Received: 31 January 2021 | Accepted: 23 February 2021

DOI: 10.1002/iub.2467

CRITICAL REVIEW

IUBMB LIFE WILEY

The effect of Chinese herbal medicine on digestive system and liver functions should not be neglected in COVID-19: An updated systematic review and meta-analysis

Shihua Shi[1] | **Fei Wang**[1] | **Jiang Li**[1] | **Yulong Li**[2] | **Weihao Li**[3] | **Xiaoping Wu**[4] | **Shuo Kou**[5] | **Yongcan Wu**[1] | **Xiaomin Wang**[1] | **Caixia Pei**[1] | **Demei Huang**[1] | **Heng Qiu**[1] | **Peili Wang**[4] | **Zhenxing Wang**[1]

[1]Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

[2]Laboratory of Ethnopharmacology, West China School of Pharmacy, West China Hospital, Sichuan University, Chengdu, China

[3]Cardiology Division, West China Hospital, Sichuan University, Chengdu, China

[4]National Clinical Research Center for Chinese Medicine, Cardiology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

[5]School of Public Health, Zhejiang Chinese Medical University, Hangzhou, China

Correspondence
Zhenxing Wang, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan Province 610072, China.
Email: wangzhenxing@vip.tom.com

Funding information
China Postdoctoral Science Foundation, Grant/Award Number: No. 2020T130010ZX

Abstract

Gastrointestinal symptoms and liver injury are common in patients with coronavirus disease 2019 (COVID-19). However, profiles of different pharmaceutical interventions used are relatively underexplored. Chinese herbal medicine (CHM) has been increasingly used for patients with COVID-19, but the efficacy of CHM used in COVID-19 on gastrointestinal symptoms and liver functions has not been well studied with definitive results based on the updated studies. The present study aimed at testing the efficacy of CHM on digestive symptoms and liver function (primary outcomes), the aggravation of COVID-19, and the time to viral assay conversion (secondary outcomes), among patients with COVID-19, compared with standard pharmacotherapy. The literature search was undertaken in 11 electronic databases from December 1, 2019 up to November 8, 2020. Appraisal of the evidence was conducted with Cochrane risk of bias tool or Newcastle Ottawa Scale. A random-effects model or subgroup analysis was conducted when significant heterogeneity was identified in the meta-analysis. The certainty of the evidence was assessed with the grading of recommendations assessment, development, and evaluation approach. Forty-eight included trials involving 4,704 participants were included. Meta-analyses favored CHM plus standard pharmacotherapy for COVID-19 on reducing the aggravation of COVID-19 and the time to viral assay conversion compared with standard pharmacotherapy. However, the present CHM as a complementary therapy for treating COVID-19 may not be beneficial for improving most gastrointestinal symptoms and liver function based on the current evidence. More well-conducted trials are warranted to confirm the potential efficacy of CHM furtherly.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHM, Chinese herbal medicine; CI, confidence interval; COVID-19, coronavirus disease 2019; GRADE, the grading of recommendations assessment, development, and evaluation; MD, mean difference; NOS, Newcastle Ottawa Scale; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCTs, randomized controlled trials; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCM, traditional Chinese medicine.

Shihua Shi, Fei Wang, and Jiang Li contributed equally and co-first authors.

KEYWORDS
coronavirus disease 2019, Chinese herbal medicine, gastrointestinal symptoms, liver function, meta-analysis

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world with substantial mortality since December 2019.[1] To date, the potential treatment options to contain the disease include antiviral medications, steroids, antibacterial medications, human immunoglobulin, and so on. Chinese herbal medicine (CHM), as recommended in national treatment guidelines in China,[2] has been increasingly used, and might pose a promising therapy for COVID-19.[3–7]

Some evidence of the efficacy of CHM for COVID-19 has emerged, suggesting that CHM may be used for COVID-19 in improving clinical symptoms, length of hospital stay, lung CT, and inflammatory biomarkers with fewer adverse events than conventional treatments.[8,9] It was believed that CHM was an effective treatment for COVID-19 in Chinese health care system. However, the previous meta-analysis studying CHM for COVID-19 paid attention to respiratory tract manifestations and fever, without enough consideration on digestive symptoms and liver function. It was understandable that digestive symptoms and liver function were neglected in the previous COVID-19 studies since it was a race to find effective measures and it was of utmost necessity to control the most commonly depicted symptoms due to the sheer magnitude of the COVID-19 pandemic. However, the goal of evidence-based medicine is to provide comprehensive clinical practice suggestions, and the digestive symptoms and liver injury are not uncommon in patients with COVID-19.[10] Emerging data have illustrated that the gastrointestinal tract and liver also represented target organs of SARS-CoV-2, according to the findings that angiotensin-converting enzyme 2, the major receptor of SARS-CoV-2, was also found in liver and gastrointestinal tract.[11] Increased attention should be paid to digestive symptoms and liver function in COVID-19 patients.

CHM as an adjuvant for COVID-19 on gastrointestinal symptoms and liver functions has not been studied with definitive results based on the latest evidence assessment. Whether CHM may constitute a basis of drug treatment for COVID-19 patients with gastrointestinal symptoms and liver dysfunctions remains unclear. Although empirical use of CHM shows potential improvement, supporting evidence remains limited. We conducted a systematic review and meta-analysis of emerging studies reporting gastrointestinal symptoms and liver function in COVID-19 patients treated with CHM plus standard pharmacotherapy. As for the follow-up of adverse events that have been studied,[8,9] we would not study it again.

2 | METHODS

This systematic review and meta-analysis, registered with the Open Science Framework (DOI: 10.17605/OSF.IO/8QCVP), was performed and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix S1).[12]

2.1 | Literature search

A systematic literature search of the PubMed, ScienceDirect, Web of Science, Scopus, Google Scholar, WorldCat Dissertations database and Index to Theses, PsycINFO, ProQuest, the Chinese National Knowledge Infrastructure, the VIP Information Database, and the Wanfang Database was conducted on November 8, 2020 (updated February 9, 2021) for relevant articles including accepted pre-proof publications in the last 1 year, to identify the latest information on COVID-19. The following grouped terms were used as search strategy and modified to suit each database to screen publications that might be valuable for the present review: ("coronavirus disease 2019" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "coronavirus" OR "novel coronavirus" OR "nCoV" OR "2019-nCoV") AND ("Medicine, Chinese Traditional" OR "Traditional Medicine, Chinese" OR "Chinese herbal medicine" OR "traditional Chinese medicine" OR "Chinese Traditional Medicine" OR "Chinese Medicine, Traditional" OR "Chinese medicine formulae" OR "Chinese medicine formulations" OR "Chinese herb" OR "Chinese herb therapy" OR "herbal medicine" OR "herb remedy" OR "herb therapy" OR "Zhong Yi Xue" OR "Chung I Hsueh" OR "Hsueh, Chung I"). Given the urgency of treating COVID-19, a gray literature search was also performed. Furthermore, COVID-19 articles in the WHO database and some key journals in this field including the New England Journal of Medicine, BMJ, the Lancet

COVID-19 Resource Centre, and JAMA were searched manually for potentially relevant publications. Additional articles were retrieved by hand based on the reference lists of relevant papers. Search strategies were attached in the supplementary (Appendix S2).

2.2 | Eligibility criteria

2.2.1 | Types of studies

Application of CHM in COVID-19 patients was less evaluated through COVID-19 randomized controlled trials (RCTs), due to ethic, feasibility, and methodology issues. Observational studies were common sources of the literature evaluating the efficacy of CHM, considering the urgency of the topic. Accordingly, we included studies on humans, which were RCTs or observational studies with a control arm.

2.2.2 | Participants

Only patients with COVID-19 were considered in this study. To ensure that all relevant articles were included, we did not set any specifications for the ages, sexes, and ethnic origin of participants.

2.2.3 | Interventions

Participants in the treatment group should receive CHM as a co-intervention with standard pharmacotherapy. Participants in the control group should be treated by standard pharmacotherapy alone or standard pharmacotherapy plus placebo.

The definition of CHM was herbal agents and materials, that originated from botanical herbal products, mineral and animal sources, based on the Pharmacopoeia of the People's Republic of China.[13] Standard pharmacotherapy, namely the standard treatment, consisted of symptomatic control and supportive care for COVID-19, such as antiviral medications, antibacterial medications, steroids, and human immunoglobulin, mostly according to the evolving Chinese national COVID-19 treatment guidelines and hospital practice.[2]

2.2.4 | Outcome measurement

The primary outcome measures were defined as gastrointestinal symptoms and liver functions. The main outcomes of gastrointestinal symptoms included the rate of nausea remission, remission of vomiting, rate of anorexia remission, and rate of diarrhea remission. The improvement rate of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as the main outcomes, represented liver function. The secondary outcome measures were defined as the aggravation of COVID-19, and the time to viral assay conversion.

2.3 | Exclusion criteria

The following studies were excluded: duplicate publications; review articles; editorials; case series without control group; viewpoints; commentaries; experimental in vitro studies; animal studies; expert opinions; studies pertaining to the suspected cases of COVID-19; and other complementary and alternative therapies beyond CHM, like massage, acupuncture, moxibustion, cupping, and music therapy, were contained in either CHM or control group; studies that did not report indicators to be discussed in this study.

2.4 | Study selection and data extraction

Two investigators (Shihua Shi and Jiang Li) independently searched the databases and screened the titles and abstracts. Disagreements about the eligibility and exclusion of a study were resolved via consensus or resolved by an arbitral reviewer (Zhenxing Wang). The following variables were independently extracted by two reviewers (Yulong Li and Xiaoping Wu) and cross-checked by another reviewer (Fei Wang): author; date; study design; patient demographics; severity of illness; interventions, and outcome parameters. We contacted the corresponding authors to resolve the incomplete data or data failed, attempting for more information, if possible.

2.5 | Risk of bias assessment

The Modification of Cochrane Tool[14] to assess the risk of bias in randomized trials was used, in which the response options for each of the domains included "definitely or probably yes" (assigned a low risk of bias) and "definitely or probably no" (assigned a high risk of bias).[15,16] The Newcastle Ottawa Scale (NOS)[17] was used to assess the risk of bias of observational studies that met the inclusion criteria. The quality of enrolled studies was independently rated by two reviewers (Yongcan Wu and Xiaomin Wang). Any disagreements were resolved by discussion or resolved by a senior reviewer (Weihao Li).

2.6 | Data synthesis

The gastrointestinal symptoms including the remission rate of diarrhea, anorexia, nausea, and vomiting; liver function parameters including the improvement rate of ALT and AST; the rate of aggravation of COVID-19 and time to viral assay conversion were evaluated and merged. Meta-analysis of the outcomes above was conducted using the Cochrane Collaboration Review Manager software (RevMan, Version 5.3). The relative treatment effects of dichotomous data and continuous data were measured using risk ratio (RR) and mean difference (MD), respectively. The standard error was calculated from the 95% confidence interval (CI). Heterogeneity was explored using the Mantel–Haenszel χ^2-test and I^2 statistic.[18] The random-effects model was utilized to address the variation across the included studies, since the pooled studies may differ in study design, duration, disease type, severity, or others. Subject to the availability of a sufficient number of studies, subgroup analyses were performed according to the study design, specific prescriptions of interventions, disease type, severity, or duration to explain the heterogeneity issues identified before data analyses. We assessed publication bias using the funnel plot[19] and the certainty of the evidence using the GRADEpro software.

3 | RESULTS

3.1 | Study selection process

Searches in the 11 databases yielded a total of 19,614 potential publications initially. 3,921 records remained after the removal of duplicates. The titles and abstracts of these papers were screened and 3,501 studies were dropped at this stage. The 420 studies, deemed to meet the criteria for full-text review, were retrieved for further eligibility assessment. Then, 375 of them failed to meet the inclusion criteria for various reasons (see Figure 1). Additional potentially relevant papers ($n = 3$) were identified through searches by hand in reference lists of reviews and included studies. Finally, 48 papers were appraised in the final stage (Table 1).

3.2 | Characteristics of studies included

In total, we analyzed 48 studies[3–7,20–60] recruiting 4,704 patients with COVID-19. Of these, 29[20,22–29,31,34–36,39,40,49–62] were observational studies with a control group, and 19[3–7,30,32,33,37,38,41–48,63] were RCTs included in the final analysis. Of these participants, 2,696 had been assigned to receive CHM as an adjuvant medicine, and 2,008 receive standard pharmacotherapy. CHM in most enrolled trials was orally administered. Other details were described in Table 1.

3.3 | Risk of bias in included studies

Table 2 summarized the risk of bias for the 19 RCTs.[3–7,30,32,33,37,38,41–48,63] Sixteen studies described the method of randomization, employing computer software,[4,6,7,63] random number tables,[3,5,30,33,37,38,41,42,44,46,48] or tossing a coin[47] for randomization. Six RCTs[3,4,30,47,48,63] were open-label studies because of the urgency of major public health events, subject to the risk of performance bias owing to the lack of placebo control. The other 13 studies[5–7,32,33,37,38,41–46] did not mention the blinding of patients and personnel. Table 3 showed the NOS details for 29 observational studies.[20,22–29,31,34–36,39,40,49–62] Eight observational studies[20,22,24,26,34,49,50,57] were judged to be of moderate methodologic quality, subject to the unsatisfying risk of bias mostly owing to the lack of adequacy of follow up and completing accounting for observational studies.

3.4 | Outcome 1: Gastrointestinal symptoms

3.4.1 | Nausea remission

Of the 48 studies, six studies[20,25,27–29,47] reported CHM on the rate of nausea remission in ordinary cases. No significant difference was found in the rate of nausea remission between the users and non-users of CHM (RR 1.04; 95% CI 0.83–1.30), and the heterogeneity was not significant ($I^2 = 0$, $p = .92$) (Figure 2a). We conducted subgroup analysis by study design, disease type, prescriptions of interventions, and duration. Similar result was found in observational trials, ordinary cases, Lianhua Qingwen group and subgroup with treatment course ≤7 days.

3.4.2 | Vomiting remission

Of the 48 studies, four studies[28,29,34,47] reported CHM on the remission of vomiting. As shown in Figure 2b, there was no significant difference in the remission of vomiting between users and non-users of CHM (RR 1; 95% CI 0.77–1.29), and heterogeneity was almost non-existent ($I^2 = 0\%$, $p = 1.00$). Similar result was observed in subgroup analysis conducted by study design, disease type, severity, or duration.

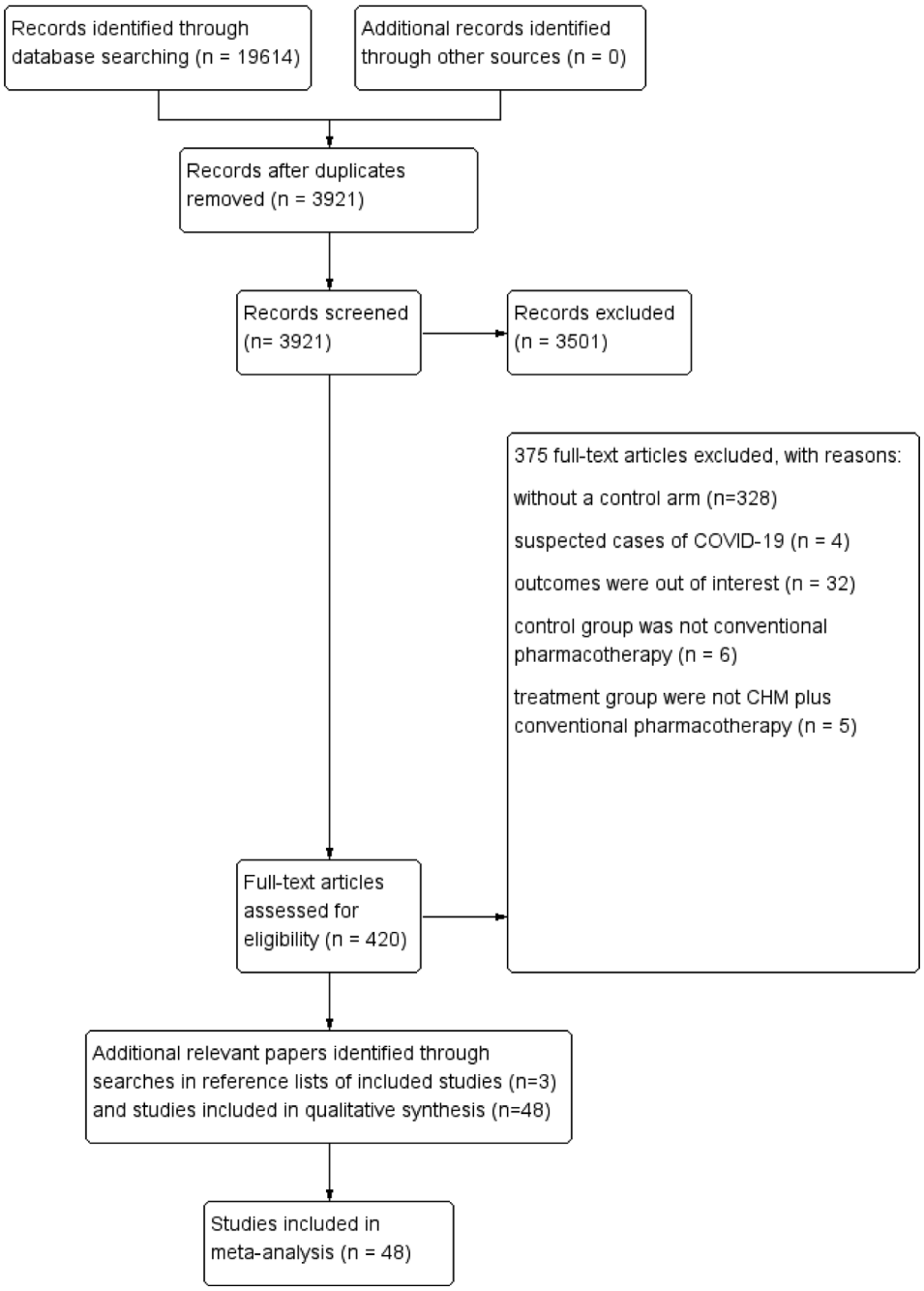


FIGURE 1 Flow diagram of search and selection process

3.4.3 | Anorexia remission

Of the 48 studies, three controlled observational studies[20,25,27] and three RCTs[37,47,63] reported the rate of anorexia remission. Of the total 160 COVID-19 patients with anorexia, 75 received CHM along with standard pharmacotherapy and 85 received only standard pharmacotherapy. Three studies[25,27,47] reported a reduction in the rate of anorexia and three[20,37,63] did not report any benefit with the use of CHM compared with the controls. The heterogeneity was significant ($I^2 = 87\%$, $p < 0.00001$), which was likely due to variations across studies, and random-effects model was used to accommodate statistical heterogeneity. As shown in Figure 2c, in the rate of anorexia remission, the combined treatment group outperformed standard pharmacotherapy alone (RR 2.09; 95% CI 1.04–4.19), with an improved disappearance rate of anorexia. We conducted subgroup analysis when ≥2 studies could be pooled, and a similar result was observed in the subgroup of observational studies.

3.4.4 | Diarrhea remission

Twelve studies explored the rate of diarrhea remission after the use of CHM for COVID-19. Six of them[6,7,32,37,47,63] were

TABLE 1 Basic characteristics of the included trials

References	Age (mean ± SD) or age range (years)	Male/female	Severity of illness	Patients (n)		Loss to follow-up	Outcome
				CHM group	Control group	T/C	
Ai et al., 2020[a]	18–75	40/27	Ordinary cases	33	34	0	③ ④
Chen, Li et al., 2021[a]	T: 50.16 ± 5.11 C: 49.52 ± 5.06	35/25	Ordinary cases Mild COVID-19	30	30	2/1	⑦ ⑧
Ding et al., 2020[a]	Age ≥ 18	78/22	All stages of COVID	51	49	0	④
Duan et al., 2020[a]	T: 51.99 ± 13.88 C: 50.29 ± 13.17	62/61	Mild COVID-19	96	48	14/7	④ ⑦
Fu et al., 2020[a]	T: 43. 26 ± 7. 15 C: 43. 68 ± 6. 45	36/29	Ordinary cases Mild COVID-19	32	33	0	⑦
Hu F. et al., 2020[a]	18 - 75	104/96	Ordinary cases	100	100	43/29	⑦ ⑧
Hu K. et al., 2020[a]	T: 50.4 ± 15.2 C: 51.8 ± 14.8	150/134	All stages of COVID	142	142	3/3	⑦
Lan et al., 2020[a]	T: 43.05 ± 13.26 C: 42.40 ± 14.47	64/21	Ordinary cases Mild COVID-19	43	42	0	⑦
Liao, 2020[a]	T: 65.25 ± 7.42 C: 67.16 ± 8.64	38/32	All stages of COVID	35	35	0	④
Lin F. et al., 2020[a]	T: 46.02 ± 12.09 C: 43.80 ± 12.34	38/44	Ordinary cases	41	41	0	⑤
Ping et al., 2021[a]	T: 23–58 C: 25–64	26/28	Ordinary cases Mild COVID-19	30	30	0/6	⑧ ⑥ ⑦ ⑧
Qiu et al., 2020[a]	T: 53.35 ± 18.35 C: 51.32 ± 14.62	27/23	Ordinary cases	25	25	0	⑦
Sun et al., 2020[a]	T: 45.4 ± 14.10 C: 42.0 ± 11.70	28/29	Ordinary cases Mild COVID-19	32	25	0	⑦
Wang L. et al., 2020[a]	T: 41.1 ± 14.5 C: 40.8 ± 13.7	51/29	Ordinary cases	40	40	0	⑧
Wang YL. et al., 2020[a]	4–70	11/11	Asymptomatic SARS-CoV-2 Infection	11	11	0	⑧
Xiao et al., 2020[a]	T: 54.58 ± 13.76 C: 54.06 ± 13.90	70/51	All stages of COVID-19	58	63	0	③ ④ ⑦
Xiong et al., 2020[a]	T: 57.10 ± 14.00 C: 62.40 ± 12.3	-	Mild to severe stages of COVID-19	22	20	0	① ② ③ ④
Ye et al., 2020[a]	T: 65 (53.5–69) C: 59 (47–67)	6/35	All stages of COVID-19	28	14	0	⑦

TABLE 1 (Continued)

References	Age (mean ± SD) or age range (years)	Male/ female	Severity of illness	Patients (n)		Loss to follow-up	Outcome
				CHM group	Control group	T/C	
Yu P. et al., 2020[a]	T: 48. 27 ± 9. 56 C: 47. 25 ± 8. 67	171/124	Mild COVID-19	147	148	0	⑦
Chen, Chen et al., 2020[b]	23–95	102/128	Ordinary cases	115	115	0	① ② ④ ⑦
Chen, Liu et al., 2020[b]	Age≥18	29/39	Ordinary cases	34	34	0	① ② ④ ⑦
Cheng D. et al., 2020[b]	18–70	53/49	Ordinary cases	51	51	0	① ③
Cheng L. et al., 2020[b]	20–91	300/316	Severe COVID-19 Pneumonia	499	117	0	⑦
Guo et al., 2020[c]	T: 52 (46–57) C: 54 (44–59)	20/12	Mild to severe stages of COVID-19	16	16	0	④ ⑧
Hu Y. et al., 2020[b]	T: 48.30 ± 16.56 C: 49.75 ± 17.15	34/18	All stages of COVID-19	31	21	0	⑦ ⑧
Huang et al., 2020[b]	T: 58.4 ± 15.5 C: 66.3 ± 14.1	22/23	All stages of COVID-19	30	15	0	⑦
Ji et al., 2020[b]	18–70	28/22	Ordinary cases	28	22	0	① ③ ④ ⑦
Ke et al., 2020[b]	T: 56.17 ± 13.35 C: 52.43 ± 10.12	59/44	Ordinary cases	81	22	0	⑦
Li et al., 2020[b]	T: 53.60 ± 0.26 C: 50.43 ± 0.34	28/32	All stages of COVID	30	30	0	⑦
Lian et al., 2020[b]	T: 61.3 ± 14.11 C: 58.07 ± 11.98	25/39	All stages of COVID	38	26	0	⑤ ⑥ ⑦
Lin Y. et al., 2020[b]	T: 51.67 ± 17.69 C: 43.36 ± 13.11	22/21	All stages of COVID	18	25	0	⑧
Lin Z. et al., 2020[b]	45.46 ± 14.87	28/40	Ordinary cases Severe COVID-19	51	17	0	② ④ ⑧
Liu et al., 2020[b]	T: 44. 06 ± 14. 23 C: 49. 85 ± 17. 10	17/15	Ordinary cases Mild COVID-19	18	14	0	⑦ ⑧
Pan et al., 2020[b]	60.01 ± 13.00		Severe and critical COVID-19 Pneumonia	26	14	0	⑤ ⑥

(Continues)

TABLE 1 (Continued)

References	Age (mean ± SD) or age range (years)	Male/ female	Severity of illness	Patients (n)		Loss to follow-up	Outcome
				CHM group	Control group	T/C	
Qin et al., 2020[b]	T: 58.0 ± 2.9 C: 58.3 ± 2.9	25/22	Severe COVID-19 Pneumonia	21	26	0	⑧
Qu et al., 2020[b]	T: 40.65 ± 8.23 C: 39.82 ± 6.40	41/29	COVID-19	40	30	0	⑧
Shi et al., 2020[b]	47.61 ± 15.18	36/31	All stages of COVID-19	49	18	0	
Song et al., 2020[b]	T: 18–80 C: 21–80	31/29	Ordinary cases Mild COVID-19	30	30	0	⑧
Su et al., 2020[b]	17–86	82/68	Ordinary cases Mild COVID-19	75	75	0	⑦
Wang L. et al., 2020[b]	T: 44.68 ± 11.42 C: 49.70 ± 13.13	38/49	All stages of COVID	47	40	0	⑦ ⑧
Wang YY. et al., 2020[b]	T: 65 (61–68) C: 66 (56–71)	39/47	Severe COVID-19	43	43	0	⑦
Xia et al., 2020[b]	23–83	23/29	All stages of COVID	34	18	0	⑤ ⑥ ⑦
Xu et al., 2020[b]	T: 52.42 ± 15.70 C: 52.04 ± 13.41	23/29	Ordinary cases	26	26	0	⑧
Yao et al., 2020[b]	Age≥18	28/14	Ordinary cases	21	21	0	① ③ ④
Yu X. et al., 2020[c]	T: 60.50 ± 2.08 C: 64.23 ± 2.51	39/50	All stages of COVID-19	43	46	0	⑧
Zeng et al., 2020[b]	T: 46.65 ± 6.21 C: 46.21 ± 5.62	124/105	COVID-19 pneumonia with Phlegm-heat obstructing lung	104	125	0	⑧
Zhang H. et al., 2020[c]	T: 43.4 ± 15.9 C: 40.7 ± 13.3	8/14	COVID-19	11	11	0	⑦
Zhang N. et al., 2020[b]	T: 51.7 ± 12.5 C: 49.2 ± 13.6	62/58	Ordinary cases	90	30	0	⑦ ⑧

Note: ①, Disappearance rate of nausea; ②, Disappearance rate of vomiting; ③, Disappearance rate of anorexia; ④, Disappearance rate of diarrhea; ⑤, Alanine aminotransferase; ⑥, Aspartate aminotransferase; ⑦, Aggravation of COVID-19; ⑧, Time of nucleic acid conversion to negative.

Abbreviations: C, control group; CHM, Chinese herbal medicine; SD, standard deviation; T, treatment group.

[a]Randomized controlled trial.

[b]Cohort study.

[c]Case-Control Study.

RCTs, and six of them[20,25,28,29,34,49] were controlled observational studies. Of the total 187 COVID-19 patients with diarrhea, 96 received CHM along with standard pharmacotherapy and 91 received only standard pharmacotherapy. The pooled analysis did not show any significant difference in the rate of diarrhea remission between

TABLE 2 Risk of bias assessment of RCTs

References	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Ai et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Chen, Li et al., 2021	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Ding et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Duan et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	14.6
Fu et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Hu F. et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	36.0
Hu K. et al., 2020	Yes	Probably yes	No	No	Probably no	Probably no	Probably yes	2.1
Lan et al., 2020	Probably no	Probably no	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Liao, 2020	Probably yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Lin F. et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Ping et al., 2021	Probably no	Probably no	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Qiu et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Sun et al., 2020	Yes	Probably yes	No	No	Probably no	Probably yes	Probably yes	0
Wang L. et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0
Wang YL. et al., 2020	Yes	Probably yes	No	No	Probably no	Probably yes	Probably yes	0
Xiao et al., 2020	Yes	Probably yes	No	No	Probably no	Probably yes	Probably yes	0
Xiong et al., 2020	Probably no	Probably yes	No	No	Probably no	Probably yes	Probably yes	0
Ye et al., 2020	Yes	Yes	No	No	Yes	Yes	Yes	0
Yu P. et al., 2020	Yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	0

the CHM and standard pharmacotherapy (RR 1.04; 95% CI 0.92–1.16; $I^2 = 0\%$) (Figure 2d). Similar results were observed in the subgroup analysis by study design, prescriptions of interventions, disease type, severity, or duration when ≥2 studies could be pooled in the subgroup.

TABLE 3 Newcastle-Ottawa Risk of bias assessment for cohort studies

	Selection				Comparability		Outcome				
	1	2	3	4	5		6	7	8		
Study ID	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	A	B	Assessment of outcome	Follow-up	Complete accounting for cohorts	Total	Quality
Chen, Chen et al., 2020	1	1	1	0	1	1	1	1	0	7	High
Chen, Liu et al., 2020	1	1	1	0	1	1	1	1	0	7	High
Cheng D. et al., 2020	1	1	1	1	1	0	1	1	0	7	High
Cheng L. et al., 2020	1	1	1	1	0	1	1	1	0	7	High
Guo et al., 2020	1	1	1	0	0	0	1	1	0	5	Moderate
Hu Y. et al., 2020	1	1	1	1	0	1	1	0	0	6	Moderate
Huang et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Ji et al., 2020	1	1	1	1	1	0	1	1	0	7	High
Ke et al., 2020	1	1	1	1	1	1	0	0	0	6	Moderate
Li et al., 2020	1	1	1	1	1	1	1	0	0	7	High
Lian et al., 2020	1	1	1	0	1	1	1	1	0	7	High
Lin Y. et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Lin Z. et al., 2020	1	1	1	0	1	1	1	1	0	6	Moderate
Liu et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Pan et al., 2020	0	1	1	0	1	1	1	0	0	5	Moderate
Qin et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Qu et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Shi et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Song et al., 2020	1	1	1	1	1	1	1	0	0	7	High
Su et al., 2020	1	1	1	1	0	1	1	1	0	7	High
Wang L. et al., 2020	1	1	1	1	1	1	1	0	0	7	High

TABLE 3 (Continued)

	Selection				Comparability		Outcome				
	1	2	3	4	5		6	7	8		
Study ID	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	A	B	Assessment of outcome	Follow-up	Complete accounting for cohorts	Total	Quality
Wang YY. et al., 2020	1	1	1	1	1	1	1	1	0	8	High
Xia et al., 2020	1	1	1	0	1	1	1	0	0	6	Moderate
Xu et al., 2020	1	1	1	1	1	1	1	0	0	7	High
Yao et al., 2020	1	1	1	1	1	0	1	0	0	6	Moderate
Yu X. et al., 2020	1	1	1	1	1	1	1	0	0	7	High
Zeng et al., 2020	1	1	1	1	1	0	1	0	0	6	Moderate
Zhang H. et al., 2020	1	1	1	1	1	1	1	0	0	7	High
Zhang N. et al., 2020	1	1	1	1	1	1	1	0	0	7	High

Note: A, Cohorts comparable on basis of age; B, Cohorts comparable on other factor(s).

3.5 | Outcome 2: The recovery of liver function

3.5.1 | Alanine aminotransferase

The effective rate of ALT returning to normal was examined by three controlled observational studies,[22,24,60] and one RCT.[44] As shown in Figure 3a, there was no significant difference in the effective rate of ALT returning to normal between the users and non-users of CHM (RR 1.23; 95% CI 0.91–1.65; $I^2 = 54\%$). Subgroup analysis could not be conducted since the number of studies was limited.

3.5.2 | Aspartate aminotransferase

The effective rate of AST returning to normal was examined by three controlled observational studies,[22,24,60] and one RCT.[44] As shown in Figure 3b, there was no significant difference in AST between the users and non-users of CHM (RR 1.22; 95% CI 0.92–1.61; $I^2 = 68\%$). We could not perform further subgroup analysis because of the limited number of studies.

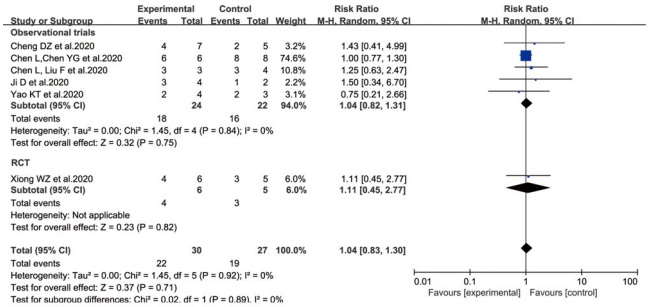
3.6 | Outcome 3: Efficacy on COVID-19

3.6.1 | Aggravation of COVID-19

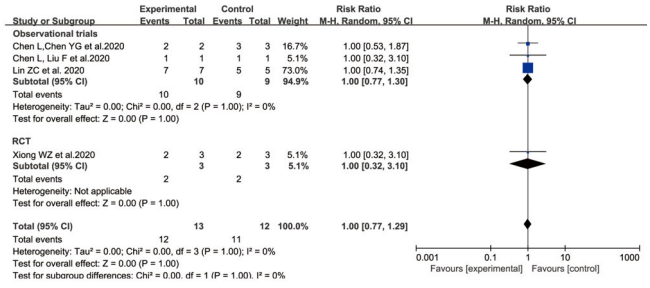
The aggravation of COVID-19 among users and non-users of CHM for COVID-19 was assessed by 28 studies including 12 RCTs[4–6,30,33,38,41–44,48,63] and 16 controlled observational studies.[22,25,26,28,29,31,35,36,39,50,52,58–62] Of the total 3,415 COVID-19 patients included, 2,011 received CHM along with standard pharmacotherapy and 1,404 received only standard pharmacotherapy. The meta-analysis showed significant difference between the two groups (RR 0.43; 95% CI 0.34–0.55), with almost non-existent heterogeneity ($I^2 = 0\%$; $p = 0.80$) (Figure 4a). These results were consistent with those in the subgroups conducted by study design, disease type, severity, prescriptions of interventions, and duration.

3.6.2 | Time to viral assay conversion

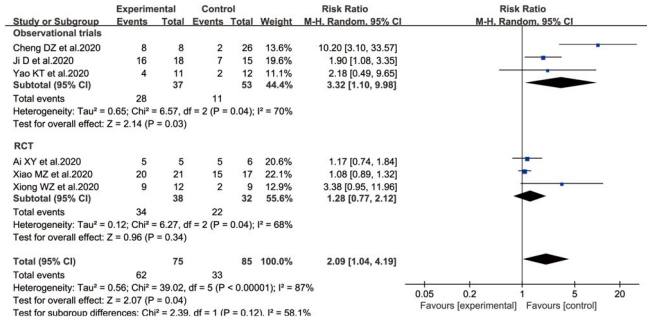
Time to viral assay conversion was reported by 19 studies including 13 controlled observational studies[26,34,40,49,51–57,59,61]



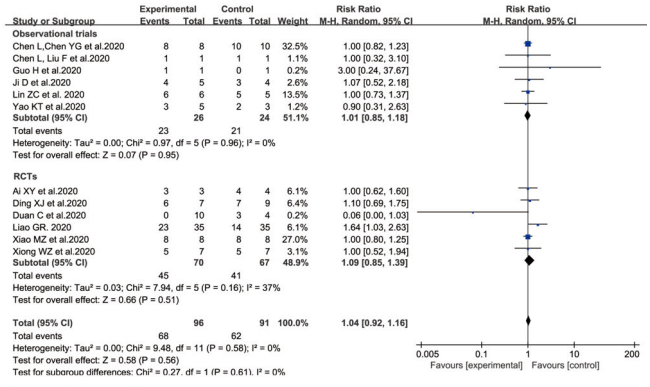
(a) The remission rate of nausea



(b) The remission rate of vomiting



(c) The remission rate of anorexia



(d) The remission rate of diarrhea

FIGURE 2 Forest plot of the comparison of CHM versus standard pharmacotherapy for the outcome of gastrointestinal symptoms

and six RCTs.[3,5,41,44–46] Of the total 1,349 COVID-19 patients included, 712 received CHM along with standard pharmacotherapy and 637 received only standard pharmacotherapy. It was found that CHM plus standard pharmacotherapy had a shorter time to viral assay conversion than the comparators (MD −3.48; 95% CI −4.33 to −2.64) with significant heterogeneity (I^2=84%; $p < 0.00001$), and random-effects model was used to accommodate statistical heterogeneity (Figure 4b). These results were consistent with those in the subgroups conducted by study design, duration, disease type, and severity.

3.7 | Publication bias

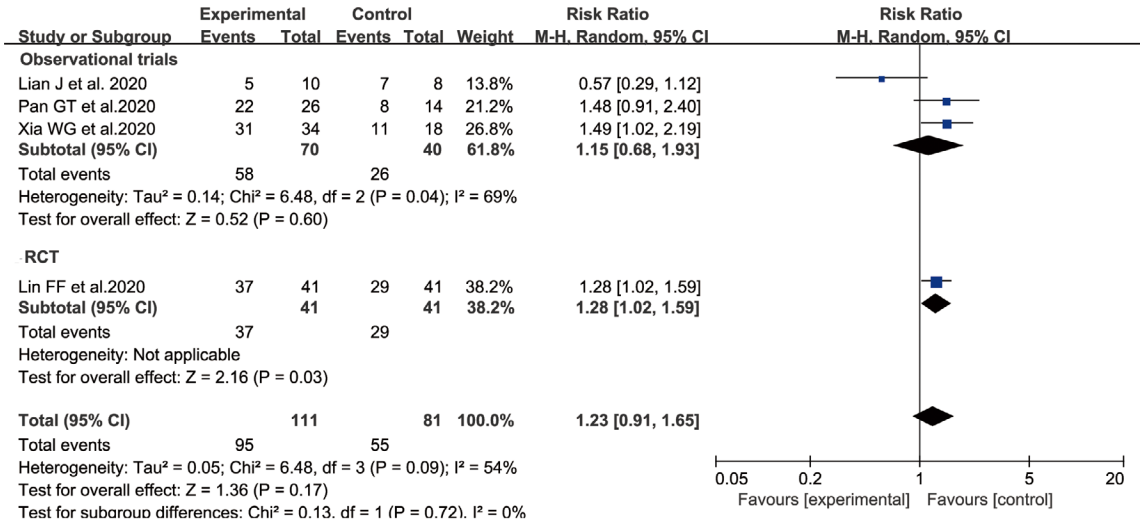
Potential publication bias was found by the visual inspection of the funnel plot in the meta-analysis of CHM's effects on the aggravation of COVID-19. The funnel plot was asymmetric, suggesting a mild publication bias of this meta-analysis (Figure 5).

3.8 | Certainty of the evidence

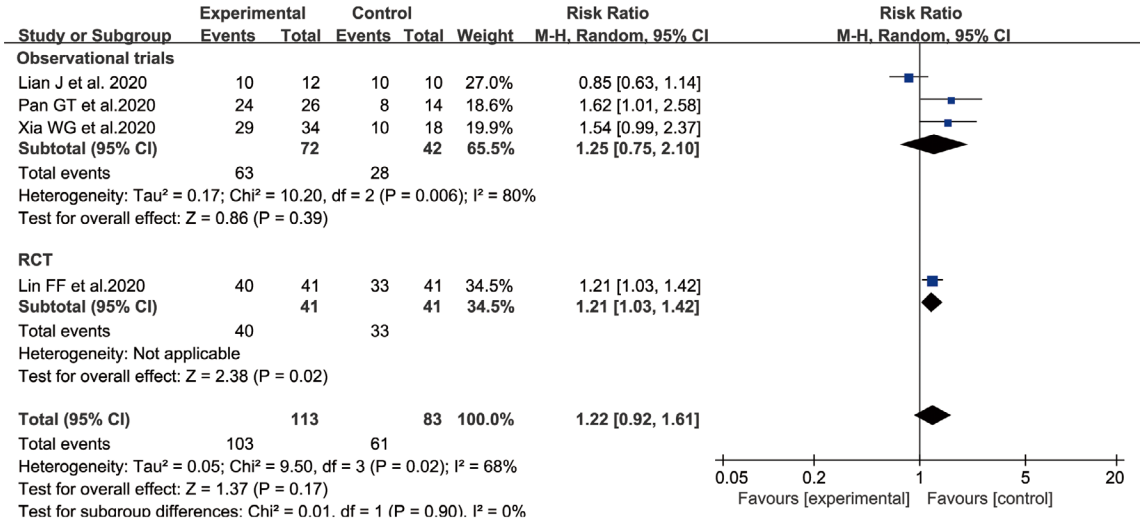
The certainty of evidence relevant to the aggravation of COVID-19 in RCTs had high quality. Diarrhea remission in RCTs, anorexia remission in observational trials, and the aggravation of COVID-19 in observational trials had a moderate quality of evidence. The certainty of evidence relevant to the following outcomes was low: the rate of nausea remission, anorexia remission, and vomiting remission in RCTs; the effective rate of ALT and AST returning to normal in RCT; the rate of nausea remission, and diarrhea remission in observational trials. Additionally, the quality of findings relevant to the time to viral assay conversion, the remission of vomiting in observational trials, and the effective rate of ALT and AST returning to normal in observational trials, was very low, suggesting that those outcomes should be interpreted carefully and may be changed after future researches (Table 4).

4 | DISCUSSION

According to the data released by WHO, as of 11:21 pm on 29 November 2020, there were 61,869,330 confirmed COVID-19 cases and 1,448,896 confirmed deaths in 220 countries, areas, or territories.[64] A vast number of clinical studies have reported about COVID-19 treatment. Several initial observational studies were reported in rapid succession with poor methodologic quality, and most did not report outcomes of gastrointestinal symptoms and liver function. Nevertheless, COVID-19 patients experienced gastrointestinal symptoms, such as anorexia, nausea, vomiting, and diarrhea; they may also present with abnormal liver functions, which manifested as an increase in ALT and AST; digestive symptoms and liver



(a) The effective rate that ALT level returned to normal

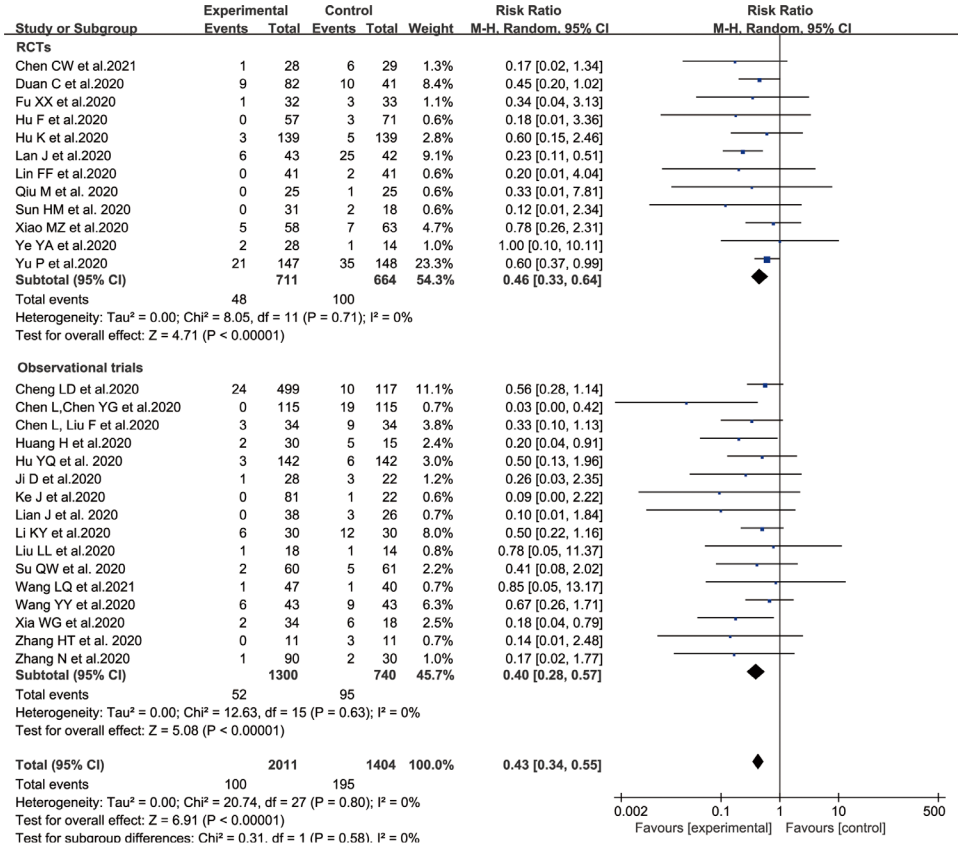


(b) The effective rate that AST level returned to normal

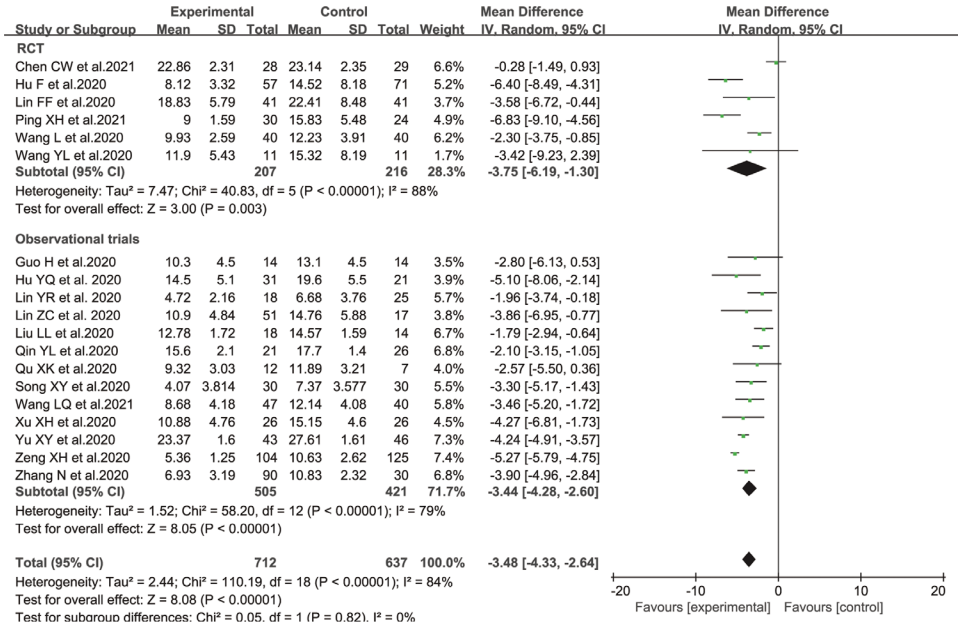
FIGURE 3 Forest plot of the comparison of CHM versus standard pharmacotherapy for the outcome of liver function

injury became more pronounced as the severity of the disease increased.[65] Hence, identifying the efficacy of potential therapeutics not only on COVID-19 but also on gastrointestinal symptoms and liver function, needed to be considered.

Among the various medications tried, CHM has received noticeable attention. Traditional Chinese medicine believed patients can be diagnosed and generalized into certain patterns according to clinical manifestations, and treated with herbal medicine. With the increasing relevant evidence including RCTs, we investigated the pooled efficacy of CHM on gastrointestinal symptoms and liver function in patients with COVID-19, and found that CHM plus standard pharmacotherapy may reduce the rate of COVID-19 aggravation and the nucleic acid-negative conversion time, but did not improve liver functions, compared with standard pharmacotherapy. In addition, the present CHM aimed at COVID-19 had no advantages on most gastrointestinal symptoms compared with standard pharmacotherapy, which may be caused by the large number of applications of cold-natured herbs with the function of clearing away heat and removing toxins to treat the emergency symptoms of COVID-19.



(a) Aggravation of COVID-19



(b) Nucleic acid-negative conversion time

FIGURE 4 Forest plot of the comparison of CHM versus standard pharmacotherapy for the outcome of efficacy on COVID-19

This study has several strengths. Firstly, this meta-analysis systematically assessed the efficacy of CHM on gastrointestinal symptoms and liver functions among COVID-19 patients through analysis of both RCTs and observational studies based on the latest studies, providing a comprehensive synthesis of up-to-date evidence. Our findings underlined the need of paying attention to COVID-19 patients who were suffering gastrointestinal

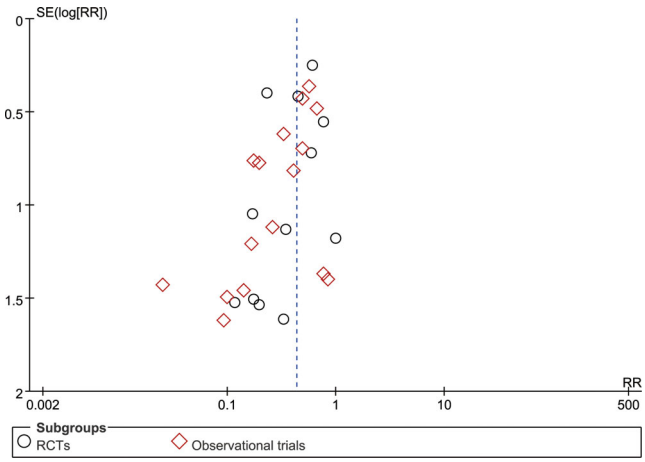


FIGURE 5 Funnel plot of the comparison of CHM versus standard pharmacotherapy for the outcome of aggravation of COVID-19

symptoms and liver injury, which may inspire future COVID-19 studies. Besides, we conducted subgroup analysis according to study design, duration, prescriptions of interventions, disease type, and severity to rule out the influence of variations and eliminate heterogeneity. In addition, we evaluated the current results based on the grading of recommendations assessment, development, and evaluation (GRADE) assessment, which may be beneficial to the revision and promotion of the new diagnosis and treatment guidelines in the later stage.

Nevertheless, some limitations should be noted in our meta-analysis. First, most of our included studies were conducted in China. Limited information on other ethnic groups may have admission bias and selection bias. Second, as for the controlled observational studies included, some confounding factors may influence the certainty of the evidence. The sample size of some studies was small, so the test efficiency of some outcomes may be insufficient. Third, clinical studies evaluating the efficacy of CHM on COVID-19 usually had several limitations such as no placebo and poor methodologic quality.

In view of the public anxiety on COVID-19 worldwide, this systematic review and meta-analysis, critically appraising CHM and presenting evidence, may provide some evidence on this important issue. CHM achieved synergistic efficacy in reducing the rate of COVID-19 aggravation and the time to viral assay conversion when combined with standard pharmacotherapy, which may give meaningful hints to the clinical practice, and inspiration for the development of new drugs. Our results may allow clinicians and COVID-19 patients to comprehensively understand the efficacy of CHM on the digestive system and liver functions and make informed decisions. Certainly, the CHM that aimed at COVID-19 with a protective effect on the liver and digestive system needs to be investigated furtherly. Due to the limited understanding of the mechanism and precise therapeutic components of CHM, the standardization or evidence-based rationale for CHM used in COVID-19 still needs further studies. Additionally, the relevant placebo-controlled trials with double-blind are warranted in future COVID-19 researches.

5 | CONCLUSION

This meta-analysis of CHM on gastrointestinal symptoms and liver function for COVID-19 patients seemingly indicated that although CHM had some benefits in reducing the rate of COVID-19 aggravation and nucleic acid-negative conversion time, the present CHM against COVID-19 showed limited advantages in improving gastrointestinal symptoms and liver function in conjunction with conventional medical care for COVID-19 patients, based on the latest evidence. Further exploration of current findings and well-conducted trials are warranted.

ACKNOWLEDGMENT

Funding was provided by China Postdoctoral Science Foundation, Grant Number: 2020T130010ZX.

CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

AUTHOR CONTRIBUTIONS

Shihua Shi and Zhenxing Wang conceived the study. Zhenxing Wang and Fei Wang supervised the overall study. Shihua Shi, Jiang Li, and Yulong Li drafted the manuscript and produced the tables and pictures. Shihua Shi and Jiang Li separately performed the literature searches. Yulong Li and Xiaoping Wu separately conducted the data extraction of each of the included studies. Yongcan Wu, Caixia Pei, Demei Huang, and Xiaomin Wang conducted methodological quality evaluation of the eligible studies. Jiang Li and Heng Qiu conducted statistical analysis. Peili Wang, Weihao Li, Shuo Kou, and Zhenxing Wang critically revised the manuscript for important intellectual content. All the authors participated in making the decision to submit the manuscript for publication.

ORCID

Shihua Shi https://orcid.org/0000-0001-6475-2349
Fei Wang https://orcid.org/0000-0002-8158-0742
Zhenxing Wang https://orcid.org/0000-0001-6832-9652

TABLE 4 Certainty of evidence

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plus vs.CPT**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Disappearance rate of nausea—Observational trials												
5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	18/24 (75%)	16/22 (72.7%) 66.7%	RR 1.04 (0.82 to 1.31)	29 more per 1000 (from 131 fewer to 225 more) 27 more per 1000 (from 120 fewer to 207 more)	⨁⨁OO LOW	CRITICAL
Disappearance rate of nausea—RCT												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	4/6 (66.7%)	3/5 (60%) 60%	RR 1.11 (0.45 to 2.77)	66 more per 1000 (from 330 fewer to 1000 more) 66 more per 1000 (from 330 fewer to 1000 more)	⨁⨁OO LOW	CRITICAL
Disappearance rate of vomiting—Observational trials												
3	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	None	10/10 (100%)	9/9 (100%) 100%	RR 1 (0.77 to 1.3)	0 fewer per 1000 (from 230 fewer to 300 more) 0 fewer per 1000 (from 230 fewer to 300 more)	⨁OOO VERY LOW	CRITICAL
Disappearance rate of vomiting—RCT												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	2/3 (66.7%)	2/3 (66.7%)	RR 1 (0.32 to 3.1)	0 fewer per 1000 (from 453 fewer to 1000 more)	⨁⨁OO LOW	CRITICAL

TABLE 4 (Continued)

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plus vs.CPT	Control	Relative (95% CI)	Absolute	Quality	Importance
								66.7%		0 fewer per 1000 (from 454 fewer to 1000 more)		
Disappearance rate of anorexia—Observational trials												
3	Observational studies	No serious risk of bias	Serious[c]	No serious indirectness	No serious imprecision	Strong association[d]	28/37 (75.7%)	11/53 (20.8%)	RR 3.32 (1.1 to 9.98)	482 more per 1000 (from 21 more to 1000 more)	⨁⨁OO LOW	CRITICAL
								16.7%		387 more per 1000 (from 17 more to 1000 more)		
Disappearance rate of anorexia—RCTs												
3	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	Strong association[d]	34/38 (89.5%)	22/32 (68.8%)	RR 1.28 (0.77 to 2.12)	192 more per 1000 (from 158 fewer to 770 more)	⨁⨁⨁O MODERATE	CRITICAL
								83.3%		233 more per 1000 (from 192 fewer to 933 more)		
Disappearance rate of diarrhea—Observational trials												
6	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	23/26 (88.5%)	21/24 (87.5%)	RR 1.01 (0.85 to 1.18)	9 more per 1000 (from 131 fewer to 157 more)	⨁⨁OO LOW	CRITICAL
								87.5%		9 more per 1000 (from 131 fewer to 157 more)		

(Continues)

TABLE 4 (Continued)

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plus vs.CPT**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Disappearance rate of diarrhea—RCTs												
6	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/70 (64.3%)	41/67 (61.2%)	RR 1.09 (0.85 to 1.39)	55 more per 1000 (from 92 fewer to 239 more)	⨁⨁⨁O MODERATE	CRITICAL
								76.4%		69 more per 1000 (from 115 fewer to 298 more)		
ALT—Observational trials												
3	Observational studies	Serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	58/70 (82.9%)	26/40 (65%)	RR 1.15 (0.68 to 1.93)	97 more per 1000 (from 208 fewer to 604 more)	⨁OOO VERY LOW	CRITICAL
								61.1%		92 more per 1000 (from 196 fewer to 568 more)		
ALT–RCT												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	37/41 (90.2%)	29/41 (70.7%)	RR 1.28 (1.02 to 1.59)	198 more per 1000 (from 14 more to 417 more)	⨁⨁OO LOW	CRITICAL
								70.7%		198 more per 1000 (from 14 more to 417 more)		
AST–Observational trials												
3	Observational studies	Serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	63/72 (87.5%)	28/42 (66.7%)	RR 1.25 (0.75 to 2.1)	167 more per 1000 (from 167 fewer to 733 more)	⨁OOO VERY LOW	CRITICAL
								57.1%		143 more per 1000 (from 143 fewer to 628 more)		

TABLE 4 (Continued)

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plus vs.CPT**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
AST–RCT												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	40/41 (97.6%)	33/41 (80.5%)	RR 1.21 (1.03 to 1.42)	169 more per 1000 (from 24 more to 338 more)	⨁⨁OO LOW	CRITICAL
								80.5%		169 more per 1000 (from 24 more to 338 more)		
Aggravation of COVID-19—RCTs												
12	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association[f]	48/711 (6.8%)	100/664 (15.1%)	RR 0.46 (0.33 to 0.64)	81 fewer per 1000 (from 54 fewer to 101 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
								10.1%		55 fewer per 1000 (from 36 fewer to 68 fewer)		
Aggravation of COVID-19—Observational trials												
16	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association[f]	52/1300 (4%)	95/740 (12.8%)	RR 0.4 (0.28 to 0.57)	77 fewer per 1000 (from 55 fewer to 92 fewer)	⨁⨁⨁O MODERATE	IMPORTANT
								12.6%		76 fewer per 1000 (from 54 fewer to 91 fewer)		
Time of nucleic acid conversion to negative—RCTs (Better indicated by lower values)												
6	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	Reporting bias[g]	207	216	–	MD 3.75 lower (6.19 to 1.3 lower)	⨁OOO VERY LOW	IMPORTANT

(Continues)

TABLE 4 (Continued)

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plus vs.CPT	Control	Relative (95% CI)	Absolute	Quality	Importance
Time of nucleic acid conversion to negative—Observational trials (Better indicated by lower values)												
13	Observational studies	No serious risk of bias	Serious[c]	No serious indirectness	No serious imprecision	None	505	421	–	MD 3.44 lower (4.28 to 2.6 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

[a]Randomization allocation and the blinding were unclear, and we decided to downgrade the quality of evidence as the risk of bias.
[b]Results were imprecise since the study includeed relatively few patients and few events.
[c]There was serious heterogeneity among the studies included in the analysis of this outcome. Overall, we decided to downgrade by one level considering these issues along with inconsistency.
[d]RR > 2 based on consistent evidence from at least two studies.
[e]The average NOS score of this outcome was six, and the risk of bias of it was moderate.
[f]RR < 0.5 based on consistent evidence from at least two studies.
[g]Visual inspection of the funnel plot showed an asymmetry in the meta-analysis.

REFERENCES

1. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA. 2020;324(5):460–470.
2. General Office of National Health Commission of the People's Republic of China Office of National Administration of Traditional Chinese Medicine. Diagnosis and treatment of corona virus disease-19 (8th trial edition). Chin Med. 2020;15(10): 1494–1499.
3. Wang Y, Xue J, Dai E, et al. Clinical study on the treatment of patients with novel coronavirus pneumonia and asymptomatic infection with integrated traditional Chinese and western medicine. Hebei J TCM. 2020;42(5):645–649.
4. Hu K, Guan W-J, Bi Y, et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. Phytomedicine. 2020. http://dx.doi.org/10.1016/j.phymed.2020.153242.
5. Hu F, Guo A, Huang L, et al. Jinyinhua liquid at different dosage combined with western medicine conventional treatment for common type COVID-19: a multicenter trial of 187 cases. J Tradit Chin Med. 2020;62(2):510–515.
6. Duan C, Xia W, Zheng C, et al. Clinical observation on Jinhua Qinggan granule combined with conventional western medicine therapy in treating mild cases of coronavirus disease 2019. J Tradit Chin Med. 2020;6(17):1473–1477.
7. Ding X, Zhang Y, He D, et al. Clinical effect and mechanism of Qingfei Touxie Fuzheng recipe in the treatment of COVID-19. Herald Med. 2020;39(5):640–643.
8. Fan AY, Gu S, Alemi SF, Research Group for Evidence-based Chinese M. Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis. J Integr Med. 2020;18(5):385–394.
9. Xiong X, Wang P, Su K, Cho W, Xing Y. Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis. Pharmacol Res. 2020. http://dx.doi.org/10.1016/j.phrs.2020.105056.
10. Mao R, Qiu Y, He J-S, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. The Lancet Gastroenterol Hepatol. 2020;5(7):667–678.
11. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020;526(1):135–140.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
13. Xiong X, Yang X, Li X, et al. Efficacy and safety of Chinese herbal medicine for patients with postmenopausal hypertension: A systematic review and meta-analysis. Pharmacol Res. 2019;141:481–500.
14. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(oct18 2):d5928.
15. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. J Clin Epidemiol. 2012;65(3): 262–267.

16. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. JAMA. 2018;320(23):2448–2460.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–605.
18. Higgins JP, Thompson SG, Deeks J, JAltman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560.
19. Stuck AE, Rubenstein L, ZWieland D. Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ. 1998; 316(7129):469–477.
20. Yao K, Liu M, Li X, Huang JCai H. Retrospective clinical analysis on treatment of coronavirus disease 2019 with traditional Chinese Medicine Lianhua Qingwen. Chin J Exp Tradit Med Formulae. 2020;26(11):8–12.
21. Yang Q, Sun Q, Jiang B, et al. Retrospective clinical study on treatment of COVID-19 patients with integrated traditional Chinese and western medicine. Chin Tradit Herb Drugs. 2020; 51(8):2050–2053.
22. Xia W, An C, Zheng C, et al. Clinical observation on 34 patients with novel coronavirus pneumonia (COVID-19) treated with intergrated traditional Chinese and Western Medicine. J TCM. 2020;61(5):375–382.
23. Shi J, Yang Z, Ye C, et al. Clinical observation on 49 cases of non-critical COVID-19 in Shanghai treated by integrated traditional Chinese and western medicine. Shanghai J Tradit Chin Med. 2020;54(4):30–35.
24. Pan G, Du C, Liu Y, et al. Integrated traditional Chinese and Western Medicine in the Treatment of 40 cases of critical patients with COVID-19. Acta Med Univ Sci Technol Huazhong. 2020;49(2):202–207.
25. Ji D, Feng P, Fei X. Retrospective study of clinical efficacy of integrated Chinese and Western medicine in treatment of COVID-19. Shandong J Tradit Chin Med. 2020;39(7):645–653.
26. Hu Y, Lu J, Huang J, et al. Clinical observation of 31 cases with corona virus disease 2019 treated with Guizhi Erchen decoction based on triple-Jiao sequential therapy. Chin Arch TCM. 2020; 38(10):1–5.
27. Cheng D, Wang W, Li Y, et al. Analysis of curative effect of 51 patients with novel coronavirus pneumonia treated with Chinese medicine Lianhua Qingwen: a multicentre retrospective study. Tianjin J TCM. 2020;37(5):509–516.
28. Chen L, Liu F, Wu J, et al. Clinical efficacy of Shufeng Jiedu capsule combined with Western medicine in treatment of common COVID-19 patients by retrospective analysis. Chin J Exp Tradit Med Formulae. 2020;26(16):14–20.
29. Chen L, Chen Y, Cheng Z, et al. Retrospective analysis on clinical efficacy of Ganlu Xiaodu decoction combined with Western medicine in treatment of common COVID-19 patients. Chin J Exp Tradit Med Formulae. 2020;26(19):60–67.
30. Sun H, Xu F, Zhang L, et al. Study on clinical efficacy of Lianhua Qingke granule in treatment of mild and ordinary COVID-19. Chin J Exp Tradit Med Formulae. 2020;26(14): 29–34.
31. Su Q, Qiu M, Tao C, et al. Analysis of clinical results of 75 cases of COVID-19 treated by integrated Traditional Chinese and Western medicine—based on the theory of Fengwen Yi. Lishizhen Med Mater Med Res. 2020;31(6):1450–1453.
32. Liao G. Study on the effect and safety of self-made traditional Chinese medicine decoction in patients with COVID-19. Int Infect Dis. 2020;9(2):353.
33. Qiu M, Li Q, Zhu D, et al. Efficacy observation of maxing Xuanfei Jiedu decoction on moderate COVID-19 patients. JETCM. 2020;29(7):1129–1132.
34. Lin Z, Yu J, Xiao C, et al. Clinical observation on integrated traditional Chinese and western medicine in the treatment of 51 cases of Corona Virus Disease 2019 in Hangzhou area. Chin J Tradit Chin Med Pharm. 2020;35(8):4222–4225.
35. Huang H, Tan S, Zuo X, et al. Analysis of TCM syndrome characteristics and clinical efficacy of 72 patients with COVID-19. Mod J Integr Tradit Chin West Med. 2020;29(22):2395–2483.
36. Cheng L, Jiang Y, Cheng B LWang X. Analysis of drug use in 616 patients with coronavirus disease 2019 in a hospital. Chin Pharm. 2020;29(10):50–53.
37. Ai X, Lin L, Xie MTan X. Effect of integrated traditional Chinese and Western medicine on T lymphocyte subsets of patients with normal type of COVID-19. Guangdong Med J. 2020;41(12):1203–1206.
38. Yu P, Li Y, Wan SWang Y. Effects of Lianhua Qingwen granules plus arbidol on treatment of mild corona virus disease-19. Chin Pharm J. 2020;55(12):1042–1045.
39. Li K, An W, Xia F, et al. Observation on clinical effect of modified Qingfei Paidu Decoction in treatment of COVID-19. Chin Tradit Herb Drugs. 2020;51(8):2046–2049.
40. Qin Y, Song Y, Zhou L, Cui YZhang A. Clinical efficacy of reduning injection combined with methylprednisolone in the treatment of severe coronavirus disease 2019. Chin Pharm. 2020;29(9):19–22.
41. Chen C, Li X, Liu YChen S. Clinical study of Lianhua Qingwen capsule in the treatment of corona virus disease 2019. Res Integr Tradit Chin West Med. 2021;13(1):1–4.
42. Fu X, Lin LTan X. Clinical observation on effect of Toujie Quwen granules in treatment of COVID-19. Chin J Exp Tradit Med Formulae. 2020;26(12):44–48.
43. Lan J, Fan G, Meng L. Clinical efficacy and mechanism of Qushi Paidu Fuzheng Recipe in treatment of corona virus disease 2019 with syndrome of cold dampness lung stagnation and epidemic toxin closing lung. Chin J TCM WM Crit Care. 2020;27(3):262–266.
44. Lin FF, Huang JP, Yang J, et al. Clinical study on Xuanfei Qingre decoction as an adjuvant treatment for ordinary cases of COVID-19. Zhejiang J Int Tradit Chin West Med. 2020;30 (12):977–981.
45. Ping X, Xu H, Fu D, et al. Clinical observation of Jiawei Yupingfeng powder combined with western medicine in the treatment of the novel coronavirus pneumonia. Med Forum. 2021;25(2):149–151.
46. Wang L, Xu M, Wang Y, et al. Clinical study on Shengmai Powder combined with Shenling Baizhu Powder in the treatment of common Corona Virus Disease 2019. CJTCMP. 2020; 35(8):4268–4271.
47. Xiong WZ, Wang G, Du Jai W. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: a pilot randomized clinical trial. Integr Med Res. 2020;9(3):4.
48. Ye YA, G-CHAMPS Collaborative Group. Guideline-based Chinese herbal medicine treatment plus standard care for severe

coronavirus disease 2019 (G-CHAMPS): Evidence From China. Front Med. 2020;7(256):1–7.
49. Guo H, Zheng J, Huang G, et al. Xuebijing injection in the treatment of COVID-19: a retrospective case-control study. Ann Palliat Med. 2020;9(5):3235–3248.
50. Ke J, Tian F, Lin H, et al. Analysis of curative effect of integrated traditional Chinese and Western medicine on new coronavirus Pneumoni. World Latest Med Inf. 2020;20(78):256–257.
51. Lin Y, Wu F, Xie Z, et al. Clinical study of artesunate in the treatment of coronavirus disease 2019. Chin Crit Care Med. 2020;32(4):417–420.
52. Liu L, Yuan L, Feng Y, et al. Clinical study on combined scheme of Lianhuaqingwen Capsules and abidole in the treatment for coronavirus disease 2019. Guangdong Med J. 2020;41(12):1207–1210.
53. Qu X, Hao S, Ma J, et al. Observation on clinical effect of Shufeng Jiedu Capsule combined with Arbidol Hydrochloride Capsule in treatment of COVID-19. Chin Tradit Herb Drugs. 2020;51(5):1167–1170.
54. Song X. Clinical retrospective study on novel coronavirus pneumonia treated with triple focus treatment, Master Thesis. *Hubei University of Chinese Medicine (Wuhan, Hubei Province)*. 2020.
55. Xu X, Dong H, Tu S, et al. Retrospective analysis of Jinye Baidu Granules and Lianhua Qingwen Capsules in the treatment of ordinary cases of COVID-19. Res Integr Tradit Chin West Med. 2020;12(6):383–389.
56. Yu XY, Zhang S, Yan FF, Su DZ. Comparison of clinical efficacy of Qingfei Paidu decoction combined with western medicine in 43 cases and single western medicine in 46 cases in the treatment of COVID-19. J Shandong Univ (Health Sci). 2020;58(12):47–53.
57. Zeng XH, Ma W HWang J. Effect of Qingfei Paidu decoction on clinical efficacy of COVID-19 pneumonia with Phlegm heat blocking lung. Med J West Chin. 2020;32(12):1799–1806.
58. Zhang HT, Huang MX, Liu X, et al. Evaluation of the adjuvant efficacy of natural herbal medicine on COVID-19: a retrospective matched case-control study. Am J Chin Med. 2020;48(4):1–14.
59. Zhang N, Qu Y, Jin Y, et al. Retrospective study of traditional Chinese Medicine "Ma Xing Shigan decoction" combined with Western Medicine in the treatment of ordinary COVID-19. J Front Med. 2020;10(15):31–34.
60. Lian J, Zhang S, Li G, et al. Retrospective analysis of 38 cases with coronavirus disease 2019 treated by integrated traditional Chinese and Western Medicine. J Tradit Chin Med. 2020;61(24):2126–2130.
61. Wang L, Hu G, Ba Y, et al. A Retrospective Study on the Treatment of Coronavirus Disease 2019 with "Pneumonia No.1" Combined with Conventional Western Medicine. JETCM. 2021;30(1):10–12.
62. Wang Y, Liu Y, Lv Q, et al. Effect and safety of Chinese herbal medicine granules in patients with severe coronavirus disease 2019 in Wuhan, China: a retrospective, single-center study with propensity score matching. Phytomedicine. 2020. http://dx.doi.org/10.1016/j.phymed.2020.153404.
63. Xiao M, Tian J, Zhou Y, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: a randomized controlled trial. Pharmacol Res. 2020;161:105126.
64. WHO. Coronavirus disease 2019 (COVID-19) outbrake situation [Internet]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed 5 November 2020).
65. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol, 2020;92(10):1902–1914.

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: Shi S, Wang F, Li J, et al. The effect of Chinese herbal medicine on digestive system and liver functions should not be neglected in COVID-19: An updated systematic review and meta-analysis. *IUBMB Life*. 2021;73:739–760. https://doi.org/10.1002/iub.2467