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Research article

Effectiveness of seven oral traditional Chinese medicines against mild or moderate COVID-19: An updated systematic review and network meta-analysis

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the outbreak of COVID-19 in Wuhan, China. As a highly infectious epidemic, SARS-CoV-2 rapidly evolves. Presently, COVID-19 coexists with humans, mainly with mild or moderate disease. The latest Guidelines for the Diagnosis and Treatment of COVID-19 (trial version of the 10th Edition) recommend several oral traditional Chinese medicines (TCMs) for treatment. This study aims to evaluate the evidence-based benefits of these TCMs as adjunctive therapies to conventional western medicine (CWM) for patients with mild or moderate COVID-19.

Methods: We conducted a systematic review and meta-analysis adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, utilizing the PRISMA checklist. We searched PubMed, Cochrane Library, Embase, CNKI, and Wan-Fang databases to retrieve randomized controlled trials and retrospective cohort studies of TCM in combination with CWM on the treatment of mild or moderate COVID-19 that were published as of December 25, 2023. A network meta-analysis using the frequency model was employed to evaluate the benefits of different interventions.

Results: A total of 30 eligible studies, enrolling 4144 participants, utilized 7 marketed oral TCMs in China. Compared with CWM alone, the integration of TCMs with CWM can significantly reduce severe conversion rate. This combined approach also enhances the clinical effective rate, shortens the negative conversion time of nucleic acid, and improves both symptoms and blood biochemical markers in patients. The network meta-analysis provided preliminary evidence of the superiority of specific TCMs for various outcomes: Qingfei Paidu for raising the CT improvement rate and clinical effective rate, and shortening the negative conversion time of nucleic acid; Huashi Baidu for reducing severe conversion and improving cough; Xuanfei Baidu for improving fatigue; Jinhua Qinggan for improving fever; Lianhua Qingwen for shortening the recovery time of fatigue and cough; and Shufeng Jiedu for shortening the recovery time of fever.

Conclusions: TCM in combination with CWM may be beneficial for patients with mild or moderate COVID-19. Each TCM may have distinct benefits in COVID-19.

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was the major culprit for COVID-19 in Wuhan, China. Four years later, the COVID-19 pandemic continues to impact global health. WHO has reported 772, 838, 745 COVID-19-related cases and 6,988,697 deaths as of December 17, 2023 (https://covid19.who.int/).

Infection with SARS-CoV-2 is highly infectious and changes rapidly, falling into the categories of epidemic disease. In the early stages of the pandemic, the lack of effective chemical drugs led to the widespread administration of traditional Chinese medicine (TCM) in China. TCM demonstrated a significant protective role against COVID-19 during this period. Despite the gradual popularization of chemical and biological agents, TCM continues to offer unique benefits for COVID-19 treatment. On March 31, 2022, the importance of integrated herbal formulations and Western medicine for COVID-19 was explicitly emphasized by the World Health Organization (WHO), and the members of the WHO were encouraged to learn from the Chinese model. Currently, the use of TCM is promoted in many countries for prophylaxis and treatment of COVID-19 [1]. According to the International Clinical Trials Registry Platform, there were numerous clinical trials related to TCM used for prophylaxis and cure of COVID-19. Various studies have found that TCM combined with conventional western medicine (CWM) can improve patients' symptoms of fatigue, fever, and cough [2]. Boli Zhang, a renowned Chinese academician, indicated that TCM has transformed from a participatory character to an indispensable workhorse in COVID-19 prevention and treatment. The latest Guidelines for the Diagnosis and Treatment of COVID-19 (trial version of the 10th Edition) recommended six TCMs: Lianhua Qingwen (LHQW), Qingfei Paidu (QFPD), Jinhua Qinggan (JHQG), Shufeng Jiedu (SFJD), Xuanfei Baidu (XFBD), and Huashi Baidu (HSBD) for the prophylaxis and treatment of mild or moderate cases. They were all approved for marketing in China due to their good therapeutic effects. Additionally, Toujie Quwen (TJQW) has shown a definite beneficial effect on patients with mild cases, prevented cases of the mild-to-severe disease, and is popularly known as Pneumonia Prescription No. 1. Therefore, in this study we also considered the inclusion of TJQW.

In this review, we identified randomized controlled trials (RCTs) involving the seven aforementioned TCMs and included retrospective cohort studies (RCSs) to ensure comprehensiveness. Previous reports on this topic had certain limitations. First, previous network meta-analyses contained only 10 RCTs, whereas many studies have been published over the past three years. In our study, we included a total of 20 RCTs. Second, the TCMs included in the prior meta-analysis may involve injections, however, the seven TCMs included in our study have been marketed in China and the routes of administration are oral, which are easy to use and have good accessibility. Third, previous studies lacked an analysis of symptom recovery time, so we compared the different TCMs regarding symptom recovery to offer refined treatments for COVID-19 patients. Fourth, the trials that directly compared different TCMs are relatively rare, dispersed over a variety of conditions, and difficult to identify. Hence, it is challenging to use traditional meta-analysis to comprehensively evaluate clinical evidence on different TCMs for COVID-19. We aimed to summarize the available evidence on TCMs against COVID-19 using network meta-analysis systematically. To our knowledge, our analysis was the best suited to the current epidemic state, including commonly used TCMs. At present, COVID-19 coexists with humans, mainly with mild or moderate disease. By focusing the treatment regiments of previous studies and focusing on patients with mild and moderate symptoms, we anticipate that this network meta-analysis will provide reliable and accurate information on COVID-19 treatment.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a PRISMA checklist [3]. We have registered this protocol in the International Prospective Register and endorsed it with a registration number (PROSPERO; CRD42023404679). Institutional review board approval was not required because all the data had been previously published and did not involve individual patient information.

2.1. Data sources and searches

Literature searches were conducted to retrieve RCTs and RCSs on the treatment of COVID-19 using TCM combined with CWM that were published as of December 25, 2023, in the PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, and Wan-Fang databases. To ensure a comprehensive collection of relevant studies, we also conducted additional searches. These included examining the reference lists of identified meta-analyses, performing manual searches of review references, related articles, grey literature, and unpublished studies on Clinical Trials.gov. The detailed search strategy is provided in the Appendix (Table S1).

2.2. Study selection

Two researchers independently reviewed the titles and abstracts of the RCTs and RCSs to exclude unrelated articles. These exclusions included reviews, case reports, animal studies, pharmacological experiments, editorials, letters, and opinion pieces. The full text of the remaining literature was then checked to identify eligible studies. In instances where one study overlapped with another, we included the more detailed or recent publication. If there was a disagreement, a third researcher was consulted for arbitration.

Criteria for study inclusion were as follows: 1) participants: patients with mild or moderate COVID-19 [4]; 2) study types: RCTs and RCSs on TCM for COVID-19, in any language; 3) interventions: the control group was CWM, including antiviral therapy, antimicrobials or other measures, while the experimental group received add-on of a TCM in combination with the CWM; 4) outcome indicators: primary outcomes included clinical effective rate, severe conversion rate, and negative conversion time (NCT) of nucleic acid, while the improvement of lung imaging on computed tomography (CT), improvement of main symptoms (fever, fatigue, cough), and blood

biochemical indicators, such as white blood cell (WBC), lymphocyte (LYM), and C-reactive protein (CRP) was included as secondary outcomes.

Criteria for study exclusion were as follows: 1) patients with suspected, severe, critical COVID-19 disease, or in convalescent recovery; 2) simultaneous use of more than one TCM; 3) self-controlled trials and non-control group studies; 4) age younger than 18 years.

Definitions of outcome measures were as follows: 1) clinical effective rate: clinical effectiveness is defined as the resolution of fever, significant improvement of respiratory symptoms, significant absorption of inflammation on lung imaging, and two consecutive negative nucleic acid tests on respiratory specimens; 2) severe conversion rate: severe conversion is defined as a patient who becomes sicker after treatment, requires transfer for treatment following a significant reduction in white blood cell or lymphocyte count on two or more consecutive routine blood tests, or shows significant progression of lung lesions by more than 50 % on imaging; 3) NCT of nucleic acid: the time from admission to the second negative conversion time; 4) CT improvement rate: reduction in the extent of lung lesions by 30 % or more on chest CT; 5) effective rates of symptoms (fever, fatigue, cough): the proportion of patients whose scores for fever, cough, and fatigue, calculated using the TCM syndrome quantification scale based on the "Guidelines for Clinical Research of New Chinese Medicines" decreased by 30 % or more, or whose symptoms significantly improved or disappeared after treatment; 6) Recovery time of symptoms (fever, fatigue, cough): the time until the symptoms disappear [5].

2.3. Data extraction and quality assessment

The following information was recorded: 1) basic information (first author's name, publication year, nationality, and study design); 2) basic patient characteristics (course of disease, number of patients, median age); 3) details of study intervention (treatment names and cycles); and 4) outcomes (clinical effective rate, severe conversion rate, symptoms [fever, cough, fatigue, chest tightness] improvement rate and recovery time, NCT of nucleic acid, CT improvement rate, and improvement in blood biochemical indicators [WBCs, LYMs, CRP]).

To assess the quality of the included studies, both reviewers used the modified Cochrane risk of bias tool (RoB 2.0) [6] for RCTs and the Newcastle-Ottawa Scale (NOS) [7] for non-randomized studies. The RoB 2.0 tool evaluates potential biases in five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. It provides an overall risk of bias judgment. Researchers categorize the risk of bias for each domain as "low risk," "some concerns," or "high risk." If all five domains are rated as low risk, the overall bias is low. If none are high risk but any are rated as some concerns, the overall bias is some concerns. If any domain is rated as high risk, or multiple domains are rated as some concerns with high impact, the overall bias is high. The NOS assesses non-randomized studies based on the selection of study groups, comparability of cohorts, and outcome assessment, using a star rating system. A maximum score of nine indicates higher quality. Scores of seven or more are considered high quality. By employing these tools, we ensured a rigorous and systematic quality assessment, thereby enhancing the robustness and credibility of our findings. When necessary, a third researcher helped reach consensus on methodological quality.

2.4. Data synthesis and analysis

Calculations and graphs were performed by Review Manager 5.3 and Stata 16.0 software.

Review Manager 5.3 was utilized to conduct the traditional meta-analysis of outcome measures and to draw forest maps. The results of RCTs and RCSs were analyzed separately. Odds ratio (ORs) was used for data measurement of dichotomous outcomes, while Mean difference (MD) for continuous outcomes. All data are expressed with 95 % Confidence interval (CI). We used the fixed-effects model when no statistical heterogeneity was identified (heterogeneity test, $P \geq 0.1$, or $I^2 \leq 50$ %); otherwise, we applied the random-effects model. If $P < 0.05$, it was considered to indicate a significant difference.

Network meta-analysis was performed using Stata 16.0 and the hybrid linear model based on the frequency framework. The summary OR with a 95%CI was used to estimate the dichotomous outcomes, and the summary MD with a 95%CI was used to estimate continuous data. If the 95%CI of the OR did not contain 1, or the 0 was not among the 95%CI of the MD, the differences between groups were considered statistically significant. A network map was generated to illustrate direct and indirect comparisons of different interventions. The size of the nodes represented the sample size of each TCM, and the thickness of the lines represented the number of studies directly comparing TCMs with CWM. τ^2 statistics, as well as both the 95%CI and 95 % Prediction interval (PrI), intersected or disinterested the invalid line of unity was used to assess network heterogeneity. Because the comparisons of TCMs were indirect, no consistency test was needed. The probabilities of the Surface under the cumulative ranking curve (SUCRA) were used to rank the efficacy of all interventions, with high SUCRA values indicating a possible correlation with good efficacy [8]. The presence of publication bias was evaluated using a corrected comparison funnel plot and Egger's test [9].

If the network estimates produced conflicting results for both interventions, We preferred to use direct paired comparison results as the best estimate. When an indirect estimate was inconsistent with the SUCRA result, we preferred to use indirect paired comparisons as the best estimates. Nevertheless, the results were sometimes dubious when the comparisons of different interventions were provided in the absence of sufficient research data on the network. For such instances, we would calculate network estimates of direct and indirect comparisons and assess their consistency to ensure the reliability of results.

3. Results

The search strategy identified 4047 records across five databases. After removing duplicates, 2043 items were screened based on titles and abstracts, with 1791 being excluded. We reviewed the full text of 252 studies and ultimately included 30 published studies in our analysis. In line with the PRISMA guidelines[4], we developed a literature screening flow chart (Fig. 1).

3.1. Characteristics of the included studies

We included 20 RCTs (3112 participants) [10–29] and 10 RCSs (1032 participants) [30–39], comprising 13 publications in English and 17 in Chinese. A total of 4144 mild or moderate patients were included, with 2133 patients in the experimental group and 2011 patients in the control group. The disease severity was mild/moderate in 19 trials (2652 participants), mild in one trials (200 participants), and moderate in 10 trials (1292 participants). All patients were recruited from China, with 55.60 % from Hubei province. Except for one RCT recruited from April 2022 [20], the other studies were conducted at the beginning of the outbreak (December 2019 to May 2020). The duration of medication in all studies ranged from 4 to 15 days. The mean age of the patients was 51.80 years, with females comprising 49.07 % of the sample. The most common comorbidities were hypertension and cardiovascular disease. Supportive treatment followed the Chinese "Diagnosis and Treatment Protocol for COVID-19" (3rd to 7th Edition) and included bed rest, monitoring of vital signs, oxygen therapy, prone position therapy, immunotherapy, antiviral, antibacterial, or anticoagulation therapy. The 30 studies involved seven drugs, including LHQW (4 RCTs and 5 RCSs), QFPD (3 RCTs and 2 RCSs), JHQG (2 RCTs and 1 RCS), SFJD (4 RCTs and 2 RCSs), XFBD (3 RCTs), HSBD (2 RCTs), and TJQW (2 RCTs). The characteristics of the 30 included studies are given in Table 1.

3.2. Quality evaluation and risk bias assessment

All 30 of the studies [10–39] included in our analysis were conducted in China. Among the 20 included RCTs, all exhibited varying degrees of bias risk, with six studies demonstrating high overall bias risk. The baseline characteristics of the trial and control groups were comparable. Eleven studies explicitly mentioned not implementing allocation concealment, while nine studies did not report related details. All studies reported randomization; however, six did not disclose the randomization method. None of the studies used blinding for researchers and participants; only one study reported that outcome assessors were blinded to the treatment and grouping. Although most outcome measures were objective, symptom improvement might involve subjective judgment, potentially introducing bias. One study had significantly fewer patients at the conclusion than at the start and did not report missing data, indicating potential bias due to missing data. Eight studies pre-registered and reported their protocols, indicating no risk of selective reporting. The

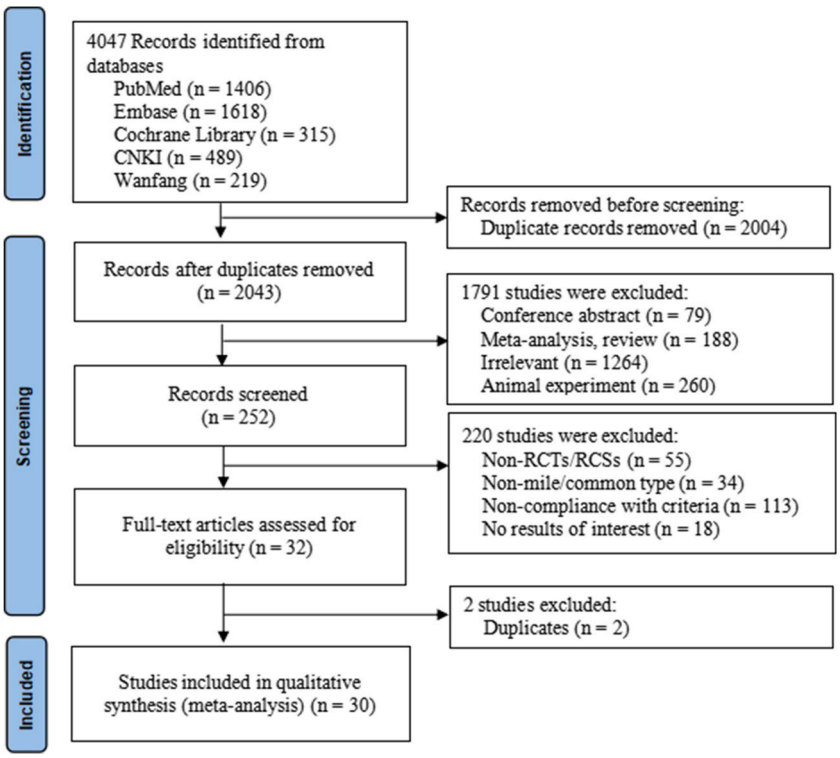

Fig. 1. Flow chart of evidence search and selection.

Table 1
Characteristics of the 30 trials.

Study	Year	Course	City	Type	Interventions		Age (year)		Sample		Outcome
					Treatment	Control	Treatment	Control	Treatment	Control	
Yu P et al., 2020 [10]	2020.02–2020.03	7 Days	Wuhan	RCT	LHQW + CWM	CWM	48.27 ± 9.56	47.25 ± 8.67	147	148	1,2,7,11,13
Xiao MZ et al., 2020 [11]	2020.02–2020.03	14 Days	Wuhan	RCT	LHQW + CWM	CWM	58	50	58	63	1,3,4,5,6
Hu K et al., 2019 [12]	2020.02–2020.03	14 Days	Multicenter	RCT	LHQW + CWM	CWM	50.4 ± 15.2	51.8 ± 14.8	142	142	1,2,7
Chen CW et al., 2021 [13]	2019.12–2020.02	10 Days	Shenzhen	RCT	LHQW + CWM	CWM	50.16 ± 5.11	49.52 ± 5.06	28	29	1,8,9,10,13,14
Wang Y et al., 2021 [14]	2020.02–2020.03	10 Days	Xiangyang	RCT	QFPD + CWM	CWM	48 ± 13.2	49.4 ± 13.3	70	70	1,2,11,12,13
Zeng XH et al., 2020 [15]	2019.12–2020.02	–	Beijing	RCT	QFPD + CWM	CWM	46.65 ± 6.21	46.21 ± 5.62	104	125	7,14
Fu XX et al., 2020 [16]	2020.01–2020.02	15 Days	Guangzhou	RCT	TJQW + CWM	CWM	45.26 ± 7.25	44.68 ± 7.45	37	36	1,2,7,11,12,13
Li T et al., 2023 [17]	2020.02–2021.12	14 Days	Henan	RCT	XFBD + CWM	CWM	41.91 ± 14.39	47.44 ± 14.16	34	34	3,4,5,14
Yu XY et al., 2020 [18]	2020.02–2020.04	10–14 Days	Wuhan	RCT	QFPD + CWM	CWM	64.32 ± 2.51	60.5 ± 2.08	43	46	12,13,14
Xiao Q et al., 2020 [19]	2020.01–2020.02	14 Days	Wuhan	RCT	SFJD + CWM	CWM	60.9 ± 8.7	62.2 ± 7.5	100	100	2,7,8,9,10,11,12
Zhang J et al., 2022 [20]	2022.04–2022.05	7 Days	Shanghai	RCT	SFJD + CWM	CWM	–	–	120	120	1,2
Qu XK et al., 2021 [21]	2020.01–2020.02	10 Days	Haozhou	RCT	SFJD + CWM	CWM	39.65 ± 11.2	41.6 ± 10.5	40	40	2,7,8,9,10,11,12
Yan CG et al., 2022 [22]	2020.01–2021.01	14 Days	Nanyang	RCT	SFJD + CWM	CWM	60.26 ± 7.32	59.48 ± 8.24	50	50	1,8,9,10,11,12,14
Duan C et al., 2020 [23]	2020.02–2020.03	5 Days	Hubei	RCT	JHQG + CWM	CWM	51.99 ± 13.88	50.29 ± 13.17	82	41	1,3,4,5
An XD et al., 2021 [24]	2020.02–2020.03	14 Days	Wuhan	RCT	JHQG + CWM	CWM	50.18 ± 12.55	44.74 ± 11.65	92	31	1,3,4,5,6
Pang WT et al., 2022 [25]	2020.03–2020.04	14 Days	Tianjin	RCT	XFBD + CWM	CWM	42	40	120	60	3,4,5
Xiong WZ et al., 2020 [26]	2020.01–2020.02	7 Days	Wuhan	RCT	XFBD + CWM	CWM	57.1 ± 14	62.4 ± 12.3	22	20	3,4,5,6
Fu XX et al., 2020 [27]	2020.01–2020.02	10 Days	Guangzhou	RCT	TJQW + CWM	CWM	43.26 ± 7.15	43.68 ± 6.45	32	33	1,2,11,12,13
Zhao C et al., 2021 [28]	2020.02–2020.03	7 Days	Wuhan	RCT	HSBD + CWM	CWM	52	49	204	204	1
Liu J et al., 2021 [29]	2020.02–2020.03	14 Days	Wuhan	RCT	HSBD + CWM	CWM	56.5	56	99	96	1,4,5,6,7,14
Li KY et al., 2020 [30]	2020.01–2020.03	–	Hubei	RCS	QFPD + CWM	CWM	53.6 ± 0.26	50.43 ± 0.34	30	30	1,2,8,10
Yao KT et al., 2020 [31]	2020.01–2020.02	–	Wuhan	RCS	LHQW + CWM	CWM	57.1 ± 14	62.4 ± 12.3	21	21	3,4,5,6,8
Cheng DZ et al., 2020 [32]	2020.01–2020.02	5 Days	Wuhan	RCS	LHQW + CWM	CWM	55.5 ± 12.3	55.8 ± 11.6	51	51	1,3,4,5,7,8,9,10
Fan SJ et al., 2022 [33]	2020.01–2020.04	14 Days	Guangzhou	RCS	LHQW + CWM	CWM	42.35 ± 0.23	42.53 ± 0.12	33	33	2,3,4,5,8,9,10,14
Lv RB et al., 2020 [34]	2020.01–2020.02	10 Days	Wuhan	RCS	LHQW + CWM	CWM	59.12 ± 16.56	60.20 ± 17.01	63	38	1,3,4,5,6
Chen J et al., 2021 [35]	2020.01–2020.02	14 Days	Wuhan	RCS	SFJD + CWM	CWM	60.2 ± 6.6	60.4 ± 6.6	100	100	2,7,8,9,10,11,12
Qu XK et al., 2020 [36]	–	10 Days	–	RCS	SFJD + CWM	CWM	40.65 ± 8.23	39.82 ± 6.40	40	30	7,8,9,10,14
Shen P et al., 2021 [37]	2020.03–2020.04	5–7 Days	Shanghai	RCS	LHQW + CWM	CWM	58.73 ± 15.60	59.08 ± 15.55	90	158	13
Xin SY et al., 2020 [38]	2020.01–2020.02	–	Hubei	RCS	QFPD + CWM	CWM	46.1	50.7	37	26	11,13
Liu ZL et al., 2020 [39]	2020.01–2020.02	7 Days	Beijing	RCS	JHQG + CWM	CWM	50.73	51.75	44	36	11

1: severe conversion rate; 2: clinical effective rate; 3: effective rate of fever; 4: effective rate of fatigue; 5: effective rate of cough; 6: effective rate of chest tightness; 7: CT improvement rate; 8: recovery time of fever; 9: recovery time of fatigue; 10: recovery time of cough; 11: WBC count; 12: LYM percentage; 13: CRP level; 14: NCT of nucleic acid.
RCT: randomized controlled trial; RCS: retrospective cohort studies; LHQW: Lianhua Qingwen; JHQG: Jinhua Qinggan; HSBD: Huashi Baidu; QFPD: Qingfei Paidu; SFJD: Shufeng Jiedu; TJQW: Toujie Quwen; XFBD: Xuanfei Baidu; CWM: Conventional Western medicine.

remaining 12 studies, lacking protocol clarity, might have selective reporting bias. Overall, the twenty included RCTs exhibited varying degrees of bias risk. The statistics of bias in each study are presented in Fig. 2. Among the 10 included RCSs, nine were high-quality studies, indicating low or probably low risk of bias in all domains. One study did not consider the comparability between the exposure and non-exposure groups in design and statistical analysis, leading to a high bias risk (Table 2).

3.3. Pairwise meta-analysis

3.3.1. Severe conversion rate

Thirteen RCTs and three RCSs involving 2393 patients reported severe conversion rates. We adopted the fixed-effects model because of no statistical heterogeneity among these studies ($P = 0.99$, $I^2 = 0$ %). The results indicated that the severe conversion rates in the TCM + CWM groups were significantly lower than those in the CWM groups (OR = 0.45, 95%CI [0.31, 0.65], $P < 0.01$; Fig. 3a). Meta-analysis of the RCSs confirmed these outcomes (OR = 0.35, 95%CI [0.17, 0.70], $P = 0.003$; Fig. 3a).

3.3.2. Clinical effective rate

Eight RCTs and three RCSs involving 1703 patients reported clinical effective rates. We adopted the fixed-effects model because of no statistical heterogeneity among these studies ($P = 0.84$, $I^2 = 0$ %). The results showed that the clinical effective rates in the TCM + CWM groups were higher than those in the CWM groups (OR = 2.48, 95%CI [1.85, 3.32], $P < 0.01$; Fig. 3b). Meta-analysis of the RCSs confirmed these outcomes (OR = 2.89, 95%CI [1.54, 5.40], $P < 0.01$; Fig. 3b).

3.3.3. NCT of nucleic acid

Six RCTs and two RCSs involving 874 patients reported the NCT of nucleic acid. We adopted the random-effects model because of some statistical heterogeneity among these studies ($P < 0.01$, $I^2 = 98$ %). The results showed that the NCT of nucleic acid in the TCM + CWM groups were shorter than those in the CWM groups (MD = −2.11, 95%CI [−3.95, −0.26], $P < 0.01$; Fig. 3c). Meta-analysis of the RCSs confirmed these outcomes (MD = −2.19, 95%CI [−2.89, −1.49], $P < 0.01$; Fig. 3c).

3.3.4. Secondary outcomes

Meta-analysis of secondary outcomes in the RCTs showed that, compared with CWM alone, TCM combined with CWM statistically significantly shortened the recovery time of patients with fever, cough, and fatigue, raised the CT improvement rate, improved the symptoms of fever, cough, fatigue, and chest tightness, and improved the blood biochemical indicators ($P < 0.05$). Meta-analysis was also done for RCSs, and the results of the meta-analysis of secondary outcomes in the RCTs and RCSs were shown in Table 3.

3.4. Network meta-analysis

3.4.1. Severe conversion rate

Thirteen RCTs involving six TCMs reported severe conversion rate, of TCM combined with CWM in the treatment of COVID-19. As shown in the network map (Fig. 4a). The severe conversion rates of CWM combined with HSBD (OR = 0.32, 95%CI [0.12, 0.86]) or LHQW (OR = 0.52, 95%CI [0.32, 0.85]) were significantly lower than those with CWM treatment alone, and there were no significant differences between the six TCMs + CWM. The addition of SFJD, QFPD, TJQW, or JHQG to CWM did not significantly improve severe conversion rates, even though the rates of each combination were slightly lower than those with CWM alone. We assigned the following preliminary ranking order of each intervention on the severe conversion rate: HSBD < SFJD < QFPD < TJQW < JHQG < LHQW < CWM (Table 4 and Appendix file Table S2).

3.4.2. Clinical effective rate

Eight RCTs involving four TCMs reported clinical effective rate. As shown in the network map (Fig. 4b). The clinical effective rates of CWM combined with TJQW (OR = 4.53, 95%CI [1.68, 12.21]), SFJD (OR = 2.24, 95%CI [1.42, 3.52]), or LHQW (OR = 2.23, 95%CI [1.45, 3.42]) were significantly better than those with CWM alone, and there were no significant differences between the four TCMs.

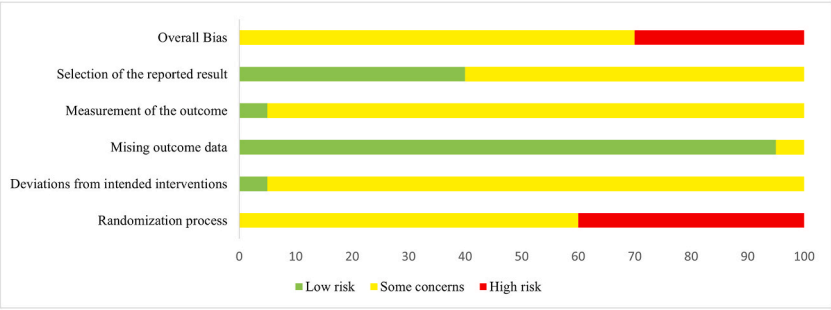

Fig. 2. Risk of bias.

Table 2
Newcastle Ottawa scale (NOS) of RCSs.

Study	Select				Comparability	Expose			Total score
	1	2	3	4	5	6	7	8	
Li KY et al., 2020 [30]	*	*	*	*	*		*	*	7*
Yao KT et al., 2020 [31]	*	*	*	*	*		*	*	7*
Cheng DZ et al., 2020 [32]	*	*	*	*	*		*	*	7*
Fan SJ et al., 2022 [33]	*	*	*	*	*		*	*	7*
Lv RB et al., 2020 [34]	*	*	*	*	*		*	*	7*
Chen J et al., 2021 [35]	*	*	*	*	*		*	*	7*
Qu XK et al., 2020 [36]	*	*	*	*	*		*	*	7*
Shen P et al., 2021 [37]	*	*	*	*			*	*	6*
Xin SY et al., 2020 [38]	*	*	*	*	*		*	*	7*
Liu ZL et al., 2020 [39]	*	*	*	*	*		*	*	7*

1 = Representativeness of exposure; 2 = Selection of non-exposed persons; 3 = Determination of exposure; 4 = Proof of no interesting results at the beginning; 5 = Comparability; 6 = Evaluation of results; 7 = Adequate follow-up time; 8 = Adequacy of follow-up.

We assigned the following preliminary ranking order of each intervention on the clinical effective rate: QFPD > TJQW > SFJD > LHQW > CWM (Table 4 and Appendix file Table S2). The efficacy of QFPD + CWM was slightly greater than that of CWM alone, TJQW, and SFJD, but the results were not significant due to the large confidence intervals.

3.4.3. NCT of nucleic acid

Six RCTs involving five TCMs reported the NCT of nucleic acid. As shown in the network map (Fig. 4c). The NCT of nucleic acid of CWM combined with QFPD (MD = −4.78, 95%CI [−5.79, −3.77]) was significantly shorter than that with CWM alone. The NCT of nucleic acid with QFPD was also significantly shorter than that with XFBD (MD = −3.46, 95%CI [−5.73, −1.19]) or SFJD (MD = −3.83, 95%CI [−5.52, −2.14]). The NCT of nucleic acid of SFJD, XFBD, HSBD, or LHQW in combination with CWM were slightly shorter than those with CWM alone, but the results were not significant. We assigned the following preliminary ranking order of each intervention on the NCT of nucleic acid: QFPD < XFBD < SFJD < HSBD < LHQW < CWM (Table 4 and Appendix file Table S3).

3.4.4. CT improvement rate

Seven RCTs involving five TCMs reported the CT improvement rate. As shown in the network map (Fig. 4d). The CT improvement rates of CWM combined with LHQW (OR = 1.93, 95%CI [1.01, 3.70]) or QFPD (OR = 3.42, 95%CI [1.20, 9.77]) were significantly better than those with CWM alone, and there were no differences between the five TCMs. The addition of HSBD, TJQW, or SFJD did not significantly change the CT improvement rates compared with CWM alone, although each combination showed slightly better efficacy than CWM alone. We assigned the following preliminary ranking order of each intervention on the CT improvement rate: QFPD > HSBD > TJQW > SFJD > LHQW > CWM (Table 4 and Appendix file Table S4).

3.4.5. Effective rates of fever

Six RCTs involving three TCMs reported effective rates in the symptoms of fever. As shown in the network map (Fig. 4e). The effective rates in fever of CWM combined with JHQG (OR = 3.94, 95%CI [1.66, 9.36]) were significantly better than those with CWM alone, and there were no differences between the three TCMs. The efficacies of XFBD or LHQW in combination with CWM were slightly greater than those with CWM alone, but the results were not significant. We assigned the following preliminary ranking order of each intervention on the effective rate of fever: JHQG > XFBD > LHQW > CWM (Table 4 and Appendix file Table S5).

3.4.6. Recovery time of fever

Four RCTs involving two TCMs reported the recovery times of fever. As shown in the network map (Fig. 4f). The recovery times of fever with SFJD (MD = −1.13, 95%CI [−1.68, −0.59]) in combination with CWM were significantly shorter than that with CWM alone. LHQW added to CWM slightly shortened the recovery times of fever compared with CWM alone, but the results were not significant. We assigned the following preliminary ranking order of each intervention on the recovery time of fever: SFJD < LHQW < CWM (Table 4 and Appendix file Table S7).

3.4.7. Effective rates of fatigue

Seven RCTs involving four TCMs reported effective rates in fatigue. As shown in the network map (Fig. 4g). The effective rates in fatigue of XFBD (OR = 3.92, 95%CI [1.40, 10.97]) or HSBD (OR = 2.42, 95%CI [1.13, 5.17]) combined with CWM were significantly better than those with CWM alone, and there were no significant differences between the four TCMs. Combinations of JHQG or LHQW with CWM were slightly more efficacious than CWM alone, but the results were not significant. We assigned the following preliminary ranking order of each intervention on the effective rate of fatigue: XFBD > HSBD > JHQG > LHQW > CWM (Table 4 and Appendix file Table S6).

3.4.8. Recovery time of fatigue

Four RCTs involving two TCMs reported the recovery times of fatigue. As shown in the network map (Fig. 4h). The recovery times of

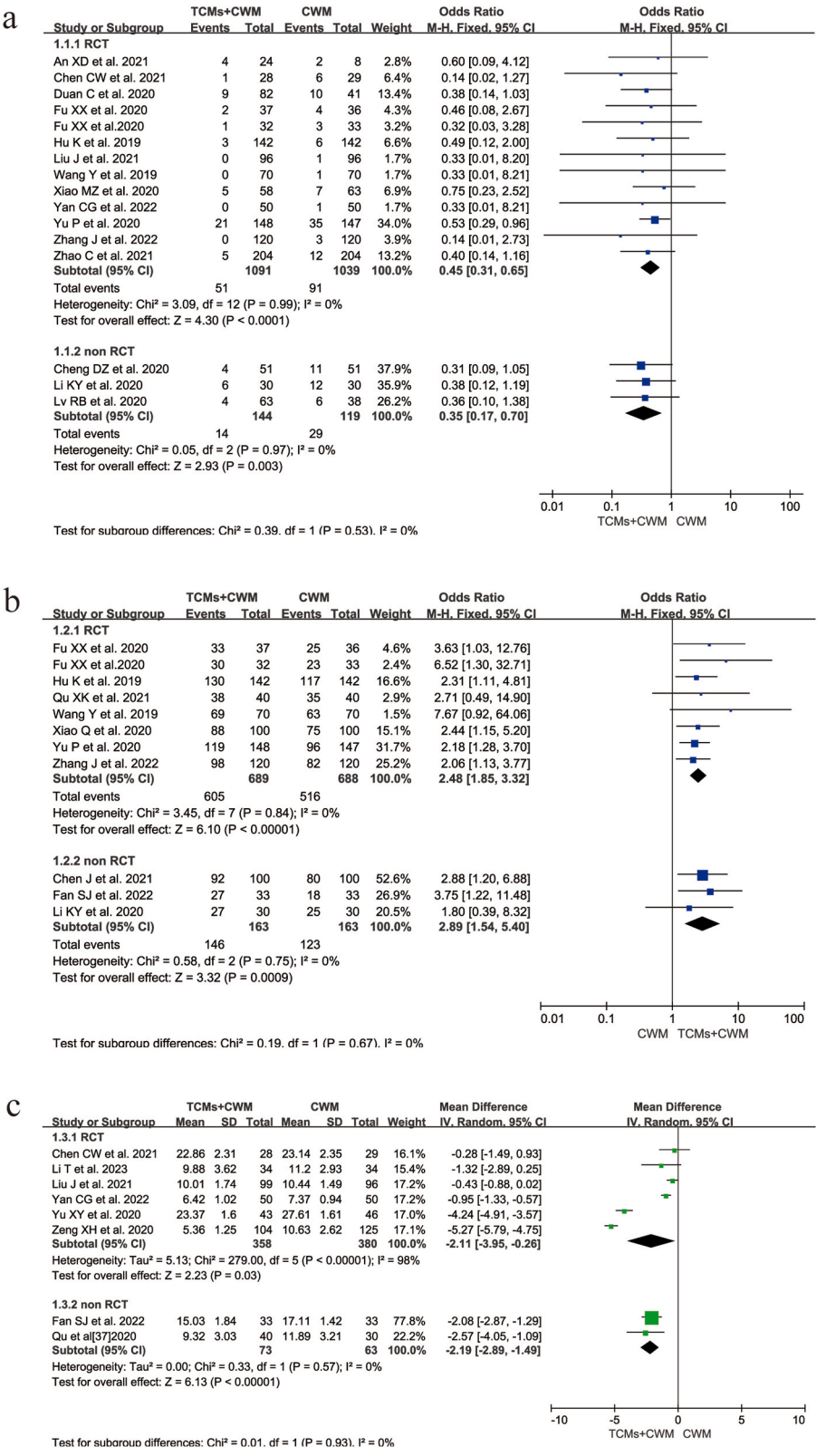

Fig. 3. Forest map of comparisons.
(a) severe conversion rates. (b) clinical effective rates. (c) NCT of nucleic acid.

Table 3
Results of meta-analysis of secondary outcomes in the included studies.

Outcomes	Type	Studies (n)	Heterogeneity test		Effective number of cases		Model	Effect quantity	Effect value and 95%CI	P
			P	I^2 (%)	TCM (n)	CWM (n)				
Improvement rate of main symptoms	Fever(RCT)	6	0.92	0	224	120	Fixed	OR	3.87 [1.94, 7.71]	<0.001
	Fever(RCS)	4	0.96	0	156	129	Fixed	OR	3.65 [2.05, 6.52]	<0.001
	Cough(RCT)	7	0.49	0	363	265	Fixed	OR	2.00 [1.37, 2.92]	<0.001
	Cough(RCS)	4	0.59	0	137	125	Fixed	OR	3.26 [1.92, 5.52]	<0.001
	Fatigue(RCT)	7	0.59	0	295	225	Fixed	OR	2.22 [1.44, 3.44]	<0.001
	Fatigue(RCS)	4	0.89	0	113	109	Fixed	OR	2.96 [1.65, 5.32]	<0.001
	Chest tightness (RCT)	4	0.34	10	190	142	Fixed	OR	2.48 [1.45, 4.26]	0.001
	Chest tightness (RCS)	2	0.17	47	31	28	Fixed	OR	2.25 [0.77, 6.58]	0.14
Recovery time of main symptoms	Fever(RCT)	4	<0.001	91	219	218	Random	MD	−0.87 [-1.53, −0.21]	0.001
	Fever(RCS)	6	0.02	62	259	239	Random	MD	−1.32 [-1.66, −0.98]	<0.001
	Cough(RCT)	4	<0.001	94	218	219	Random	MD	−1.07 [-1.25, −0.89]	0.004
	Cough(RCS)	5	<0.001	92	224	206	Random	MD	−1.84 [-1.99, −1.69]	0.02
	Fatigue(RCT)	4	<0.001	95	218	219	Random	MD	−1.13 [-1.98, −0.29]	0.008
	Fatigue(RCS)	4	<0.001	93	189	174	Random	MD	−1.01 [-1.76, −0.26]	0.008
CT improvement rate	RCT	7	0.30	17	645	669	Fixed	OR	2.32 [1.78, 3.03]	<0.001
	RCS	3	0.55	0	191	191	Fixed	OR	2.07 [1.25, 3.43]	0.005
Blood biochemical indicators	WBC(RCT)	7	<0.001	86	476	477	Random	MD	0.42 [0.18, 0.66]	<0.001
	WBC(RCS)	4	0.06	60	271	320	Random	MD	0.60 [0.08, 1.11]	0.02
	LYM(RCT)	7	<0.001	95	372	375	Random	MD	2.06 [0.15, 3.96]	0.03
	LYM(RCS)	1	–	–	100	100	Random	MD	3.60 [3.14, 4.06]	<0.001
	CRP(RCT)	6	<0.001	93	357	362	Random	MD	−5.53 [-7.11, −3.96]	<0.001
	CRP(RCS)	1	–	–	89	156	Random	MD	−6.52 [-23.50, 10.46]	0.45

RCT: randomized controlled trial; RCS: retrospective cohort studies; OR: Odds ratio; MD: Mean difference; CWM: Conventional Western medicine; TCM: Traditional Chinese medicine; WBC: White blood cell; LYM: Lymphocyte; CRP: C-reactive protein.

fatigue with LHQW combined with CWM (MD = −2.11, 95%CI [−3.75, −0.47]) were statistically shorter than those with CWM alone, and there were no differences between the two TCMs. SFJD added to CWM slightly shortened the recovery times of fatigue compared with CWM alone, but the results were not significant. We assigned the following preliminary ranking order of each intervention on the recovery time of fatigue: LHQW < SFJD < CWM (Table 4 and Appendix file Table S8).

3.4.9. *Effective rates of cough*

Seven RCTs involving four TCMs reported effective rates in cough. As shown in the network map (Fig. 4i). Regarding the effective rate of cough, there were no significant differences between the four TCMs, but the combination of HSBD (OR = 2.63, 95%CI [1.13, 6.12]), XFBD (OR = 2.52, 95%CI [1.28, 4.93]), or JHQG (OR = 1.97, 95%CI [1.02, 3.79]) with CWM were significant more efficacious than CWM alone. We assigned the following preliminary ranking order of each intervention on the effective rate of cough: HSBD > XFBD > JHQG > LHQW > CWM (Table 4 and Appendix file Table S6).

3.4.10. *Recovery time of cough*

Four RCTs involving two TCMs reported the recovery times of cough. As shown in the network map (Fig. 4j). Regarding the recovery time of cough, there were no significant differences between the two TCMs; however, the recovery times with each combination

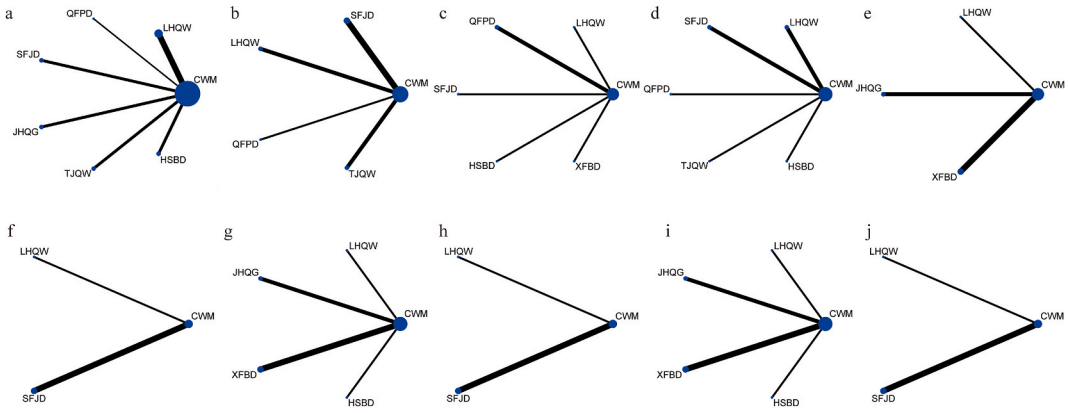

Fig. 4. Network plot of comparisons.
(a) severe conversion rate. (b) clinical effective rate. (c) NCT of nucleic acid. (d) CT improvement rate. (e) effective rate of fever. (f) recovery time of fever. (g) effective rate of fatigue. (h) recovery time of fatigue. (i) effective rate of cough. (j) recovery time of cough.

were slightly shorter than those with CWM alone. We assigned the following preliminary ranking order of each intervention on the recovery time of cough: LHQW < SFJD < CWM (Table 4 and Appendix file Table S7).

3.5. Inconsistency test

Due to the lack of direct comparison of TCM, no loop closure was found in the NMA. Inconsistency tests could not be performed. Therefore, we analyzed the results using a consistency model.

3.6. Publication bias analysis and sensitivity analysis

A funnel plot to detect the bias in the severe conversion rate. The plot exhibited an imperfectly asymmetric distribution, suggesting potential publication bias (Fig. 5). This may be related to small sample size or inherent publication bias. Fewer than 10 studies were included for the other outcomes, hence publication bias was not tested for these cases. To further evaluate publication bias, we conducted Egger's test. The p-values for various outcomes were as follows: severe conversion rate (0.122), clinical effective rate (0.007), NCT of nucleic acid (0.712), CT improvement rate (0.280), effective rate of fever (0.551), recovery time of fever (0.753), effective rate of cough (0.547), recovery time of cough (0.058), effective rate of fatigue (0.401), and recovery time of fatigue (0.072). Except for the clinical effective rate ($p = 0.007$), all other outcomes had p-values greater than 0.05 (Appendix file: Fig. S1 and Fig. S2). This indicates that while publication bias might affect the clinical effective rate, other outcomes seem less influenced by this bias. The potential publication bias mainly affects the interpretation of the clinical effective rate. Nevertheless, since Egger's tests for other outcomes were not significant, we believe the effect of publication bias on these results is minimal.

We performed sensitivity analyses by systematically excluding each study to evaluate the impact of individual studies on the overall results. The sensitivity analyses for severe conversion rate, clinical effective rate, nucleic acid NCT, CT improvement rate, fever effective rate, fatigue effective rate, cough effective rate, fever recovery time, fatigue recovecry time, and cough recovery time revealed no significant changes following the exclusion of any single study. This consistency confirms the stability and reliability of our findings (Appendix file: Fig. S3).

4. Discussion

4.1. Summary of findings

In our evaluation of the efficacy of seven TCMs for mild or moderate COVID-19 using network meta-analysis, QFPD emerged as the most effective in raising the CT improvement rate and clinical effectiveness rate, and in reducing the NCT of nucleic acid. HSBD was the best TCM for reducing severe conversion and improving cough. XFBD provided the greatest improvement in fatigue, followed by HSBD, while JHQG was superior in improving fever, followed by XFBD. LHQW was the most effective in shortening recovery time for fatigue and cough, while SFJD excelled in shortening the recovery time for fever. Overall, the network meta-analysis indicated that combining TCM with CWM may benefit mild and moderate COVID-19 patients. Due to the absence of pairwise trials between different TCMs, we performed a network meta-analysis to indirectly compare treatment approaches. Both direct and indirect comparisons were assessed to improve the accuracy of efficacy evaluation. SUCRA was utilized to rank the competing treatments and identify the best choices for each outcome.

The traditional meta-analysis demonstrated that combining TCM with CWM significantly decreased the severe conversion rate, increased clinical effectiveness and CT improvement rates, and reduced the NCT of nucleic acid. Compared to CWM alone, adding a

Table 4
SUCRA rankings of each intervention.

Severeconversionrate		Clinicaleffectiverate		CTimprovementrate		NCTofnucleicacid		Effectiverateoffever		Effectiverateoffatigue		Effectiverateofcough		Recoverytimeoffever		Recoverytimeoffatigue		Recoverytimeofcough	
Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA	Medicine	SUCRA
HSBD	67.00 %	QFPD	84.10 %	QFPD	72.30 %	QFPD	100.00 %	JHQG	67.90 %	XFBD	88.20 %	HSBD	78.00 %	SFJD	98.70 %	LHQW	95.40 %	LHQW	66.40 %
SFJD	64.20 %	TJQW	78.00 %	HSBD	64.80 %	XFBD	61.00 %	XFBD	62.70 %	HSBD	67.50 %	XFBD	76.40 %	LHQW	30.10 %	SFJD	52.30 %	SFJD	60.00 %
QFPD	56.90 %	SFJD	43.90 %	TJQW	60.90 %	SFJD	54.10 %	LHQW	61.90 %	JHQG	61.90 %	JHQG	59.60 %	CWM	21.20 %	CWM	2.30 %	CWM	23.60 %
TJQW	55.40 %	LHQW	43.10 %	SFJD	58.60 %	HSBD	36.50 %	CWM	7.40 %	LHQW	18.20 %	LHQW	25.70 %						
JHQG	54.20 %	CWM	0.90 %	LHQW	40.50 %	LHQW	32.00 %			CWM	14.20 %	CWM	10.30 %						
LHQW	43.20 %			CWM	2.80 %	CWM	16.50 %												
CWM	9.10 %																		

SUCRA: Surface under the cumulative ranking curve; LHQW: Lianhua Qingwen; JHQG: Jinhua Qinggan; HSBD: Huashi Baidu; QFPD: Qingfei Paidu; SFJD: Shufeng Jiedu; TJQW: Toujie Quwen; XFBD: Xuanfei Baidu; CWM: Conventional Western medicine.

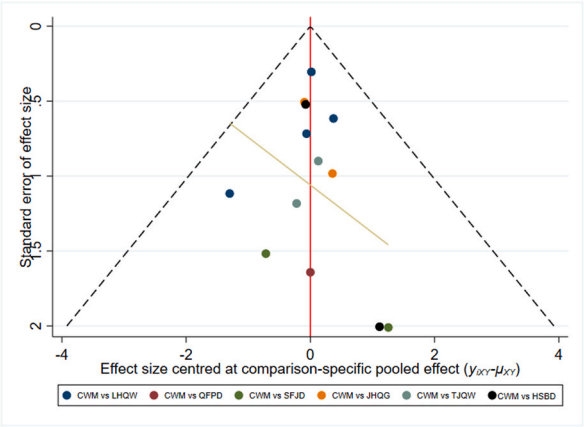

Fig. 5. Funnel plot of publication bias.

TCM also improved symptoms like fever, cough, fatigue, and chest tightness, and shortened recovery times for these symptoms. After treatment, WBC counts and LYM percentages were elevated, and CRP expression was down-regulated in the TCM combined with CWM group compared to the CWM alone.

We assessed publication bias using a funnel plot and Egger's test. The funnel plot for the severe conversion rate suggested potential publication bias, likely due to small sample sizes or inherent bias. Egger's test indicated significant publication bias for the clinical effective rate, while other outcomes were less affected. Sensitivity analyses, conducted by systematically excluding each study, showed no significant changes across various outcomes, confirming the robustness and reliability of our findings.

4.2. Mechanisms of action and clinical implications

TCM has shown efficacy in alleviating clinical symptoms, shortening the course of disease, and preventing mild cases from progressing to severe cases. In TCM theory, COVID-19, which affects the lungs, is categorized under epidemic dampness diseases characterized by dampness, heat, toxicity, and stasis. Modern pharmacological studies have demonstrated that TCM properties, such as clearing heat and detoxification, transforming dampness, and resolving the exterior, possess inhibitory effects on viruses [1].

TCM has demonstrated effectiveness against COVID-19, which is supported by pharmacological mechanism research. The primary antiviral mechanism of TCM is direct viral inhibition, mainly through herbs that clear heat and resolve toxins, such as lonicera, forsythia, and gypsum. For example, Wei et al. [40] found that ephedra decoction exhibited anti-influenza A (H1N1) virus properties by significantly blocking viral invasion into host cells and inhibiting intracellular viral biosynthesis. Herbal formulae such as LHQW, SFJD, JHQG, and TJQW predominantly include lonicera, forsythia, and gypsum. LHQW, JHQG, SFJD, QFPD, HSBD, and XFBD incorporate ephedra and apricot kernel, which promote sweating, resolve the exterior, diffuse the lung, and calm panting. Additionally, QFPD, HSBD, and XFBD are variations of the "Ephedra Decoction". LHQW and JHQG include "Ephedra, Apricot Kernel, Gypsum, and Licorice Decoction" and "Lonicera and Forsythia Powder," respectively. These formulations enhance effectiveness against COVID-19. Given the limited treatment options in CWM, TCM herbs and formulations offer a viable means to alleviate COVID-19 symptoms and could serve as potential sources for new therapeutic targets [41].

LHQW and JHQG are well-documented therapeutic agents for influenza, particularly effective in managing toxic heat syndrome, which commonly affects the lungs. Pharmacologic studies have demonstrated that both LHQW and JHQG possess broad-spectrum antiviral and antibacterial properties. They inhibit respiratory inflammation, reduce fever, and alleviate cough symptoms [42,43]. Our study further substantiates these findings, indicating that LHQW significantly outperforms CWM in several key clinical metrics. Specifically, LHQW showed superior results in reducing the severe conversion rate, enhancing the clinical effective rate, improving CT scans, and shortening the recovery time for fatigue. Moreover, the use of LHQW is associated with fewer adverse reactions, such as vomiting and diarrhea, common with chemical medications. This advantage improves patient compliance and addresses some of the shortcomings of CWM treatments, thereby enhancing their overall efficacy and safety. These benefits have substantial clinical implications, suggesting that LHQW can be a viable alternative to conventional treatments, offering a safer and more effective therapeutic option [44]. Similarly, JHQG is recognized for its rapid antipyretic effects and its capacity to reduce the reliance on acetaminophen [45]. Our research supports the superiority of JHQG in resolving fever symptoms compared to other TCMs. This reinforces the potential of JHQG as the preferred choice for managing fever in influenza patients.

SFJD exhibits broad-spectrum antiviral, antibacterial, anti-inflammatory, immune regulatory, antipyretic, and analgesic effects. Its multifaceted therapeutic profile supports its widespread use in treating viral pneumonia [46]. Our study confirms these benefits, showing that SFJD significantly surpasses CWM in clinical efficacy, CT improvement rate, and fever recovery time. Notably, SFJD has a significant advantage in shortening fever duration compared to other TCMs. Wang et al. [47] evaluated SFJD's effectiveness and safety in upper respiratory tract infections. They found that SFJD not only provided definitive efficacy but also lacked toxicity and side effects. These findings are consistent with our results, further positioning SFJD as the preferred choice for shortening fever duration.

QFPD decoction demonstrates immune regulatory effects and was developed by Youwen Ge under the State Administration of Traditional Chinese Medicine's special project, "Screening Research on Effective Traditional Chinese Medicine Prescriptions for the Prevention and Treatment of COVID-19." This initiative aimed to guide the therapeutic observation of new formulas with a focus on urgency, practicality, and effectiveness and was piloted in Shanxi, Hebei, Heilongjiang, and Shaanxi provinces [48]. The results showed that the overall effectiveness of QFPD decoction exceeded 90 %. In clinical practice, QFPD is primarily used for patients with mild, moderate, and severe COVID-19 and may also be applied to critically ill patients. As a special decoction in the fight against COVID-19, QFPD has proven efficacy in inhibiting endotoxins and preventing or delaying inflammatory storms, which contributes to favorable patient outcomes [1]. Our study found that QFPD significantly enhances lung imaging appearance and reduces NCT of nucleic acid. Prior network pharmacology analyses have identified numerous active natural compounds in QFPD, such as baicalin, glycyrrhizic acid, hesperidin, hypericin, and quercetin. These compounds interact with COVID-19 target proteins and are involved in a complex signaling network responsible for immune regulation, anti-inflammatory effects, and multi-organ protection [49]. These findings illustrate that QFPD decoction not only improves essential clinical parameters but also achieves a high overall effectiveness rate. Consequently, QFPD can be considered a potent therapeutic option for COVID-19.

Both HSBD and TJQW exhibit beneficial effects in clearing the lungs, calming panting, supporting upright Qi, and dispelling pathogens. The innovative compatibility of these prescriptions lies in early intervention through increased concentrations of heat-clearing and detoxification ingredients to swiftly eliminate pathogens while protecting and nurturing upright Qi. HSBD was the first TCM approved for clinical trials against COVID-19. It was developed by a research team in Wuhan during the initial phase of national TCM clinical research and subsequently used as the basic prescription at Jin Yintan Hospital. Our study identified HSBD as the most efficacious TCM in reducing the progression to severe COVID-19, underlining its pivotal role in treatment. Additionally, HSBD demonstrated the highest efficacy in improving cough symptoms compared to other TCMs. Yao et al. [50] and Xu et al. [51] found that HSBD's mechanisms might include blocking the inflammatory cytokine storm, regulating immunity, calming panting, and improving hemodynamics. Consequently, HSBD can be considered the optimal treatment choice in both aspects for COVID-19. The Guangdong Provincial Drug Administration examined and conditionally approved TJQW, making it the first institutional TCM preparation in China to be validated based on human experience and real-world clinical data. This study demonstrated TJQW's significant clinical effectiveness. On February 8, 2020, the Guangdong Provincial Drug Administration issued a notice regarding the Clinical Use of TJQW, facilitating rapid medical institutional response to thc

XFBD, a TCM prescription designed by academician Boli Zhang and Professor Qingquan Liu, has several benefits, including lung diffusion, phlegm dispersion, heat clearance, lung drainage, and toxin resolution. This prescription has been shown to significantly alleviate symptoms in patients with mild to moderate COVID-19. Our study reinforces these findings by demonstrating that XFBD significantly increases the effective rate of fatigue and cough reduction. Network pharmacology studies suggest that XFBD operates through the synergy of its ingredients, primarily targeting the lungs to regulate the body's response to infection. It modulates the pathological process of COVID-19 by affecting viral infection, immune response, liver and bile metabolism, and energy metabolism. Specifically, XFBD plays a crucial role in regulating immunity, reducing inflammation, and countering viral infections and viral protein transcription [52]. The significant increase in the effective rate of fatigue reduction is particularly noteworthy since fatigue is a common and debilitating symptom in COVID-19 patients. By understanding the pharmacological mechanisms of XFBD, healthcare providers can better appreciate its therapeutic potential and consider its clinical application.

Many studies suggested that instead of single treatments, combination therapies may be more effective [53]. Therefore, early intervention and integration of TCM and CWM are essential tools to increase the cure rate and improve clinical symptoms of COVID-19.

4.3. Strengths and limitations

Our study found TCM as adjuvant therapy achieved significantly advantages, which is consistent with the previous meta-analysis [54–56].

This study presents several key advantages. One of our strengths is the comprehensive inclusion of recent RCTs and RCSs published in the past three years. We focused on the most commonly used and effective TCMs, as recommended by the latest Guidelines for the Diagnosis and Treatment of COVID-19 (trial version of the 10th Edition). These TCMs, administered orally and marketed in China, are among those we analyzed. Unlike previous network meta-analyses that focused solely on symptom improvement rates, our study also considered symptom recovery times, utilizing a hybrid linear model based on the frequency framework. Given the potential heterogeneity due to varying follow-up durations in studies, symptom recovery time offers a more accurate measure of TCM therapeutic effects. Our study included patients with mild or moderate COVID-19, which are currently the most common cases. We conducted traditional meta-analysis for different trial types and network meta-analysis exclusively for RCTs to ensure randomness and meet the homogeneity hypothesis as closely as possible. Recognizing that mechanical reporting of network meta-analysis results could be misleading, we consulted original and related studies to ensure the reliability of our evaluations. This comprehensive approach supports more refined therapy for patients with mild or moderate COVID-19.

Our study has several limitations. First, the lack of large sample studies and randomized controlled trials directly comparing different Traditional Chinese Medicines led us to use conventional Western medicine for indirect comparisons. This impacts the stability of our results. Second, most studies reported only the effective rate of different symptoms without detailing the symptoms' recovery time. This affects the overall quality of the included data. Third, all included randomized controlled trials were conducted in China, leading to regional publication bias that limits the generalizability of our findings. Fourth, unlike objective indicators, the improvement of symptoms in Traditional Chinese Medicine might be subject to subjective judgment bias due to the lack of allocation concealment. This could limit the interpretation of our results. Finally, the studies often lacked rigorous design and reporting due to the

complicated reality of the epidemic, such as the absence of allocation concealment during randomization and a lack of blinding. These factors reduce the reliability of our findings.

4.4. Future research directions

Considering the strengths and limitations identified in our study, several key areas warrant further investigation. First, large-scale RCTs that directly compare different TCMs are critically needed. Such studies would provide more definitive and stable results, reducing reliance on indirect comparisons with CWM. Second, future research should prioritize reporting detailed recovery times for symptoms rather than just the effective rate. This change will enhance data quality and offer a more comprehensive understanding of TCM efficacy. Third, conducting RCTs outside of China is crucial to mitigate regional publication bias and improve the generalizability of the findings. Fourth, to minimize subjective judgment in assessing symptom improvement, future studies should implement allocation concealment. Emphasizing methodological rigor, including proper randomization, allocation concealment, and blinding, will ensure reliability and validity. Additionally, improving the design and reporting standards of studies is essential. These improvements will not only enhance the credibility of TCM research but also contribute to a deeper understanding of its role in modern medical practice. Enhancing these methodological aspects will create a clearer and more reliable evidence base for the use of TCM, facilitating its integration into global healthcare systems.

5. Conclusion

Adjuvant treatment of COVID-19 with TCM can improve the clinical effective rate, reduce the severe conversion rate, and improve symptoms of discomfort and laboratory indicators significantly. Specific TCMs have demonstrated notable benefits for various outcomes. QFPD increases the CT improvement rate and clinical efficacy while reducing the NCT of nucleic acid. HSBD reduces progression to severe disease and alleviates cough symptoms. XFBD improves fatigue symptoms, while JHQG reduce fever. SFJD shortens fever recovery time, and LHQW expedite the recovery from fatigue and cough. Each of the six TCMs recommended by the latest Guidelines for the Diagnosis and Treatment of COVID-19 analyzed here may have distinct benefits in COVID-19. However, given the limited number and quality of the included studies, these results should be considered preliminary. Further high-quality studies are needed to confirm these findings.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Tian Zhang, Ting Li, Fei Zhao, Tongzhou Li, Miaomiao Zhang, and Pengfei Jin agreed to publish the manuscript.

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Data availability statement

We searched PubMed, Cochrane Library, Embase, CNKI, and Wan-Fang databases. All relevant data for this study are available in the public databases.

CRediT authorship contribution statement

Tian Zhang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ting Li:** Writing – review & editing, Methodology, Investigation, Data curation. **Fei Zhao:** Writing – review & editing, Methodology, Investigation, Data curation. **Tongzhou Li:** Investigation, Data curation. **Miaomiao Zhang:** Investigation, Data curation. **Pengfei Jin:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35081.

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