1006-4931.2020.09.006

Zheng, Z. Z., Bai, Z. G., Li, C. J., Ge, S. P., Luo, Y., & He, G. D. (2020). Observation on the effect of TCM syndrome differentiation on COVID-19. *Medical Journal of Communication*, *34*(2), 117–118. https://doi.org/10.19767/j.cnki.32-1412.2020.02.005

Zhou, W. M., Zhao, F. M., Li, B. L., & Tian, Z. Q. (2020). Clinical value of glycyrrhizinate in the treatment of patients with common new coronavirus pneumonia. *BingDu XueBao*, *36*(2), 160–164. https://doi.org/10.13242/j.cnki.bingduxuebao.003679

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., … Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *The New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/NEJMoa2001017

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Jiang, F., Xu, N., Zhou, Y., Song, J., Liu, J., Zhu, H., Jiang, J., Xu, Y., & Li, R. (2021). 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. *Phytotherapy Research*, *35*(11), 5992–6009. https://doi.org/10.1002/ptr.7209