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Chinese herbal medicine in adults with mild to moderate coronavirus disease 2019(COVID-19): A systematic review and meta-analysis

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Keywords:	Coronavirus disease 2019, Chinese herbal medicine, Systematic review, Meta-analysis, Randomized controlled trials
Abstract:	Introduction Coronavirus disease 2019 (COVID-19) infected by SARS-CoV-2 has spread all over the world, which is a serious threat to human life and health. In China's experience in fighting COVID-19, traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), has played an important role. Human studies reported the beneficial effects of CHM in the treatment of adult patients with mild to moderate COVID-19. Presently there is no systematic evaluation of the clinical efficacy of CHM in adult patients with mild to moderate COVID-19. Therefore, this review was designed to evaluate the efficacy and safety of CHM in the treatment of adult patients with mild to moderate COVID-19. Methods RCTs about CHM for mild to moderate COVID-19 were searched in the following eight electronic databases: PubMed, EMBASE, Cochrane Central Register of Controlled trials, the Clinical Trials.gov website, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and China Biology Medicine (CBM) from December 2019 to November 2020. Two reviewers independently searched, selected studies and extracted data according to the eligibility criteria. Cochrane Risk of Bias (ROB) tool was used to assess the methodological quality of the included RCTs. And Revman5.3.0 software was used for statistical analysis. Results Twelve eligible RCTs were included with a total sample size of 1393. Our meta-analyses found that compared with the conventional western medicine (CWM) treatment, the effective rate of lung CT [RR=1.26, 95%CI (1.15, 1.38), P < 0.00001], and clinical cure rate [RR=1.26, 95%CI (1.16, 1.38), P < 0.00001] of the CHM treatment were better. Besides, CHM could reduce the rate of conversion to severe cases [RR=0.48, 95%CI (0.32, 0.73), P =0.0005], TCM symptom score of fever [MD=-0.62, 95%CI (-0.79, -0.45), P < 0.00001], the cough cases [RR=1.43, 95%CI (1.16, 1.75), P =0.0006], TCM symptom score of cough[MD=-1.07, 95%CI (-1.29, -0.85), P < 0.00001], TCM symptom score of fatigue[MD=-0.66, 95%CI (-1.05, -0.28), P =0.0007], CRP[MD=-5.46, 95%CI (-8.19, -2.72), P < 0.0001], and improve WBC count[MD=0.38, 95%CI (0.31, 0.44), P < 0.00001], and the above meta-analysis results were robust and reliable through sensitivity analysis. Conclusion Chinese herbal medicine is effective and safe in the treatment of adults with mild to moderate COVID-19. And Chinese herbal medicine may be a promising candidate for the treatment of mild to moderate COVID-19.
Order of Authors:	Xuqin Du
	Lipeng Shi
	Wenfu Cao
	Biao Zuo

	Aimin Zhou
Additional Information:	
Question	**Response**
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Format for specific study types **Human Subject Research (involving human participants and/or tissue)** • Give the name of the institutional review board or ethics committee that approved the study • Include the approval number and/or a statement indicating approval of this research • Indicate the form of consent obtained (written/oral) or the reason that consent was not obtained (e.g. the data were analyzed anonymously) **Animal Research (involving vertebrate animals, embryos or tissues)** • Provide the name of the Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board that reviewed the study protocol, and indicate whether they approved this research or granted a formal waiver of ethical approval • Include an approval number if one was obtained • If the study involved *non-human primates*, add *additional details* about animal welfare and steps taken to ameliorate suffering • If anesthesia, euthanasia, or any kind of animal sacrifice is part of the study, include briefly which substances and/or methods were applied **Field Research** Include the following details if this study involves the collection of plant, animal, or other materials from a natural setting: • Field permit number • Name of the institution or relevant body that granted permission	
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Chinese herbal medicine in adults with mild to moderate coronavirus disease 2019(COVID-19): A systematic review and meta-analysis

Xuqin Du[1,2], Lipeng Shi [3,*], Wenfu Cao [1,2,4,*] , Biao Zuo[1,2], Aimin Zhou[3]

[1] College of Traditional Chinese Medicine, Chongqing Medical University, Chongqing 400016, People's Republic of China

[2] Chongqing Key Laboratory of Traditional Chinese Medicine for Prevention and Cure of Metabolic Diseases, Chongqing 400016, People's Republic of China

[3] Department of Cardiovascular Unit, Traditional Chinese medicine hospital Dianjiang Chongqing, Chongqing 408300, People's Republic of China

[4] Department of Chinese Traditional Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China

* shilipeng0206@163.com； caowenfu9316@163.com

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ABSTRACT

Introduction

Coronavirus disease 2019 (COVID-19) infected by SARS-CoV-2 has spread all over the world, which is a serious threat to human life and health. In China's experience in fighting COVID-19, traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), has played an important role. Human studies reported the beneficial effects of CHM in the treatment of adult patients with mild to moderate COVID-19.

Presently there is no systematic evaluation of the clinical efficacy of CHM in adult patients with mild to moderate COVID-19. Therefore, this review was designed to evaluate the efficacy and safety of CHM in the treatment of adult patients with mild to moderate COVID-19.

Methods

RCTs about CHM for mild to moderate COVID-19 were searched in the following eight electronic databases: PubMed, EMBASE, Cochrane Central Register of Controlled trials, the Clinical Trials.gov website, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and China Biology Medicine (CBM) from December 2019 to November 2020. Two reviewers independently searched, selected studies and extracted data according to the eligibility criteria. Cochrane Risk of Bias (ROB) tool was used to assess the methodological quality of the included RCTs. And Revman5.3.0 software was used for statistical analysis.

Results

Twelve eligible RCTs were included with a total sample size of 1393. Our meta-analyses found that compared with the conventional western medicine (CWM) treatment, the effective rate of lung CT [RR=1.26, 95%CI (1.15, 1.38), $P<0.00001$], and clinical cure rate [RR=1.26, 95%CI (1.16, 1.38), $P<0.00001$] of the CHM treatment were better. Besides, CHM could reduce the rate of conversion to severe cases [RR=0.48, 95%CI (0.32, 0.73), $P=0.0005$], TCM symptom score of fever [MD=-0.62, 95%CI (-0.79, -0.45), $P<0.00001$], the cough cases [RR=1.43, 95%CI (1.16, 1.75), $P=0.0006$], TCM symptom score of cough[MD=-1.07, 95%CI (-1.29, -0.85), $P<0.00001$], TCM symptom score of fatigue[MD=-0.66, 95%CI (-1.05, -0.28), $P=0.0007$], CRP[MD=-5.46, 95%CI (-8.19, -2.72), $P<0.0001$], and improve WBC count[MD=0.38, 95%CI (0.31, 0.44), $P < 0.00001$], and the above meta-analysis results were robust and reliable through sensitivity analysis.

Conclusion

on

space

The results section is only made up of one long sentence, which make it hard to understand. Also, the spacing is not consistent. This needs to be broken down to several sentence

Chinese herbal medicine is effective and safe in the treatment of adults with mild to moderate COVID-19. And Chinese herbal medicine may be a promising candidate for the treatment of mild to moderate COVID-19.

Not advisable to start a sentence with the word 'and'

Introduction

Kindly rewrite this sentence as it is not gramatically correct

Coronavirus disease 2019 (COVID-19) is a novel coronavirus "2019-nCoV" causing a clinical syndrome dominated by the acute respiratory tract, with a large-scale epidemic [1-2]. Up to now, the epidemic has been basically brought under control in China, but the situation in many countries is still grim. As of November 21, 2020, 16765323 cases have been confirmed worldwide; 57969680 cases have been cumulatively diagnosed; 1375205 cases have died, and the mortality rate is 2.4%. COVID-19 has developed into a global public health emergency. Therefore, it is an urgent task to control COVID-19 effectively.

language check

Ref?

Suggest to use more scientifically accurate words (this apply to the entire manuscript throughout, this is just an example. The word 'basically' here is vague and not a precise word to be used in a scientific manuscript.

In China's experience in fighting COVID-19, traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), has played an important role [3]. A large number of epidemiological investigations showed that mild to moderate COVID-19 accounted for the largest proportion [4]. Conventional western medicine (CWM) in the treatment of mild to moderate COVID-19 is mainly antiviral and symptomatic support treatment, so far, no specific drug for the virus has been developed. CHM treatment which is based on syndrome differentiation could effectively alleviate clinical symptoms, reduce the rate of conversion to severe cases, and improve the cure rate [5]. Although ~~there are~~ several reviews ~~of~~ CHM for COVID-19 published [5-7], only retrospective studies were included in the reviews[5-6], and no subgroup analysis of mild to moderate COVID-19 was performed [5-7].

largest proportion of cases

Break into two sentence. .... treatment. So far, no.....

'developed' is an inaccurate word here. Sugest to discuss about approved antivirals and their efficacy instead of saying no drug has been developed.

evaluating the efficacy of

were

break into two sentence. review. Furthermore, no.....

In our review, the RCTs on CHM in the treatment of adult patients with mild to moderate COVID-19 have been searched since the outbreak of the epidemic. And the efficacy and safety of CHM in adults with mild to moderate COVID-19 were objectively evaluated by systematic evaluation and meta-analysis, in order to further provide evidence-based evidence for CHM in the treatment of COVID-19.

abbreviation not abbreviated on first encounter

Methods

Need language check and proof read on sentence structuring, grammar, and words selection.

was conducted

This review ~~was~~ based on the ~~guidelines of~~ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. ~~Also~~, the protocol for our review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020213528.

the

Please also check the use of connective words.

Eligibility criteria

Types of studies

Only RCTs of CHM for adults with mild to moderate COVID-19 were included in this review. The retrospective study, observational study, studies with data duplication, cross-over RCTs, and laboratory studies were excluded.

Check language, study, studies, singular, plural

by laboratory you meant preclinical studies?

Types of participants

need to define/ quote reference that define mild to moderate covid-19

Adult patients (aged≥18 years) diagnosed as mild to moderate COVID-19 ~~could be~~ ~~enrolled~~ in this review without the restriction of race or gender.

was included

Identical is a strong word. Are they really identical? This is the method section hence the eligibility criteria should present the inclusion criteria instead e.g. CHM of all formulations. Characteristics of included studies should be presented in results instead

Types of interventions

with

Adult patients in the treatment group were treated ~~by~~ a combination of CHM and CWM. The dosage forms of CHM for mild to moderate COVID-19 in this review contained decoction, granule, capsule, and oral liquid. Patients in the control group were treated ~~by~~ CWM. ~~Also~~, CWM in the treatment group and the control group was ~~identical~~. ~~Furthermore~~, RCTs would be excluded if the treatment group was treated with TCM injection, moxibustion, acupuncture, massage, etc.

what is etc. in the exclusion criteria? and what is the rationale of exclusion criteria (for injection) here

Types of outcome measures

suggest to define clearly each outcome, and present them clearly in categories

The primary outcome of this review was lung computed tomography (CT). High-resolution CT was utilized to observe changes in the chest and lung field before and after treatment. The secondary outcomes included the following items: clinical cure rate, viral nucleic acid testing, rate of conversion to severe cases, clinical symptoms (fever, cough, fatigue), inflammatory biomarkers including white blood cell (WBC) count, lymphocyte (LYM) count, LYM percentage, neutrophils (NEU) percentage, C-reactive protein (CRP), and adverse drug reactions (number of adverse effects cases, nausea and vomit, diarrhea, liver damage).

adverse effects? adverse events? related/ not related to drug/CHM? kindly specify

Literature search

Here mentioned as adverse events instead

RCTs assessing the efficacy and adverse events of CHM for adults with mild to moderate COVID-19 were searched in the following eight electronic databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, the Clinical Trials.gov website, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and China Biology Medicine (CBM) from December 2019 to November 2020. ~~Besides~~, there was no language restriction in our review. ~~And~~, the search terms included "coronavirus disease 2019", "COVID-19", "novel coronavirus pneumonia", "traditional Chinese medicine", "Chinese herbal medicine", "Chinese herb", "clinical trial", "randomized controlled trial", "randomised controlled trial".

Study selection and data extraction

use of tenses here needs to be corrected, everything should be in past tense

The study selection and data extraction of our review were conducted independently by two reviewers (Du XQ and Shi LP) according to the eligibility criteria. The following information ~~would be extracted~~ was from the included RCTs: basic characteristics ~~of included RCTs~~ (the title ~~of RCTs~~, first authors' name, publication date, sample size, and methodological quality), participant characteristics (age, gender, ~~number in each group~~ sample size), intervention details (~~the type of~~ description of interventions, ~~type of~~ description of ~~controls~~, dose, route of ~~oral~~ administration), and outcome measures including primary and secondary outcome measures, as well as adverse events. Any disagreements ~~would be~~ was resolved by ~~consultation with~~ a third reviewer (Cao WF).

Methodological quality is part of data analysis, not part of data extracted

no duration?

Assessment of methodological quality

~~According to the Cochrane Collaboration's tool [9],~~ the methodological quality of the included RCTs was assessed by two reviewers (Du XQ and Shi LP) independently using the Cochrane Collaboration's tool [9]. Seven items of risk of bias (ROB) including adequate sequence generation, concealment of allocation, blinding (patient, investigator and assessor), incomplete outcome data addressed, free of selective reporting, and other biases were evaluated. Each item of ROB was assessed to be low ROB, high ROB, or unclear ROB. Additionally, any disagreements of ROB were resolved by consultation with a third reviewer (Cao WF).

Statistical analysis (Suggested title: Meta-analyses)

spacing

Revman5.3.0 software (The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical quantitative analysis. The relative risk (RR) was adopted for ~~the~~ dichotomous variables. ~~And the~~ mean difference (MD) or standard mean difference (SMD) were adopted for the continuous variables. ~~Also, we would set the~~ confidence intervals (CIs) were set as 95%. ~~The heterogeneity test utilized~~ with $p < 0.005$ considered as statistically significant difference. Heterogeneity was assessed with the $P \geq 0.10$ or $I^2 \leq 50\%$, a fixed-effect model ~~would be~~ was adopted ~~to assess the difference~~, ~~otherwise,~~ Otherwise a random-effects model ~~would be selected~~ was applied. ~~Besides, we would conduct a~~ subgroup analysis of the primary outcome according to different treatment courses what are treatment courses? ~~And the~~ was sensitivity analysis ~~would be~~ performed by removing each included RCT of both primary outcome and secondary outcomes in turn. ~~When the number of included~~ RCTs on an outcome measure was larger than ten, was a funnel plot analysis ~~would be~~ performed to evaluate the reporting bias for outcome measures with more than 10 RCTs. Moreover, $P < 0.05$ was considered as a ~~statistical difference.~~

Results

Eligible studies

The flow diagram of study selection and identification ~~was showed~~ is shown in Fig. 1. ~~And~~ the characteristics of included RCTs were listed in Table 1. In this review, a total of twelve eligible RCTs were included [10-21]. Among the twelve RCTs [10-21], three were multi-centered trials [13,14,17] and the rest nine were single-centered trials. All twelve RCTs were conducted in mainland China in 2020. One RCT was ~~online~~ published online in English [14], and the rest were ~~online~~ reported online in Chinese. The sample size of the included RCTs ranged from 45 to 284 (total 1393). All twelve RCTs assessed the effects of oral CHM combined with CWM compared to CWM alone. The name, usage, dosage of western medicine used in the treatment group were identical to the control group. The treatment duration varied from 5 to 15 days. Seven RCTs [11,14-19] described the effective rate of lung CT. Five RCTs [11-12,14,17,21] described the clinical cure rate. Four RCTs [13-14,17,20] described the viral nucleic acid testing. Nine RCTs [11-18,20] described the rate of conversion to severe cases. Clinical symptoms of fever, cough and fatigue was described in seven RCTs [10-12,16-18,20], of which three RCTs [10,16,20] described number of

fever/cough/fatigue reduction cases, and four RCTs [11-12,18-19] described TCM symptom score of fever/cough/fatigue. Inflammatory biomarkers were described in six RCTs [11-12,17-19,21], of which four RCTs [11-12,18-19] described WBC count, four RCTs [11-12,17-18] described LYM count, three RCTs [11-12,19] described LYM percentage, two RCTs [11,17] described NEU percentage, and six RCTs [11-12,17-19,21] described CRP. Adverse ~~effects~~ events were described in ten RCTs [10-14,17-21].

I am guessing that you meant that there was unclear risk of bias on allocation concealment, blinding and selective reporting. These sentences represent different meaning and needs to be rewritten

Assessment of methodological quality

The methodological quality of the included RCTs was assessed according to the Cochrane handbook criteria. As shown in Fig.2a and Fig.2b, green and "+" indicate "Low risk"; yellow and "?" indicate "Unclear". Detailed information on sequence generation of randomization was described in ten trials (~~10/12,~~ 83.33%) [10-18,21]. Detailed information on allocation concealment, blinding of the patient, and blinding of the investigator was not described in this review. One RCT reported blinding of the assessor [14]. All included RCTs described incomplete outcome data addressed. And free of selective reporting and other biases of the included RCTs were unclear.

Attrition bias is scored as 100% low risk which is in contrast to this sentence

Efficacy and safety assessment

Effective rate of lung CT

Seven RCTs [11,14-19] reported effective rate of lung CT. A significant improvement in lung CT was identified by CHM treatment in this meta-analysis [n=845, RR=1.26, 95%CI (1.15, 1.38), I^2=8%, P＜0.00001] (Fig. 3).

Clinical cure rate

Five RCTs evaluated the effects of CHM on clinical cure rate [11-12,14,17,21]. CHM exhibited a significant improvement on clinical cure rate [n=821, RR=1.26, 95%CI (1.16, 1.38), I^2=0%, P＜0.00001] (Fig. 4).

Viral nucleic acid testing

Viral nucleic acid testing was reported in four RCTs [13-14,17,20]. Compared with CWM, no statistical difference on viral nucleic acid testing was identified [n=581, RR=1.09, 95%CI (0.98, 1.21), I^2=57%, P=0.13] (Fig. 5).

Rate of conversion to severe cases

Rate of conversion to severe cases was reported in nine RCTs [11-18,20]. CHM significantly reduced the rate of conversion to severe cases [n=1121, RR=0.48, 95%CI (0.32, 0.73), I^2 = 0%, P=0.0005] (Fig. 6).

Clinical symptoms of fever, cough and fatigue

Clinical symptoms of fever, cough and fatigue was reported in seven RCTs [10-12,16-18,20]. Among them, three RCTs [10,16,20] reported number of fever/cough/fatigue reduction cases, and four RCTs [11-12,17-18] reported TCM symptom score of fever/cough/fatigue.

Please consider rewriting this whole section with clearer sentences

Meta-analysis revealed no statistical difference on the number of ~~fever reduction~~ treated groups cases between CHM and CWM [n=205, RR=1.14, 95%CI (0.58, 2.25), I^2=95%, P=0.70] (Fig.7a). TCM symptom score of fever ~~is~~ was significantly reduced by CHM [n=482, MD=-0.62, 95%CI (-0.79, -0.45), I^2=79%, P＜0.00001] (Fig.7b).

CHM significantly reduced the cough cases [n=205, RR=1.43, 95%CI (1.16, 1.75), I^2 = 0%, P=0.0006] (Fig.7c); as ~~well as~~ a significant reduction in TCM symptom score of cough was identified by CHM [n=482, MD=-1.07, 95%CI (-1.29, -0.85), I^2=84%, P＜0.00001] (Fig.7d).

It has been identified that fatigue cases is reduced by CHM[n=205, RR=1.23, 95%CI (1.03, 1.47), I^2=28%, P=0.02] (Fig.7e); also a significant reduction in TCM symptom score of fatigue by CHM [n=482, MD=-0.66, 95%CI (-1.05, -0.28), I^2=98%, P=0.0007] (Fig.7f).

Inflammatory biomarkers

Inflammatory biomarkers were reported in six RCTs [11-12,17-19,21], of which four RCTs [11-12,18-19] reported WBC count, four RCTs [11-12,17-18] reported LYM count, three RCTs [11-12,19] reported LYM percentage, two RCTs [11,17] reported NEU percentage, and six RCTs [11-12,17-19,21] reported CRP.

Meta-analysis revealed a significant improvement on WBC count by CHM [n=478, MD=0.38, 95%CI (0.31, 0.44), I^2=5%, P ＜ 0.00001] (Fig.8a); a significant improvement on LYM count by CHM [n=482, MD=0.26, 95%CI (0.05, 0.47), I^2=97%, P=0.01] (Fig.8b); a significant improvement on LYM percentage by CHM

[n=183, MD=6.65, 95%CI (3.36, 9.94), I^2=93%, P＜0.0001] (Fig.8c); a significant reduction in NEU percentage by CHM [n=114, MD=-4.56, 95%CI (-5.76, -3.36), I^2=0%, P＜0.00001] (Fig.8d); a significant reduction in CRP by CHM [n=631, MD=-5.46, 95%CI (-8.19, -2.72), I^2=96%, P＜0.0001] (Fig.8e).

Adverse effects

adverse events? effects? Suggest to select a consistent term according to correct definition

In this review, adverse effects were reported in ten RCTs [10-14,17-21], and the rest two RCTs [15-16] did not describe drug adverse effects. Among them, no adverse effect was identified in both treatment and control groups [11-12,17-19]. Adverse effects in the rest five RCTs included gastrointestinal reactions (diarrhea, poor appetite, nausea, vomiting), headache, and abnormal liver function [10,13-14,20-21]. All reported adverse reactions were mild in the treatment and control groups, and were tolerable or alleviated after withdrawal.

while the remaining

how many studies?

Compared with CWM, there was no statistical difference in the number of adverse effects cases [n=759, RR=1.13, 95%CI (0.45, 2.83), I^2=63%, P=0.79] (Fig.9a); no statistical difference in the number of nausea and vomiting cases [n=388, RR=1.09, 95%CI (0.49, 2.41), I^2=0%, P=0.83] (Fig.9b); no statistical difference in the number of diarrhea cases [n=759, RR=1.72, 95%CI (0.34, 8.67), I^2=70%, P=0.51] (Fig.9c); no statistical difference in the number of abnormal liver function cases [n=388, RR=0.41, 95%CI (0.05, 3.69), I^2=78%, P=0.43] (Fig.9d). Additionally, the poor appetite and headache were reported in one RCT [14], and no statistical difference was identified between CHM and CWM.

total

Sub group analysis revealed

and

with

groups.

Subgroup analysis of the primary outcomes

Subgroup analysis of the primary outcomes was shown in Fig.2. Subgroup analysis revealed an improvement on lung CT of 7days treatment duration by CHM [n=845, RR=1.18, 95%CI (1.02, 1.36), I^2 =44%, P=0.03] (Fig.3); a significant improvement on lung CT of 10 to 14 days treatment duration by CHM [n=845, RR=1.34, 95%CI (1.19, 1.50), I^2 = 0%, P＜0.00001] (Fig. 3).

is

Sensitivity analysis

Sensitivity analysis revealed that there was a small change in the effect amount, and was a significant difference in effective rate of lung CT, clinical cure rate, rate of

conversion to severe cases, TCM symptom score of fever, number of cough reduction cases, TCM symptom score of cough, TCM symptom score of fatigue, WBC count, and CRP, which indicated the above meta-analysis results to be robust and reliable.

Publication bias

As the number of RCTs in any comparative outcome measure was less than ten, we did not assess the publication bias.

Discussion

[Since December 2019, COVID-19 infected by SARS-CoV-2 has spread all over the world, which is a serious threat to human life and health. COVID-19 is highly contagious and has a long incubation period. It is generally susceptible to human infection and can be transmitted to each other [22]. In addition, severe cases are more likely to have serious complications, such as shock, ARDS, arrhythmia and acute heart injury[23-24], which significantly increases the difficulty and cost of treatment. Therefore, it is of great significance to prevent COVID-19 from developing from mild and moderate to severe. Since the outbreak of COVID-19, CHM has been widely used to control COVID-19 in China. To our knowledge, this review would be the first one, which objectively assesses the efficacy and safety of CHM in the treatment of adults with mild to moderate COVID-19.]

abbreviation?

this section should be in introduction instead, however, repeat information should be avoided

~~This review systematically evaluated the efficacy and safety of CHM in the treatment of adult patients with mild to moderate COVID-19. After a comprehensive search of eight databases, twelve RCTs were enrolled in our review~~. The meta-analysis results showed that compared with CWM, ~~CHM combined with CWM has a better therapeutic effect~~. According to the theory of traditional Chinese medicine, COVID-19 belongs to epidemic disease. The pathogenesis of mild to moderate COVID-19 is dampness-heat or cold-dampness obstructing the lung. Therefore, the treatment principles of heat-clearing, eliminating dampness, resolving phlegm and dispersing cold are widely used. In the included studies, nine different oral CHM were used, including Jinhua Qinggan granule [10], Toujie Quwen granule [11-12], Jinyinhua oral liquid [13,20], Lianhua Qingwen capsule (granule) [14,18], Maxing Xuanfei Jiedu Decoction [15], Lianhua Qingke granule [16], Reyanning mixture [17],

meta-analyses (plural)

mild to moderate COVID-19 patients treated with both CHM and CWM had better outcomes in the parameters assessed in this review including xx, xx, and xx.

I suggest more explanation of how theory of traditional chinese medicine translates this to belong to epidemic disease.

Jiawei Dayuan Decoction [19], diammonium glycyrrhizinate [21]. Among the nine oral CHM, the most frequently used Chinese medicine was honeysuckle, which was used in seven trials (7/12, 58.33%) [10-14,18,20], followed by forsythia (6/12, 50.00%) [10-12,14,16,18], and ephedra (6/12, 50.00%) [10,14-16,18-19]. Honeysuckle and forsythia have the function of clearing heat-toxicity and dispersing wind-heat in the theory of TCM ref? Honeysuckle polysaccharide is an active component of honeysuckle, which can regulate non-specific immunity [25], inhibit the expression of inflammatory factors TNF-α and IL-1β [26], and inhibit a variety of viruses [27]. Phillyrin is an active component of forsythia, which has antiviral and anti-inflammatory activities [28-29]. Ephedra has the function of dissipating cold and diffusing the lung to calm panting in TCM theory ref? Ephedrine is an active component of ephedra, which can increase the production of anti-inflammatory cytokines IL-10, reduce the production of pro-inflammatory cytokines TNF-α and IL-12[30], and play an antiviral role by inhibiting viral replication [31].

In this review, it was found that CHM was effective and safe for adult patients with mild to moderate COVID-19. CHM could not only improve the lung CT, clinical cure rate and the main clinical symptoms (fever, cough and fatigue), but also reduce the rate of conversion to severe cases, and regulate the inflammatory response, with fewer adverse reactions. Therefore, CHM may be a promising candidate for the treatment of adults with mild to moderate COVID-19.

Limitations

The limitations of this review were as follows. First of all, most of the included RCTs had deficiencies in methodology design, including hidden allocation and inadequate reporting of blind methods. Secondly, the composition, dosage and frequency of CHM were different in the treatment group. Thirdly, the multicenter RCTs were lacking. In addition, the duration of the included studies ranged from 5 to 15 days. Therefore, it may be necessary to design more high-quality RCTs with a multicenter, large sample and longer follow-up to better observe the efficacy and possible adverse reactions of CHM in the treatment of adults with mild to moderate COVID-19.

Conclusion

CHM is effective and safe in the treatment of adults with mild to moderate COVID-19. It can improve the clinical cure rate, main clinical symptoms, imaging and laboratory indexes, and reduce the rate of conversion to severe cases. However, limited to the fact that COVID-19 is a sudden disease, it is difficult to carry out double-blind clinical trials, which results in the insufficient methodology of the existing-related trials. Therefore, more high-quality trials are needed to evaluate the efficacy and safety of CHM in the treatment of adults with mild to moderate COVID-19 in the future.

Supporting information

S1 Checklist. PRISMA 2009 checklist.

(DOC)

Author Contributions

Conceptualization: Lipeng Shi, Wenfu Cao.

Data curation: Xuqin Du, Lipeng Shi.

Formal analysis: Xuqin Du.

Funding acquisition: Xuqin Du.

Investigation: Xuqin Du, Lipeng Shi.

Methodology: Xuqin Du, Lipeng Shi.

Software: Xuqin Du.

Supervision: Wenfu Cao.

Validation: Biao Zuo, Aimin Zhou.

Writing – original draft: Xuqin Du.

Writing – review & editing: Xuqin Du, Lipeng Shi, Wenfu Cao, Biao Zuo, Aimin Zhou.

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The figure legend:

Fig. 1. Flow diagram of study selection and identification.

Fig.2.Assessment of methodological quality.

Fig.3 Effective rate of lung CT.

Fig.4 Clinical cure rate.

Fig.5 Viral nucleic acid testing.

Fig.6 Rate of conversion to severe cases.

Fig.7. Clinical symptoms of fever, cough and fatigue.

Fig.8. Inflammatory biomarkers.

Fig.9. Adverse effects.

The table:

Table 1 Characteristics of included RCTs.

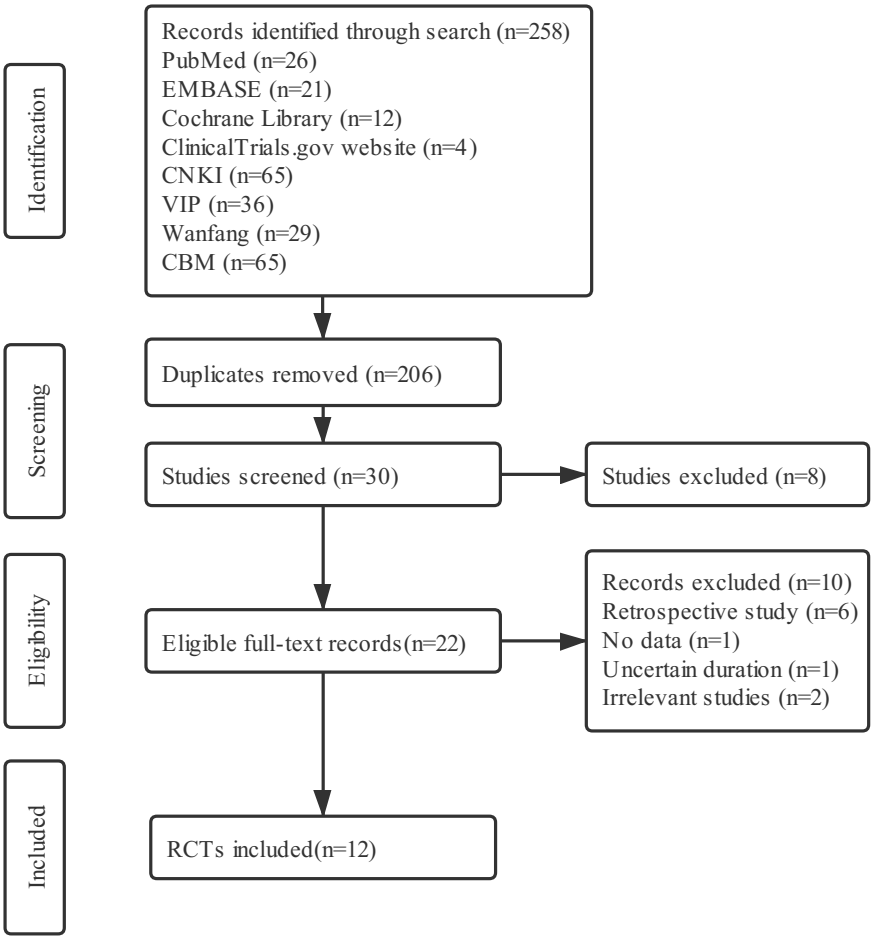

Fig. 1. Flow diagram of study selection and identification.

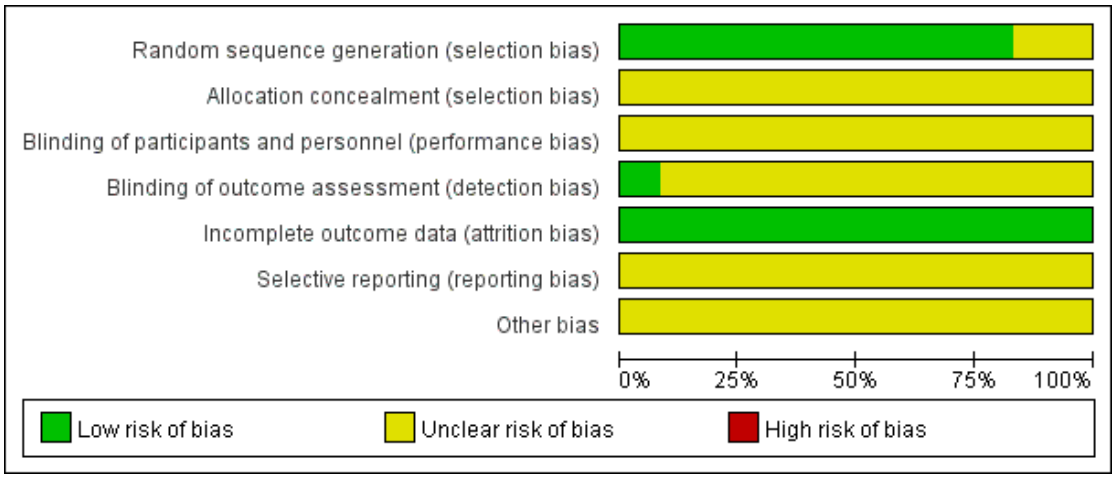

Fig.2a Risk of bias graph.

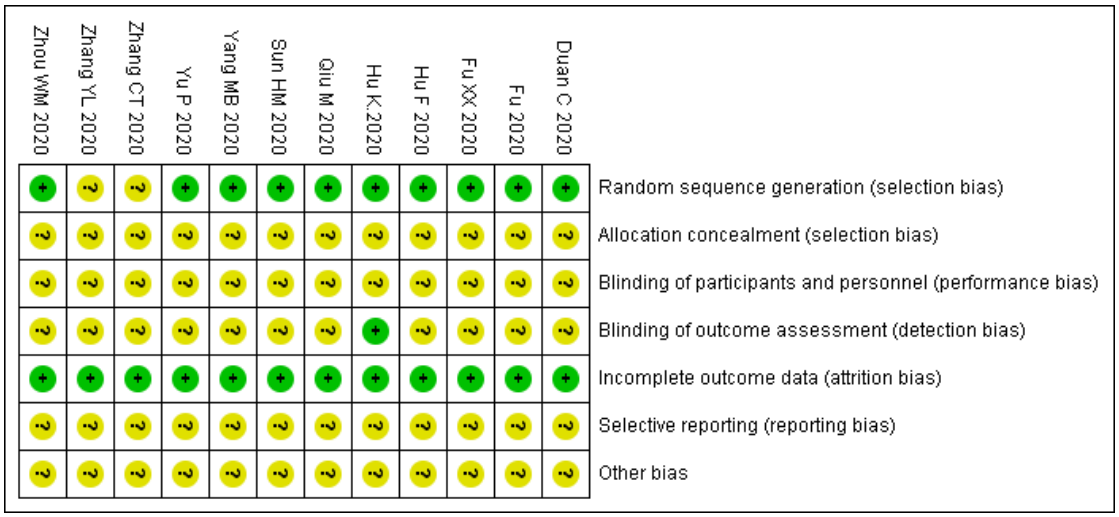

Fig.2b Risk of bias summary.

Fig.2. Assessment of methodological quality. 2a Risk of bias graph. 2b Risk of bias summary.

Figure

Click here to access/download;Figure;Fig.3. Effective rate of lung CT.pdf

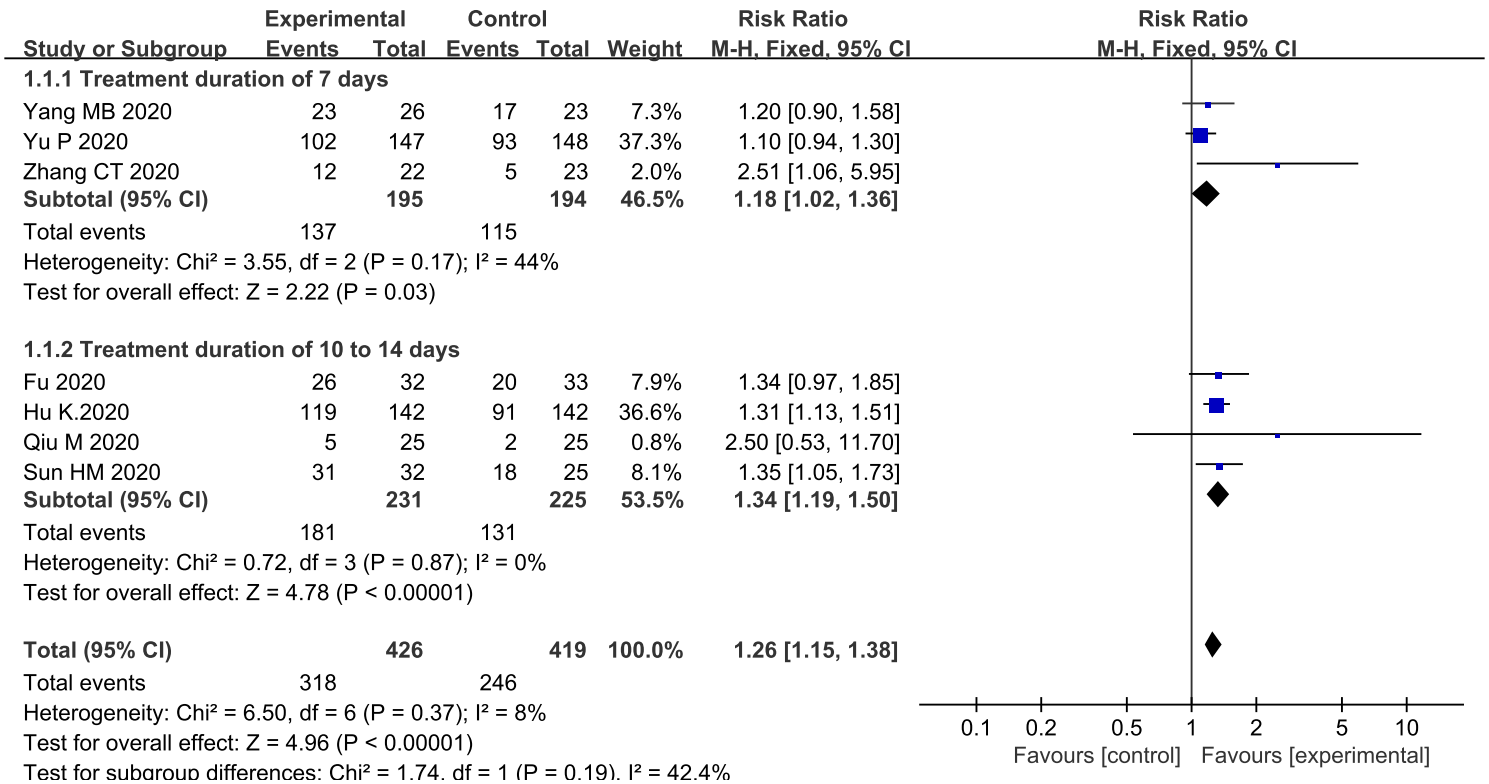

Fig.3 Effective rate of lung CT

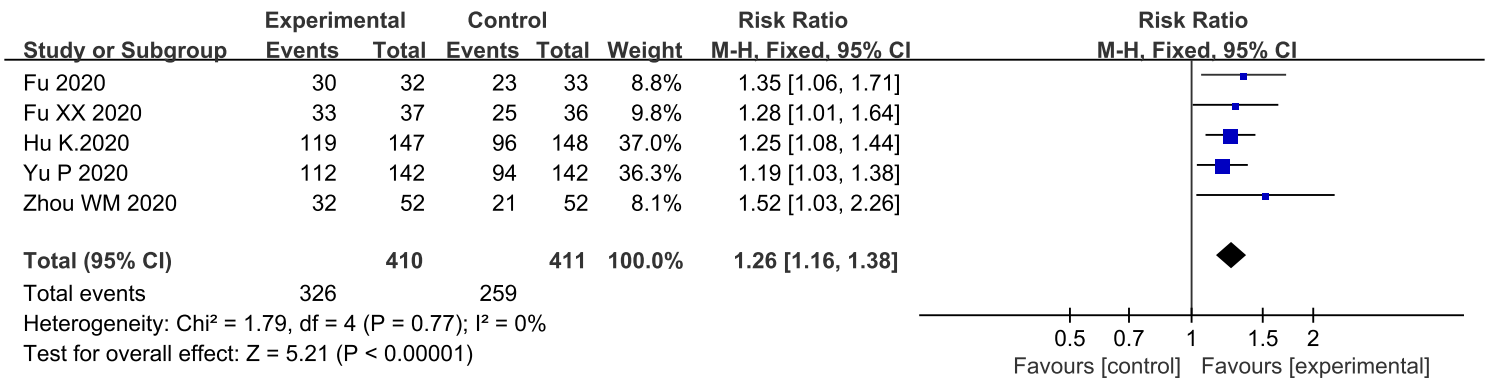

Fig.4 Clinical cure rate

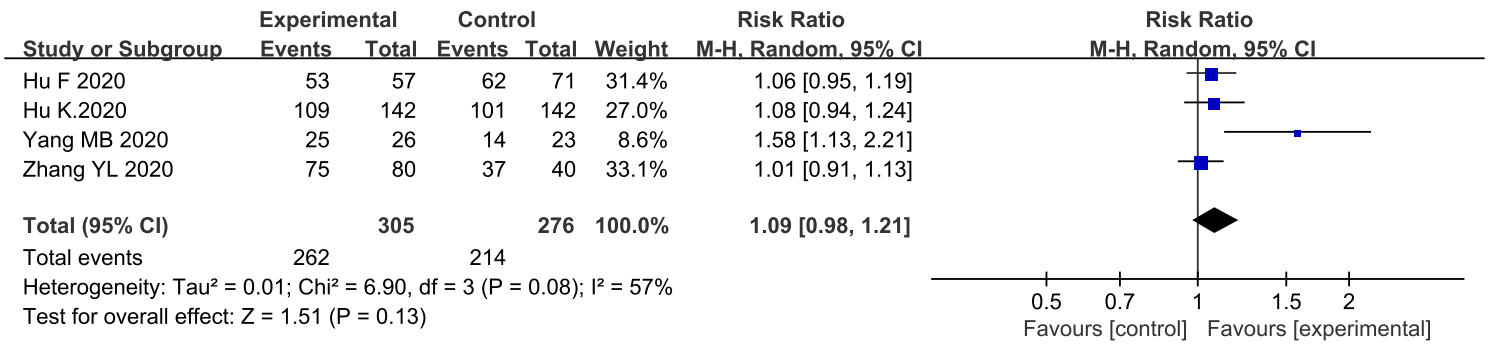

Fig. 5 Viral nucleic acid testing

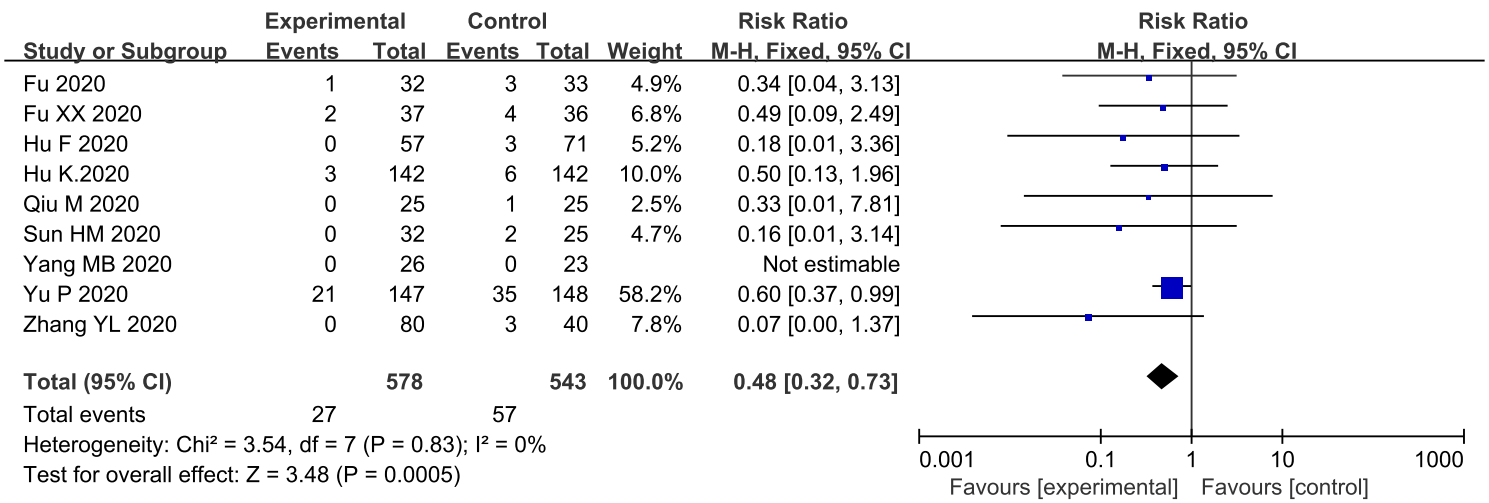

Fig. 6 Rate of conversion to severe cases

Figure

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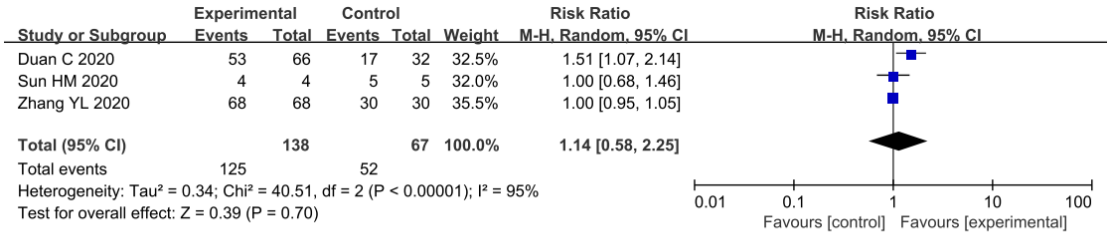

Fig.7a Number of fever reduction cases

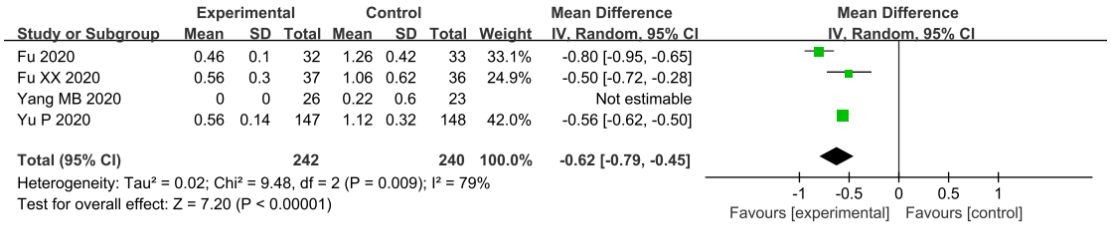

Fig.7b TCM symptom score of fever

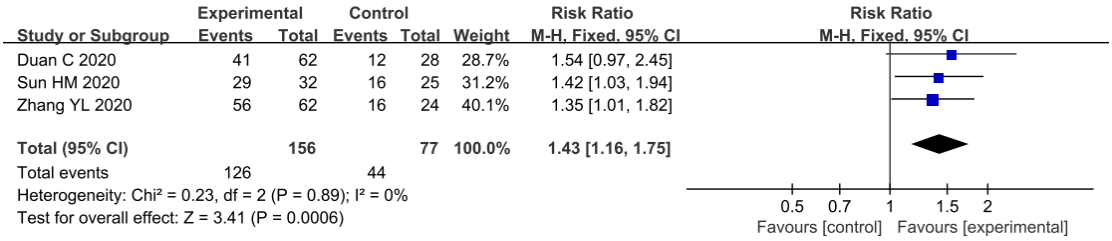

Fig.7c Number of cough reduction cases

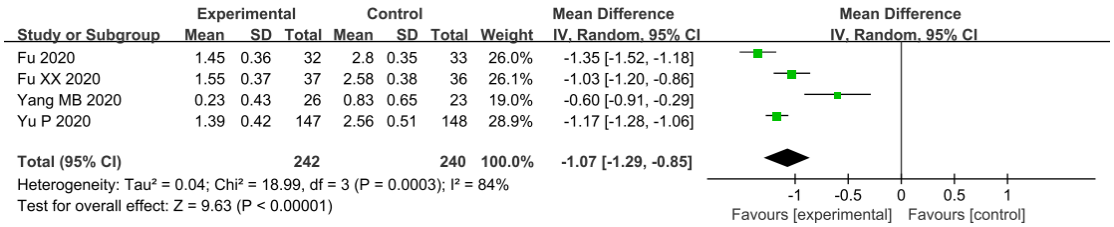

Fig.7d TCM symptom score of cough

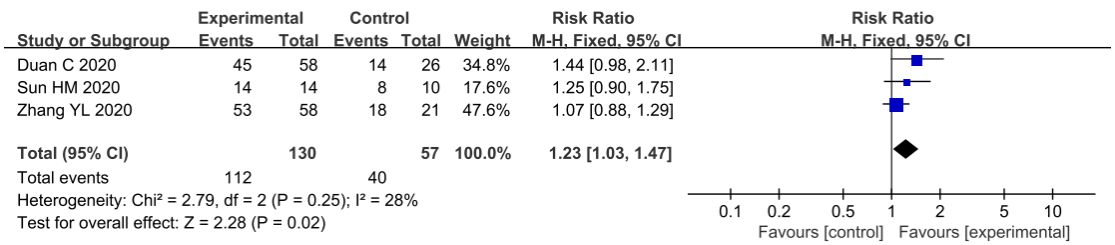

Fig.7e Number of fatigue reduction cases

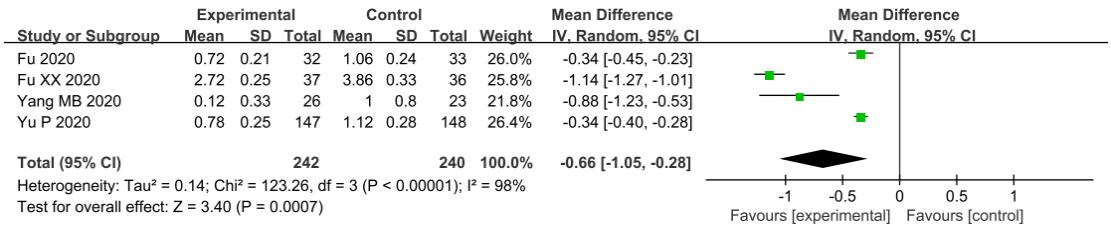

Fig.7f TCM symptom score of fatigue

Fig.7. Clinical symptoms of fever, cough and fatigue. 7a Number of fever reduction cases. 7b TCM symptom score of fever. 7c Number of cough reduction cases. 7d TCM symptom score of cough. 7e Number of fatigue reduction cases. 7f TCM symptom score of fatigue.

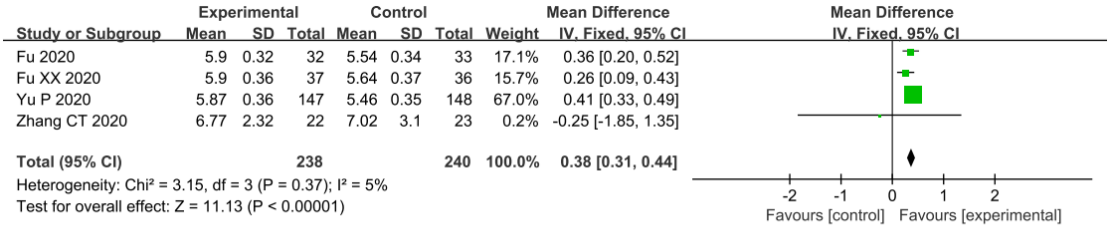

Fig.8a WBC count

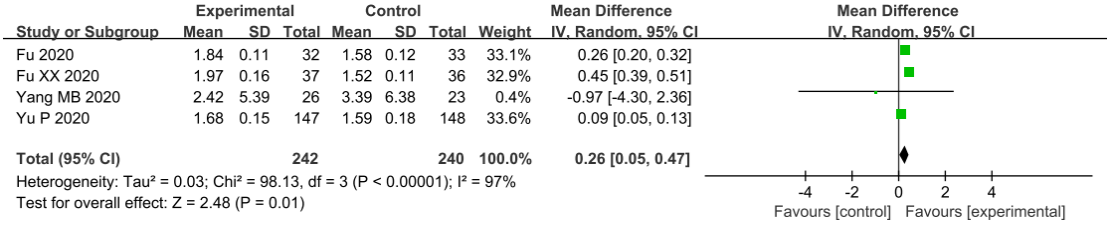

Fig.8b LYM count

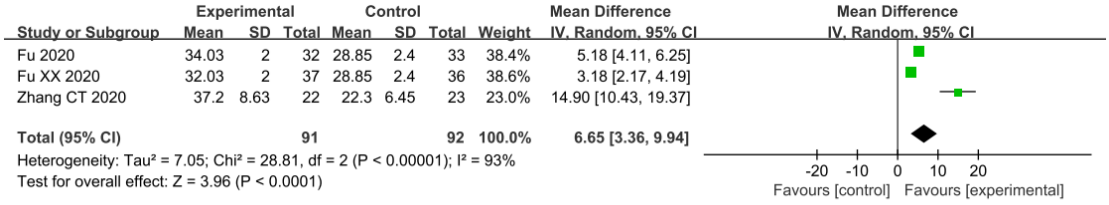

Fig.8c LYM percentage

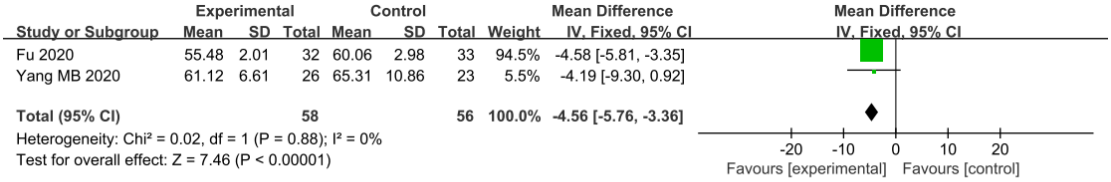

Fig.8d NEU percentage

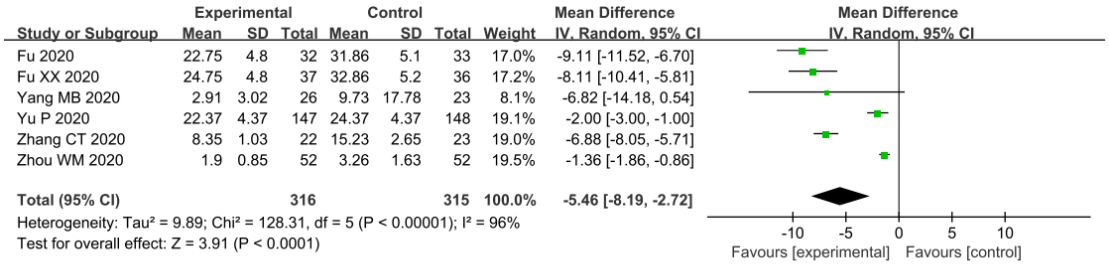

Fig.8e CRP

Fig.8. Inflammatory biomarkers. 8a WBC count. 8b LYM count. 8c LYM percentage. 8d NEU percentage. 8e CRP.

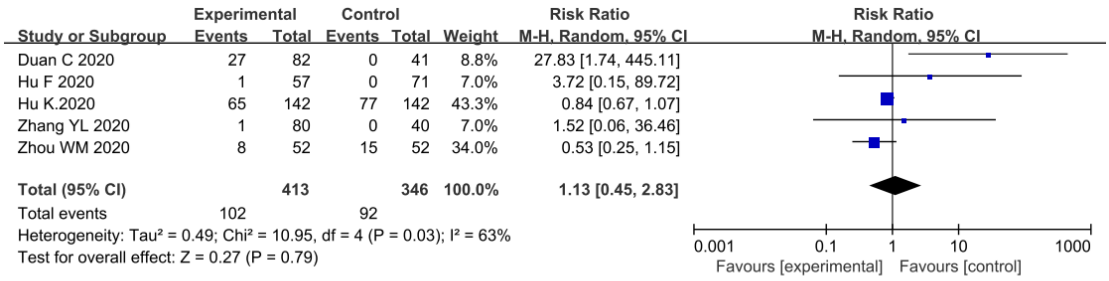

Fig.9a Number of adverse effects cases

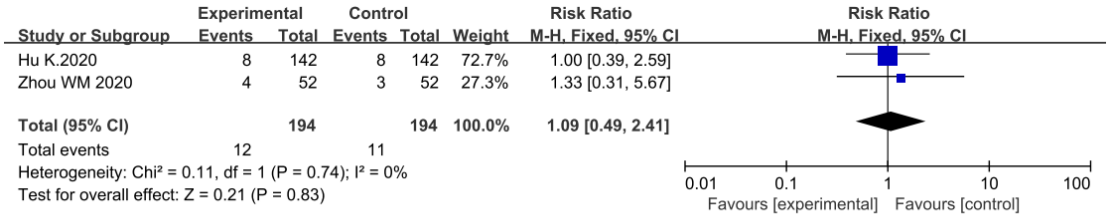

Fig.9b Number of nausea and vomiting cases

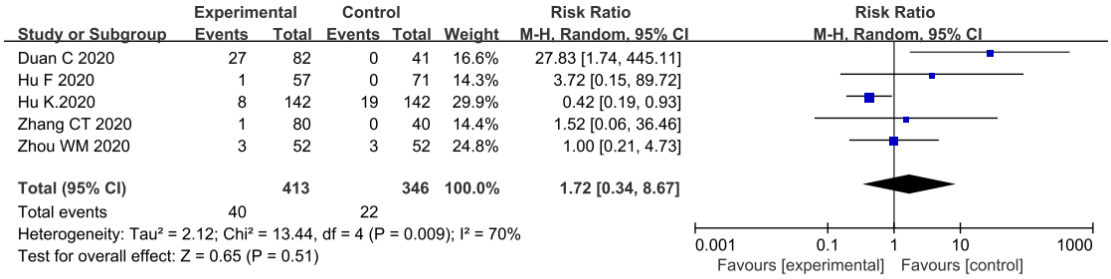

Fig.9c Number of diarrhea cases

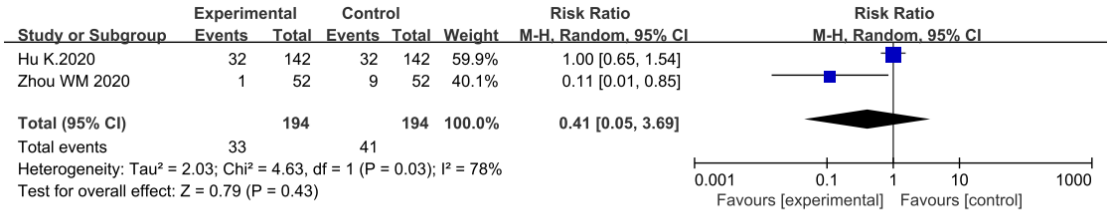

Fig.9d Number of abnormal liver function cases

Fig.9. Adverse effects. 9a Number of adverse effects cases. 9b Number of nausea and vomiting cases. 9c Number of diarrhea cases. 9d Number of abnormal liver function cases.

Table 1
Characteristics of included RCTs.

First author	Type of COVID-19	Sample size (M/F)	Age (years)	Intervention	Control	Duration	Outcome measures
Duan C [10]	mild	T:82(39/43) C:41(23/18)	T:51.99±13.88 C:50.29±13.17	Jinhua Qinggan granule + CWM	CWM including antiviral, anti-infection, and symptomatic therapies	5 days	Clinical symptoms, and adverse effects
Fu [11]	mild/ moderate	T:32(17/15) C:33(19/14)	T:43.26±7.15 C:43.68±6.45	Toujie Quwen granule + CWM	CWM including abidor tablets, moxifloxacin tablets, and ambroxol tablets	10 days	Lung CT, clinical cure rate, rate of conversion to severe cases, clinical symptoms, inflammatory biomarkers, and adverse effects
Fu XX [12]	moderate	T:37(19/18) C:36(19/17)	T:45.26±7.25 C:44.68±7.45	Toujie Quwen granule + CWM	CWM including abidor tablets, and ambroxol tablets	15 days	Clinical cure rate, rate of conversion to severe cases, clinical symptoms, inflammatory biomarkers, and adverse effects
Hu F [13]	moderate	T:100(49/51) C:100(55/45)	T:47.00±14.06 C:49.28±11.14	Jinyinhua oral liquid + CWM	CWM including interferon-α, lopinavir and tonavir tablets, symptomatic and supportive therapies	10 days	Lung CT, virus nucleic acid testing, rate of conversion to severe cases, and adverse effects
Hu K [14]	mild/ moderate	T:142(79/63) C:142(71/71)	T:50.4±15.2 C:51.8±14.8	Lianhua Qingwen capsule + CWM	CWM including oxygen therapy, antiviral, and symptomatic therapies	14 days	Lung CT, clinical cure rate, virus nucleic acid testing, rate of conversion to severe cases, clinical symptoms, and adverse effects
Qiu M [15]	moderate	T:25(13/12) C:25(14/11)	T:53.35±18.35 C:51.32±14.62	Maxing Xuanfei Jiedu Decoction + CWM	CWM including interferon-α, lopinavir and tonavir tablets	10 days	Lung CT, rate of conversion to severe cases, and clinical symptoms

Sun HM [16]	mild/ moderate	T:32(17/15) C:25(11/14)	T:45.4±14.10 C:42.0±11.70	Lianhua Qingke granule + CWM	CWM including interferon-α, lopinavir and tonavir tablets, symptomatic and supportive therapies	14days	Lung CT, rate of conversion to severe cases, and clinical symptoms
Yang MB [17]	moderate	T:26(16/10) C:23(9/14)	T:50.35±13.37 C:47.17±16.57	Reyanning mixture + CWM	CWM including interferon-α, lopinavir and tonavir tablets, abidor tablets, and ribavirin	7 days	Virus nucleic acid testing, rate of conversion to severe cases, clinical symptoms, inflammatory biomarkers, and adverse effects
Yu P [18]	mild/ moderate	T:147(82/65) C:148(89/59)	T:48.27±9.56 C:47.25±8.67	Lianhua Qingwen granule+ CWM	CWM including abidor tablets, moxifloxacin tablets, and ambroxol tablets	7 days	Lung CT, clinical cure rate, rate of conversion to severe cases, clinical symptoms, inflammatory biomarkers, and adverse effects
Zhang CT [19]	moderate	T: 22 (9/ 13) C: 23 (10/13)	T: 53.7 ± 3.5 C: 55.6 ± 4.2	Jiawei Dayuan Decoction + CWM	CWM including oxygen therapy, antivirus, and symptomatic therapies	7 days	Lung CT, clinical symptoms, inflammatory biomarkers, and adverse effects
Zhang YL [20]	moderate	T: 80 (50/ 30) C: 40(23/17)	T: 53.4±13.70 C:52.0±14.10	Jinyinhua oral liquid + CWM	CWM including interferon-α, lopinavir and tonavir tablets, symptomatic and supportive therapies	10 days	Rate of conversion to severe cases, clinical symptoms, and adverse effects
Zhou WM [21]	moderate	T: 52 (32/ 20) C: 52(28/24)	T: 52.47±10.99 C:51.11±9.87	diammonium glycyrrhizinate + CWM	CWM including lopinavir and tonavir tablets, symptomatic and supportive therapies	14 days	Clinical cure rate, inflammatory biomarkers, and adverse effects