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The role of Chinese medicine in COVID-19 pneumonia: A systematic review and meta-analysis

Chun-Yang Sun, MD^{a,*}, Ya-Lei Sun, MD^b, Xin-Min Li, MD^c

^a Public Health and Preventive Medicine Teaching and Research Center, Basic Medicine College, Henan University of Chinese Medicine, Zhengzhou 450000, China

^b Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210000, China

^c School of Basic Medicine, Henan University of Chinese Medicine, Zhengzhou 450000, China

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ABSTRACT

Introduction: Chinese medicine (CM) has been used to treat Novel Coronavirus 2019 (COVID-19) pneumonia in China. This meta-analysis was conducted to evaluate the clinical efficacy and safety of CM in the treatment of COVID-19 pneumonia.

Methods: Randomized controlled trials (RCTs) involving CM in the treatment of COVID-19 pneumonia were identified from Cochrane Central Register of Controlled Trials, PubMed, EMBASE, Chinese National Knowledge Infrastructure, Chinese Biomedical Database, Wanfang Database and VIP Information Database. The methodological quality of trials was evaluated with Cochrane Handbook criteria, and the Cochrane Collaboration's Review Manager 5.3 software was used for meta-analysis.

Results: A total of 7 valid studies involving 681 patients were included. The meta-analysis exhibited in comparison to conventional treatment, CM combined with conventional treatment significantly improved clinical efficacy (RR = 1.21, 95% CI [1.08,1.36]), and significantly increased viral nucleic acid negative conversion rate (RR = 1.49, 95% CI [1.13,1.97]). CM also prominently reduced pulmonary inflammation (RR = 1.27, 95% CI [1.12,1.44]), and improved host immune function (WBC, MD = 0.92, 95% CI [0.07,1.76]; LYM, MD = 0.33, 95% CI [0.08,0.57]; LYM%, MD = 2.90, 95% CI [2.09,3.71]; CRP, MD = -12.66, 95% CI [-24.40, -0.92]). Meanwhile, CM did not increase the incidence of adverse reactions (RR = 1.17, 95% CI [0.39,3.52]).

Conclusion: According to the allocated data, CM has demonstrated clinical efficacy and safety on COVID-19 pneumonia, which need to be confirmed by high quality, multiple-center, large sample randomized controlled trials.

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1. Introduction

Novel Coronavirus disease 2019 (COVID-19) pneumonia is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which firstly appeared in Wuhan, China [1,2]. It is highly infectious and spreads through respiratory droplets and contact [3]. It is characterized by acute onset, severe symptoms, such as dyspnea and multi-organ dysfunction [4]. The World Health Organization listed this pneumonia epidemic of Wuhan, China, as a public health emergency of international concern [5]. The world is now facing a pandemic of COVID-19, for which no proven specific therapies are available, other than supportive care.

On January 20, 2020, National Health Commission of the People's Republic of China announced that COVID-19 would be classified as category A infectious disease [6]. At the same time, Chinese medicine

experts quickly reached a consensus on Chinese medicine (CM) therapy. As medical therapy, CM treatment was written in "Diagnosis and Treatment of Pneumonia Infected by 2019-nCoV (trial implementation 7th Edition)" published by National Health Commission of the People's Republic of China [7]. However, compared with conventional treatment, there is no high-level evidence to support the effectiveness of CM treatment. Therefore, the meta-analysis method will be used to systematically review the clinical efficacy and safety of CM for COVID-19 pneumonia. This analysis is expected to obtain meaningful conclusions and provide a high level of evidence-based medicine evidence.

2. Methods

2.1. Inclusion and exclusion criteria

Studies meeting the following criteria were included: (1) randomized controlled trials (RCTs) using CM (including Chinese herbal medicine, Chinese patent medicine and Chinese medicine injections) to treat COVID-19 pneumonia regardless of blinding, allocation concealment. (2) patients enrolled were diagnosed with COVID-19 pneumonia.

* Corresponding author at: Public Health and Preventive Medicine Teaching and Research Center, Basic Medicine College, Henan University of Chinese Medicine, No. 156, East Jinshui Road, Zhengdong New District, Zhengzhou, Henan 450000, China.

E-mail address: sunchunyang427@163.com (C.-Y. Sun).

There are no restrictions on gender, course of disease, course of treatment. (3) the treatment group received CM for treating COVID-19 pneumonia, and the control group received conventional treatment. (4) the primary outcomes for this meta-analysis were clinical effective rate and incidence of adverse reactions. Besides, viral nucleic acid negative conversion rate, remission rate of pulmonary inflammation (chest CT) and biochemical markers were also evaluated. The following studies were excluded: (1) animal experiment; (2) review; (3) wrong patient population.

2.2. Search strategy

Allocation of data was systematically conducted in both English and Chinese databases from 01 December 2019 to 31 March 2020: Cochrane Central Register of Controlled Trials, PubMed, EMBASE, Chinese National Knowledge Infrastructure, Chinese Biomedical Database, Wanfang database, VIP information database. There were no language restrictions, meanwhile the medical subject headings (MeSH) and free text words were applied. The following three terms were used as search strategy and modified to suit each database: health condition (“COVID-19 pneumonia” OR “COVID-19” OR “SARS-CoV-2” OR “2019 nCoV” OR “novel coronavirus”), intervention (“Chinese medicine” OR “Chinese herbal medicine” OR “Chinese patent medicine” OR “Chinese medicine injections”), study type (randomized controlled trials). In addition, reference lists of credited published articles were verified.

2.3. Study selection and data extraction

We used NoteExpress 3.0 software to manage the retrieved articles. After the duplicate literature were removed, two review authors independently read the titles and abstracts to exclude wrong literature (e.g., review, animal experiment). The rest literature were read full text to sort out the eligible. The main components of extracted data included the following: first author, publication date, sample size, diagnosis standard, CM (e.g., Chinese herbal medicine, Chinese patent medicine and Chinese medicine injections), conventional treatment, course of treatment, clinical effective rate, incidence of adverse reactions, viral nucleic acid negative conversion rate, remission rate of pulmonary inflammation (chest CT), and biochemical markers.

2.4. Risk of bias assessment

The methodological quality of the eligible RCTs was evaluated independently, according to the Cochrane Handbook for Systematic Reviews of Interventions [8]. The details included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. Reference this statement each entry was assessed as “low risk”, “unclear risk” or “high risk”. Any disagreement was resolved by discussion with a third review author.

2.5. Statistical analysis

Cochrane Collaboration's Review Manager 5.3 software was used for meta-analysis. If two or more homogeneous studies are available, we will use aggregated data for meta-analysis. If the data are not available for quantitative analysis, we will report result by qualitative description. For dichotomous outcomes, we calculated the risk ratio (RR), 95% confidence intervals (CI) and *P* values. For continuous variable, we calculated the mean difference (MD), 95% CI and *P* values. We used the inverse variance method to calculate pooled MD values and the Mantel-Haenszel estimator to calculate RR. Studies will be evaluated for heterogeneity using *I*² and chi-squared test. If *I*² > 50%, or *P* < .05, the studies will be considered heterogeneous, and the pooling model will choose a random effects model, otherwise fixed effects model will be used. The funnel plot will be used to evaluate publication bias.

3. Results

3.1. Characteristics of included studies

716 unique citations were identified from electronic database. After duplicates removed, 697 literature remained. By reading titles and abstracts, 42 articles were downloaded. A total of 42 articles were retrieved for further assessment, among which 35 were further excluded, for the reasons: wrong patient population; self-control; retrospective studies. In total, seven [9–15] RCTs met the inclusion criteria and were subjected to data extraction (Fig. 1).

All studies included involved seven RCTs with 681 patients. Of the seven RCTs, two RCTs [9,13] reported clinical effective rate, seven RCTs [9–15] recorded incidence of adverse reactions, three RCTs [10,11,14] reported viral nucleic acid negative conversion rate, four RCTs [10,12–14] recorded remission rate of pulmonary inflammation (chest CT).

There were three RCTs [9,13,14] reported white blood cell count (WBC), three RCTs [9,10,14] reported lymphocyte count (LYM), two RCTs [9,13] reported lymphocyte ratio (LYM%), four RCTs [9,10,12,14] reported C-reactive proteins, and two RCTs [12,14] reported interleukin-6. The comparison of baseline characteristics showed there were no significant differences in gender, age, or disease duration between the treatment and control groups (*P* > .05). The characteristics of the studies are illustrated in Table 1.

3.2. Quality evaluation of the included studies

For the eligible studies, three studies [9,12,15] mentioned the use of random distribution. None of the studies provided useful information to estimate allocation concealment. All studies failed to report the use of blinding, thus the item was regarded as “High risk of bias”. The incomplete outcome data item was appraised as “Low risk of bias” since none of the included studies had incomplete data. Since there had no information available in the included studies about selective reporting or any factors that might lead to risk, the items of selective reporting and other bias were evaluated as “Unclear risk of bias”. Details about the risk of bias are presented in Fig. 1.

3.3. Meta-analysis results

3.3.1. Clinical effective rate

The clinical effective rate was tested in two RCTs involved 273 patients. The efficacy criteria were predominantly based on reduction of clinical symptoms and could be divided into three grades: cured, remarkable recovery, unrecovered. The rate calculated by this formula: (number of cured patients + number of remarkable recovery patients)/total number × 100% [16].

Heterogeneity test results (*P* = .39, *I*² = 0%) indicated that there were no statistical significant difference between the studies, and the fixed effect model was selected for meta-analysis. As can be observed in Fig. 2, CM combined with conventional treatment had a higher clinical effective rate compared with conventional treatment (RR = 1.21, 95% CI [1.08,1.36], *Z* = 3.21, *P* = .001; Fig. 2).

3.3.2. Incidence of adverse reactions

Taking incidence of adverse reactions into consideration (including seven RCTs, 681 patients), we noted there is high heterogeneity between studies (*P* = .03, *I*² = 62%). Therefore, it was decided to choose the random effect model for meta-analysis. Fig. 3 demonstrates, CM had no significant effect on the incidence of adverse reactions (RR = 1.17, 95% CI [0.39,3.52], *Z* = 0.28, *P* = .78; Fig. 3).

3.3.3. Viral nucleic acid negative conversion rate

Since high homogeneity was observed in the result (*P* = .88, *I*² = 0%), a fixed effect model was used to calculate estimation. Significant differences were observed on viral nucleic acid negative conversion rate in

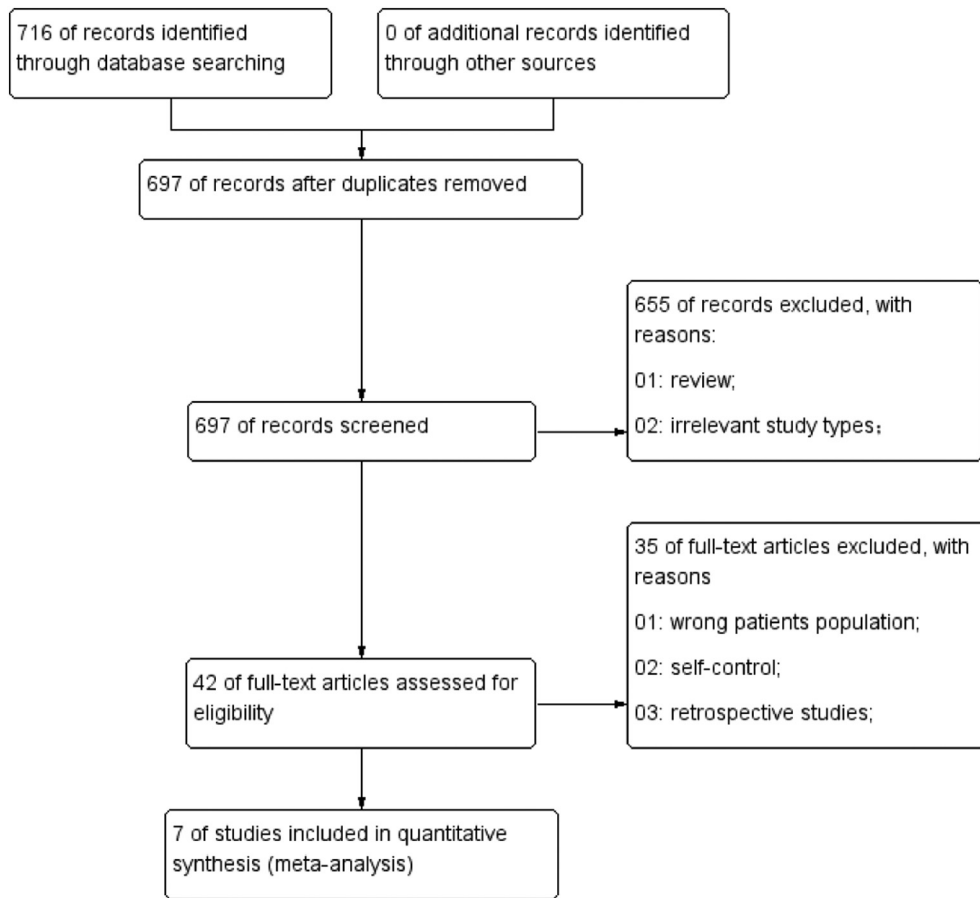


Fig. 1. Details about the risk of bias.

Table 1
Characteristics of the included randomized controlled trials.

Studies	Sample size (T/C)	Patients enrolled condition	Diagnosis standard	Treatment group	Control group	Course of treatment (d)	Outcomes
Fu et al. [9]	37/36	MOCP	6th Edition	TouxieQuwen prescription (2 dose/d) + Control group	Arbidol (0.2 g, tid) and ambroxol (30 mg, tid)	15	1/2/5/6/7/8
Yang et al. [10]	26/23	MOCP	3/4/5th Edition	Reyaning mixture (10–20 ml, bid-q6h) + Control group	Lopinavir-ritonavir (400–100 mg, bid) or recombinant human interferon α1b for injection (5 million U, bid) or ribavirin (0.5 g, bid) or arbidol (0.2 g, tid)	7	2/3/4/6/8
Qu et al. [11]	40/30	MICP and MOCP	4/5th Edition	Shufengjiedu capsule (2.08 g, tid) + Control group	Arbidol (0.2 g, tid)	10	2/3
Ding et al. [12]	51/49	T:MICP:10; MOCP:36; SCP and CCP: 5; C: MICP:11; MOCP:34; SCP and CCP: 4	5th Edition	Qingfeitouxiefuzheng prescription (1 dose/d) + Control group	Recombinant human interferon α1b for injection (5 million U, bid) or ribavirin (0.5 g, bid)	10	2/4/8/9
Xiao et al. [13]	100/100	MICP	5th Edition	Shufengjiedu capsule (2.08 g, tid) + Control group	Arbidol (0.2 g, tid)	14	1/2/4/5/7
Huang et al. [14]	52/14	T:MOCP:44; SCP:9; C: MOCP:12; SCP:3	7th Edition	Feiyanyihao prescription or feiyanerhao prescription (1 dose/d) + Control group	Lopinavir-ritonavir or recombinant human interferon α1b or ribavirin or arbidol (regular recommended dosing)	10	2/3/4/5/6/8/9
Duan et al. [15]	82/41	MICP	5th Edition	Jinhuaqinggan granule (10 g, tid) + Control group	Lopinavir-ritonavir (400–100 mg, bid) or recombinant human interferon α1b (5 million U, bid) or ribavirin (1.2 g, tid)	5	2

Abbreviation: T: treatment group; C: control group; d: day; mild case patients (MICP); moderate case patients (MOCP); severe case patients (SCP); critical case patients (CCP); 3/4/5/6/7th Edition: “Diagnosis and Treatment of Pneumonia Infected by 2019-nCoV (trial implementation 3/4/5/6/7th Edition)” published by the “National Health Commission of the People’s Republic of China.”; Outcomes: 1: clinical effective rate; 2: incidence of adverse reactions; 3: viral nucleic acid negative conversion rate; 4: remission rate of pulmonary inflammation (chest CT); 5: white blood cell count (WBC); 6: lymphocyte count (LYM); 7: lymphocyte ratio (LYM%); 8: C-reactive protein (CRP); 9: interleukin 6 (IL-6).

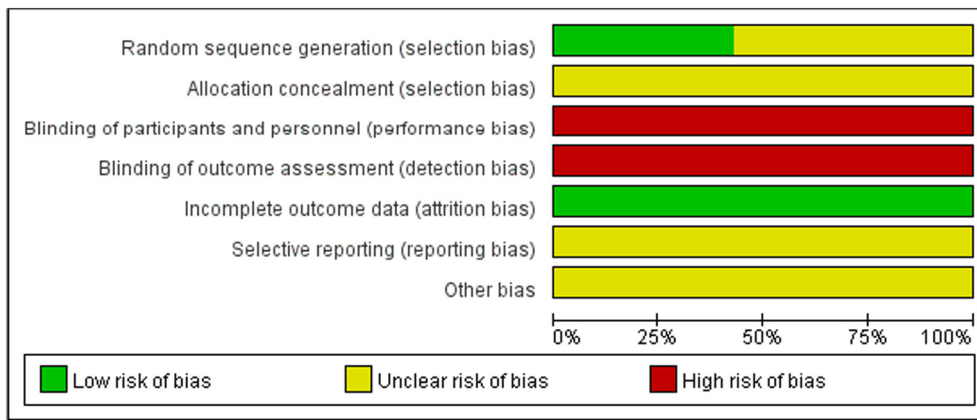


Fig. 2. Analysis of treatment group and control group with clinical effective rate.

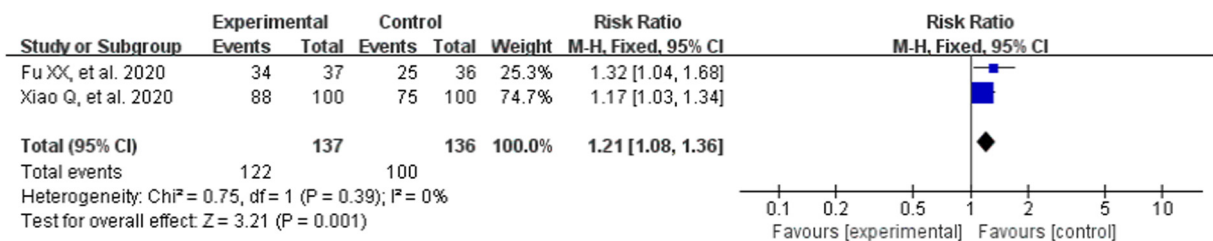


Fig. 3. Analysis of treatment group and control group with the incidence of adverse reactions.

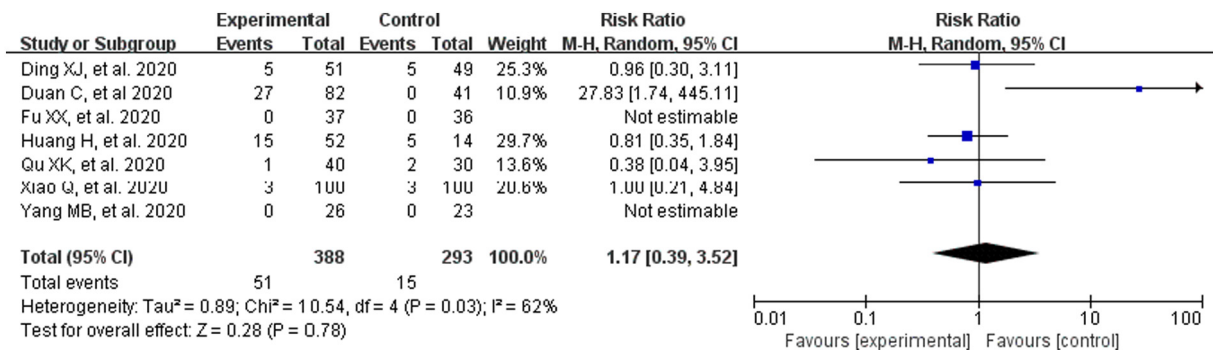


Fig. 4. Analysis of treatment group and control group with the viral nucleic acid negative conversion rate.

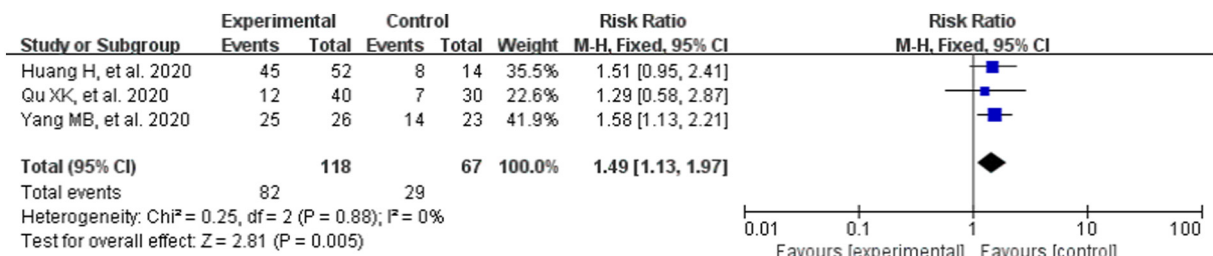


Fig. 5. Analysis of treatment group and control group with the remission rate of pulmonary inflammation (chest CT).

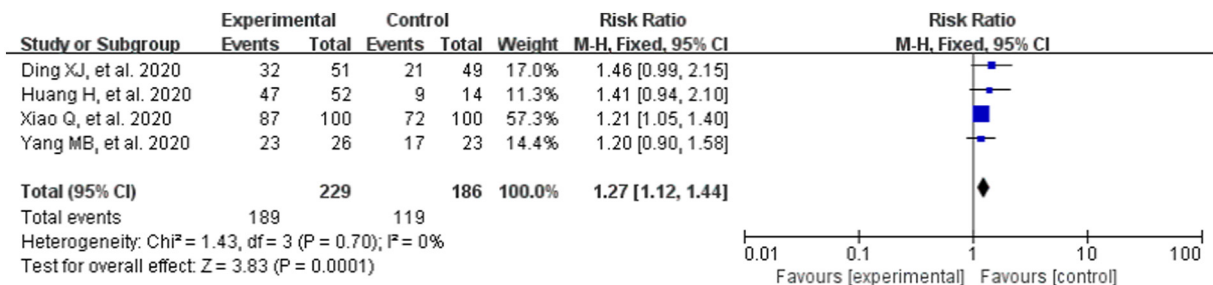


Fig. 6. Analysis of treatment group and control group with WBC.

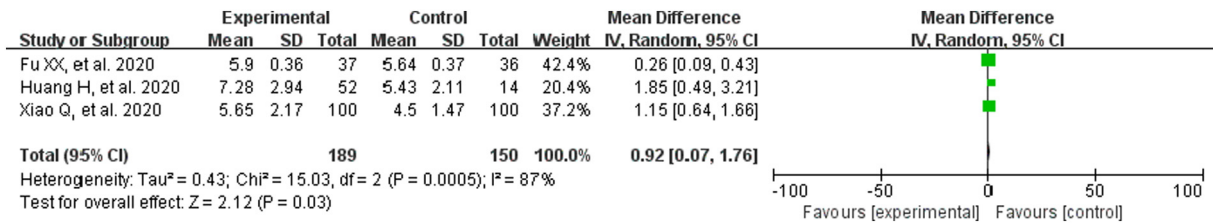


Fig. 7. Analysis of treatment group and control group with LYM.

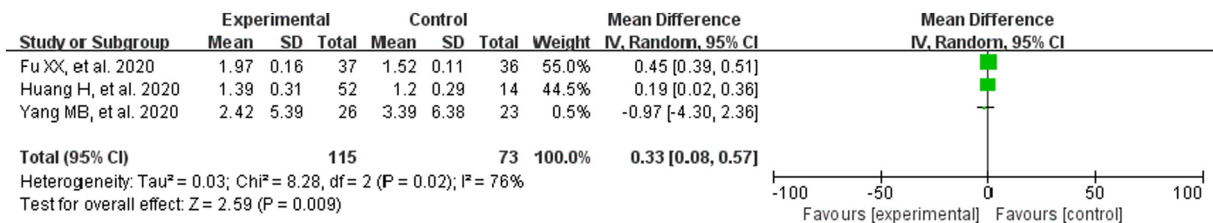


Fig. 8. Analysis of treatment group and control group with LYM%.

favor of CM combined with conventional treatment (RR = 1.49, 95% CI [1.13, 1.97], Z = 2.81, P = .005; Fig. 4). Compared with conventional treatment alone, CM combined with conventional treatment can significantly increase viral nucleic acid negative conversion rate.

3.3.4. Remission rate of pulmonary inflammation (chest CT)

The chest CT findings were typical of findings for COVID-19 pneumonia [17,18]. In the included RCTs, four RCTs compared CM combined with conventional treatment alone. The heterogeneity test result is: P = .79, I² = 0%, so the fixed effect model was adopted. We observed significant differences on remission rate of pulmonary inflammation (RR = 1.27, 95% CI [1.12, 1.44], Z = 3.83, P = .001; Fig. 5). The results indicated that, compared with conventional treatment alone, combined therapy with CM can significantly reduce pulmonary inflammation (chest CT).

3.3.5. Biochemical markers

The heterogeneity test results are: WBC (P = .0005, I² = 87%), LYM (P = .02, I² = 76%), CRP (P < .00001, I² = 97%), IL-6 (P = .06, I² = 73%), so the random effect model was utilized. LYM% (P = .37, I² = 0%), the fixed effect model was adopted. The results suggested that CM combined with conventional treatment significantly increased the white blood cell count (MD = 0.92, 95% CI [0.07, 1.76]; Fig. 6), lymphocyte count (MD = 0.33, 95% CI [0.08, 0.57]; Fig. 7), lymphocyte ratio (MD = 2.90, 95% CI [2.09, 3.71]; Fig. 8). Meanwhile, it can also reduce the amount of CRP (MD = -12.66, 95% CI [-24.40, -0.92]; Fig. 9). These results meant that the participants receiving CM can more effectively improve immune function than those with conventional treatment alone.

However, although two RCTs showed that CM treatment can reduce IL-6 levels, meta-analysis showed no significant difference (MD = -8.17, 95% CI [-22.40, 6.06]; Fig. 10).

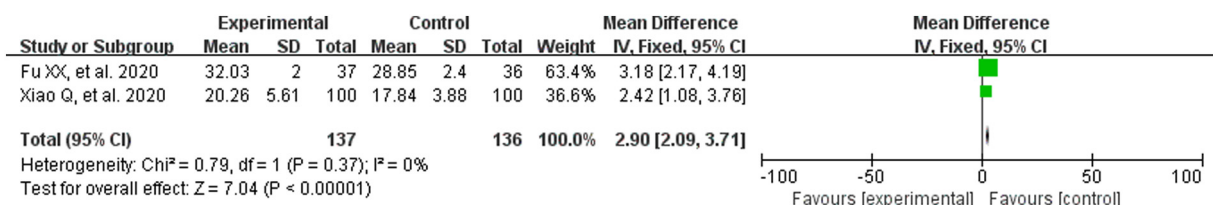


Fig. 9. Analysis of treatment group and control group with CRP.

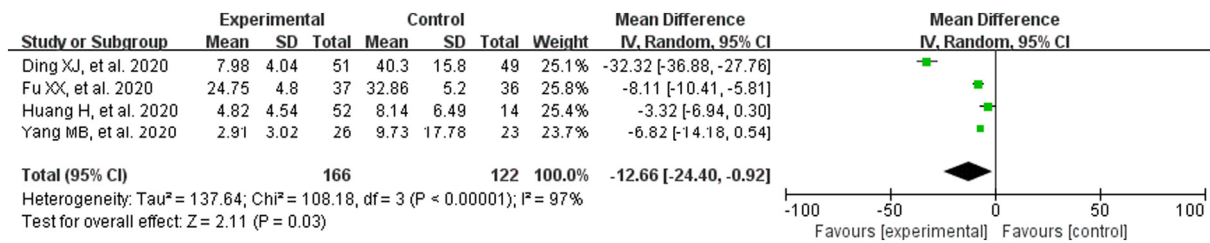


Fig. 10. Analysis of treatment group and control group with IL-6.

3.3.6. Funnel plot characteristics

A funnel plot for the remission rate of pulmonary inflammation was presented in Fig. 11. The funnel plot was considered visually asymmetry, this creates a possible publication bias.

4. Discussion

Since December 2019, many cases of “a novel coronavirus pneumonia” have emerged from the city of Wuhan in China’s Hubei Province. A previously unknown beta-coronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia of unknown cause [19]. On January 6, 2020, the 2019 novel coronavirus (2019-nCoV) was confirmed as the cause of these reported cases, and the outbreak was subsequently named COVID-19 [20]. The novel coronavirus was speculated to be linked to the Huanan Seafood Market, Wuhan [21]. However, there is no consensus on the actual origin of the COVID-19 so far. As of May 9, 2020, widespread human-to-human transmission has resulted in 3,855,788 cases in 213 countries and regions, with 265,862 deaths [22].

COVID-19 possesses particularly powerful pathogenicity and infectivity, and being infected within a very short exposure time is possible [23]. A majority of patients developed COVID-19 pneumonia, and more severely, infections causing pneumonia may lead to severe acute respiratory syndrome and even death [24].

The main diagnostic methods for COVID-19 pneumonia are physical examination, chest CT imaging examination, and viral nucleic acid detection. In general, CT findings and nucleic acid detection results are concordant. However, some studies have shown that some patients with initially negative real-time RT-PCR screening results who had typical CT findings of COVID-19 pneumonia had their RT-PCR results became positive after a few days [25]. Therefore, published clinical guidelines strongly recommend chest CT for patients with suspected COVID-19 [26]. COVID-19 can also affect the body’s immune response; for example, there are relatively lower levels of WBC and LYM, markedly higher levels of CRP and IL-6, etc. [27–29]. These immunological markers may be of importance due to their correlation with disease severity in COVID-19.

There are no specific pharmacological interventions discovered for treatment of COVID-19 pneumonia so far. The World Health Organization recommended that potential antiviral medicines should be developed [30]. However, the development of potential antiviral medicines may take months, even years. In consideration of these limitations, the application of Chinese medicine could be promoted. The Chinese

government has advised doctors to combine antiviral drugs with CM remedies in combating COVID-19 pneumonia [7]. To date, there have been some reports on the role of CM for COVID-19 pneumonia, and clinical practice results showed that CM has excellent outcomes in the treatment of COVID-19, bringing new hope for the control of COVID-19 pneumonia [9–15].

4.1. The effectiveness of CM in treating COVID-19 pneumonia

The results of this meta-analysis are encouraging. In terms of clinical effective rate, viral nucleic acid negative conversion rate, remission rate of pulmonary inflammation, and biochemical markers, CM exhibited superior performance. Meanwhile, CM has therapeutic safety.

4.2. Comparison with previous reviews

As the first meta-analysis evaluating the efficacy and safety of CM for the treatment of COVID-19 pneumonia, the wide extent of literature screening and the introduction of statistical analysis methods have ensured the validity of this review, as well as providing a rational conclusion. It is critical for clinicians to accurately determine the severity of a patients condition. At the same time, clinicians follow the theory of Chinese medicine, and determine the appropriate prescription to ensure effective treatment. Especially, in the absence of Chinese herbal medicine, a variety of Chinese patent medicines (such as Shufengjiedu capsule, Jinhuaqinggan granule, Reyanning mixture, etc.) are also effective. These findings will be valuable for clinicians selecting medical interventions for COVID-19 pneumonia treatment.

4.3. Limitations and future directions

Several limitations exist in this meta-analysis and the findings must be carefully explained. Trials were conducted in China, which limited the evaluation of results to consider other ethnicities living in different countries. The inadequate quality of the publications also affects the credibility of the conclusion of this analysis. The authors will continue to monitor the literature, and this review will be updated when new evidence emerges.

5. Conclusions

A total of seven studies encompassing 681 patients were included in this meta-analysis. According to the findings, CM combined with

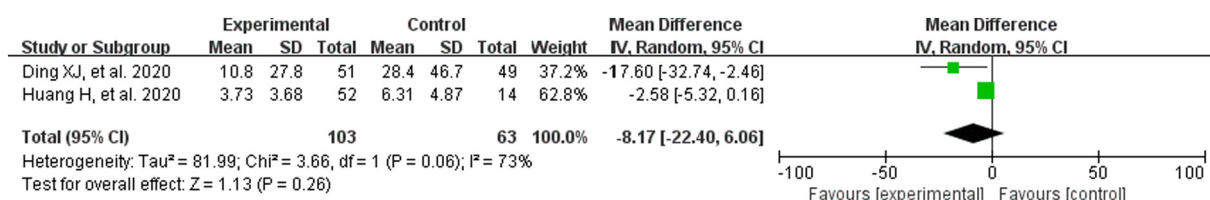


Fig. 11. Funnel plot.

conventional treatment was the better treatment choice for COVID-19 pneumonia. This result provides a high level of evidence for the CM treatment of COVID-19 pneumonia. In terms of limitations, large, multicentre clinical trials are needed to verify the credibility of the conclusion.

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Author contributions

CY Sun contributed to Conceptualization and Data curation. YL Sun and CY Sun contributed to Formal analysis and Funding acquisition. CY Sun, YL Sun and XM Li contributed to Resources and Software. YL Sun and XM Li contributed to Writing - original draft, and YL Sun contributed to Writing - review & editing. The final submitted version has been confirmed by all authors.

Ethical approval

Ethical approval is not necessary in the meta-analysis because our analysis only gather RCTs from a literature database.

Declaration of Competing Interest

None.

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