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Systematic Review

Meta-analysis on the effect of combining Lianhua Qingwen with Western medicine to treat coronavirus disease 2019

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has become a worldwide life-threatening pandemic. Lianhua Qingwen is believed to possess the ability to treat or significantly improve the symptoms of COVID-19. These claims make it important to systematically evaluate the effects of using Lianhua Qingwen with Western medicine to treat COVID-19.

Objective: To evaluate the safety and efficacy of combination therapy, employing Lianhua Qingwen with Western medicine, to treat COVID-19, using a meta-analysis approach.

Search strategy: China National Knowledge Infrastructure, Wanfang Database, VIP Database, PubMed, Embase, and Cochrane Library databases were searched for studies evaluating the effect of Lianhua Qingwen-Western medicine combination therapy in the treatment of COVID-19.

Inclusion criteria: (1) Research object: hospitalized patients meeting the diagnostic criteria of COVID-19 were included. (2) Intervention measures: patients in the treatment group received Lianhua Qingwen treatment combined with Western medicine, while the control group received either Western medicine or Chinese medicine treatment. (3) Research type: randomized controlled trials and retrospective study were included.

Data extraction and analysis: Two researchers extracted the first author, the proportion of males and females, age, body temperature, course of treatment, rate of disappearance of main symptoms, duration of fever, adverse reactions, and total effectiveness from the literature. Odds ratio (OR) and 95% confidence interval (CI) were used as the effect value for count data, and mean difference (MD) and 95% CI were used as the effect value for measurement data.

Results: Six articles met the inclusion criteria, including a total of 856 COVID-19 patients. The meta-analysis showed that Lianhua Qingwen combination therapy achieved higher rates of fever reduction (OR = 3.43, 95% CI [1.78, 6.59], $P = 0.0002$), cough reduction (OR = 3.39, 95% CI [1.85, 6.23], $P < 0.0001$), recovery from shortness of breath (OR = 10.62, 95% CI [3.71, 30.40], $P < 0.0001$) and recovery from fatigue (OR = 2.82, 95% CI [1.44, 5.53], $P = 0.003$), higher total effectiveness rate (OR = 2.51, 95% CI [1.73, 3.64], $P < 0.00001$), and shorter time to recovery from fever (MD = -1.00, 95% CI [-1.04, 0.96], $P < 0.00001$), and did not increase the adverse reaction rate (OR = 0.65, 95% CI [0.42, 1.01], $P = 0.06$), compared to the single medication control.

Conclusion: The Lianhua Qingwen and Western medicine combination therapy is highly effective for COVID-19 patients and has good clinical safety. As only a small number of studies and patients were included in this review, more high-quality, multicenter, large-sample-size, randomized, double-blind, controlled trials are still needed for verification.

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Contents

1. Introduction 27

2. Materials and methods 27

 2.1. Inclusion and exclusion criteria 27

 2.1.1. Inclusion criteria 27

 2.1.2. Exclusion criteria 27

 2.2. Search strategy 27

 2.3. Data extraction 27

 2.4. Literature quality assessment 28

 2.5. Bias risk assessment 28

 2.6. Statistical methods 28

3. Results 29

 3.1. Literature search results 29

 3.2. Literature quality evaluation 29

 3.3. Assessment of risk of bias 29

 3.4. Meta-analysis results 29

 3.4.1. Time to recovery from fever 29

 3.4.2. Rate of recovery from fever 29

 3.4.3. Rate of recovery from cough 29

 3.4.4. Recovery from shortness of breath 29

 3.4.5. Rate of recovery from fatigue 29

 3.4.6. Incidence of adverse reactions 30

 3.4.7. Total effectiveness rate 30

4. Discussion 30

5. Conclusion 32

Funding 32

Author contributions 32

Declaration of competing interest 33

References 33

1. Introduction

Coronavirus disease 2019 (COVID-19), characterized by acute respiratory tract symptoms, is caused by a novel coronavirus, “2019-nCoV,” and has become a global pandemic [1,2]. Common symptoms of the disease include fever, shortness of breath, fatigue, and cough; however, severely and critically ill patients can experience life-threatening respiratory failure and renal failure [3]. Conventional Western medicine, taken in conjunction with traditional Chinese medicine, has played a significant role in the resolution of these symptoms [4–6]. Lianhua Qingwen is believed to be able to treat COVID-19 and to improve its symptoms, including cough, fever, and fatigue [7]. The underlying mechanism may be a combination of broad-spectrum antibacterial, antiviral, and antipyretic activities that contribute to relieving cough, reducing phlegm, and regulating immunity [8–11]. In this study, a systematic approach was used to search for clinical trials and to evaluate the efficacy of Lianhua Qingwen taken in combination with Western medicine for the treatment of COVID-19; our conclusions include relevant evidence-based medical advice.

2. Materials and methods

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria

(1) Research objects: hospitalized patients meeting the diagnostic criteria of “Diagnosis and treatment of COVID-19” [12] were included. (2) Intervention measures: patients in the treatment group received a combination of Lianhua Qingwen and Western medicine treatment, while control group received either Western

or Chinese medicine treatment. (3) Research type: randomized controlled trial (RCT) and retrospective study. (4) Outcome indicators: the disappearance rate of main symptoms, duration of fever, adverse reactions, and total effectiveness rate were recorded.

2.1.2. Exclusion criteria

Studies returned in the search were excluded from this meta-analysis if they were duplicates of other literature, case reports, or reviews; if they had had incomplete or unavailable outcome indicators; if they had no control group; and if their study population excluded critically ill patients.

2.2. Search strategy

The databases for the literature search included China National Knowledge Infrastructure, Wanfang Database, VIP Database, PubMed, Embase, and Cochrane Library. The search-window was from December 1, 2019, to July 14, 2020. The keywords for the search were coronavirus disease 2019, novel coronavirus-infected pneumonia, COVID-19, 2019-nCoV, and Lianhua Qingwen. The search query was formulated as follows (taking PubMed as an example, refer to the MeSH medical keywords): coronavirus disease 2019 OR novel coronavirus-infected pneumonia OR COVID-19 OR 2019-nCoV AND Lianhua Qingwen. The reference sections of returned literature were used to expand the search to studies that were not captured by the search query.

2.3. Data extraction

Two researchers strictly followed the inclusion and exclusion criteria to independently screen the literature. When there were

disagreements, a third party participated in the discussion and decided whether or not to include the study. After first screening the title and abstract for suitability, the full text of the literature was obtained and read. Data were then extracted from the papers, including the first author, the proportion of males and females, age, body temperature, course of treatment, and outcome indicators. The main indicators included the rate of reduction in primary symptoms, duration of fever, adverse reactions, and total effectiveness rate.

2.4. Literature quality assessment

Quality evaluation was performed on all the included literature. The Jadad scoring criteria were used to evaluate the quality of the randomized controlled studies [13]. The scoring criteria included random sequence generation, allocation concealment, blind methodology, and follow-up. Low-quality research literature was rated from 1–3 points; high-quality research literature was rated from 4–7 points. The Newcastle-Ottawa Scale (NOS) [14] was used to evaluate the quality of the retrospective studies. The specific scoring standards were as follows: selection, comparability, and exposure. According to the above criteria, scores > 6 points were considered high quality, and scores < 6 points were considered low quality. The evaluation process was carried out independently by two reviewers, and a third party mediated the discussion and helped reach consensus when scores were inconsistent.

2.5. Bias risk assessment

Risk assessment was conducted to evaluate the quality of the RCTs according to the Cochrane Collaboration 5.1.0 risk of bias assessment tool, including the generation of random sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each of these items was scored as high risk, low risk and unclear risk. The evaluation process was carried out independently by two reviewers, and a third party mediated the discussion and helped reach consensus when scores were inconsistent.

2.6. Statistical methods

RevMan 5.3, provided by the Cochrane Collaboration, was used for data analysis. Odds ratio (OR) and 95% confidence interval (CI) were used as the effect measure for count data, and mean difference (MD) and 95% CI were used as the effect measure for measurement data. If there was no significant difference shown by the Q test ($P > 0.10$, $I^2 \leq 50\%$), a fixed effects model was used for analysis. If there was a significant difference ($P \leq 0.10$ and $I^2 > 50\%$), a random effects model was used. $P < 0.05$ was used as the threshold for significance.

3. Results

3.1. Literature search results

Initially, a total of 71 studies were retrieved from the databases, and one was manually retrieved. By reading the titles and abstracts, it was determined that 25 were duplicate studies, 13 were irrelevant to the research purpose, 23 were reviews, and 3 were case studies; these were all excluded. The remaining eight articles were re-screened after reading the full text; one study without a control group and one study with basic research were excluded. After the above step-by-step screening, 6 studies [15–20] were finally included. The screening process is illustrated in

Fig. 1. The data extracted from the included studies are shown in Table 1. All the results are summarized in Table 2.

3.2. Literature quality evaluation

The two RCTs [16,20] had a Jadad score of 4 and 6, respectively, while the 4 retrospective studies [15,17–19] each had a NOS score of 7. These were all high-quality studies and were comparable at baseline.

3.3. Assessment of risk of bias

Two studies [16,20] were RCTs. Both [16,20] explained their method of randomization; one study [16] described the concealment of allocation and blinding methods, and the other [20] did not. The data from the two studies [16,20] were complete, and the selective reporting of research results and other sources of bias were not mentioned. The bias risk assessment is shown in Fig. 2 and the risk of bias summary in Fig. 3.

3.4. Meta-analysis results

3.4.1. Time to recovery from fever

Four studies [15–17,19] compared the time to recovery from fever between the combination therapy group and the single medication group. There was no statistical heterogeneity between the studies ($P = 0.78$, $I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. The combination therapy group had significantly shorter time to recovery from fever in the treatment of COVID-19 than the single medication group (MD = -1.00 , 95% CI [-1.04 , 0.96], $P < 0.00001$; Fig. 4).

3.4.2. Rate of recovery from fever

Three studies [15,18,19] compared the rate of recovery from fever between the combination therapy group and the control. The average rates of recovery from fever in the combination therapy group and the control group were 85.5% (106/124) and 62.5% (60/96), respectively. No statistical heterogeneity was observed among the included studies ($P = 0.92$, $I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found that the combination therapy group had a significantly higher rate of recovery from fever than the control group in the treatment of COVID-19 (OR = 3.43, 95% CI [1.78 , 6.59], $P = 0.0002$; Fig. 5).

3.4.3. Rate of recovery from cough

Three studies [15,18,19] compared the rate of recovery from cough between the combination therapy group and the control group. The rates of recovery from cough of the combination therapy group and the control group were 56.6% (60/106) and 27.9% (26/93), respectively. No statistical heterogeneity was seen among the studies ($P = 0.39$, $I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found that the combination therapy group had a significantly higher rate of recovery from cough than the single medication group in the treatment of COVID-19 (OR = 3.39, 95% CI [1.85 , 6.23], $P < 0.0001$; Fig. 6).

3.4.4. Recovery from shortness of breath

Three studies [15,18,19] compared the recovery rate of shortness of breath between the combination therapy group and the single medication group. The rates of recovery from shortness of breath in the combination therapy group and the single medication group were 68.2% (30/44) and 15.4% (6/39), respectively. No statistical heterogeneity was observed among the studies ($P = 0.75$, $I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found that the combination therapy group had a significantly higher rate of recovery from shortness of breath

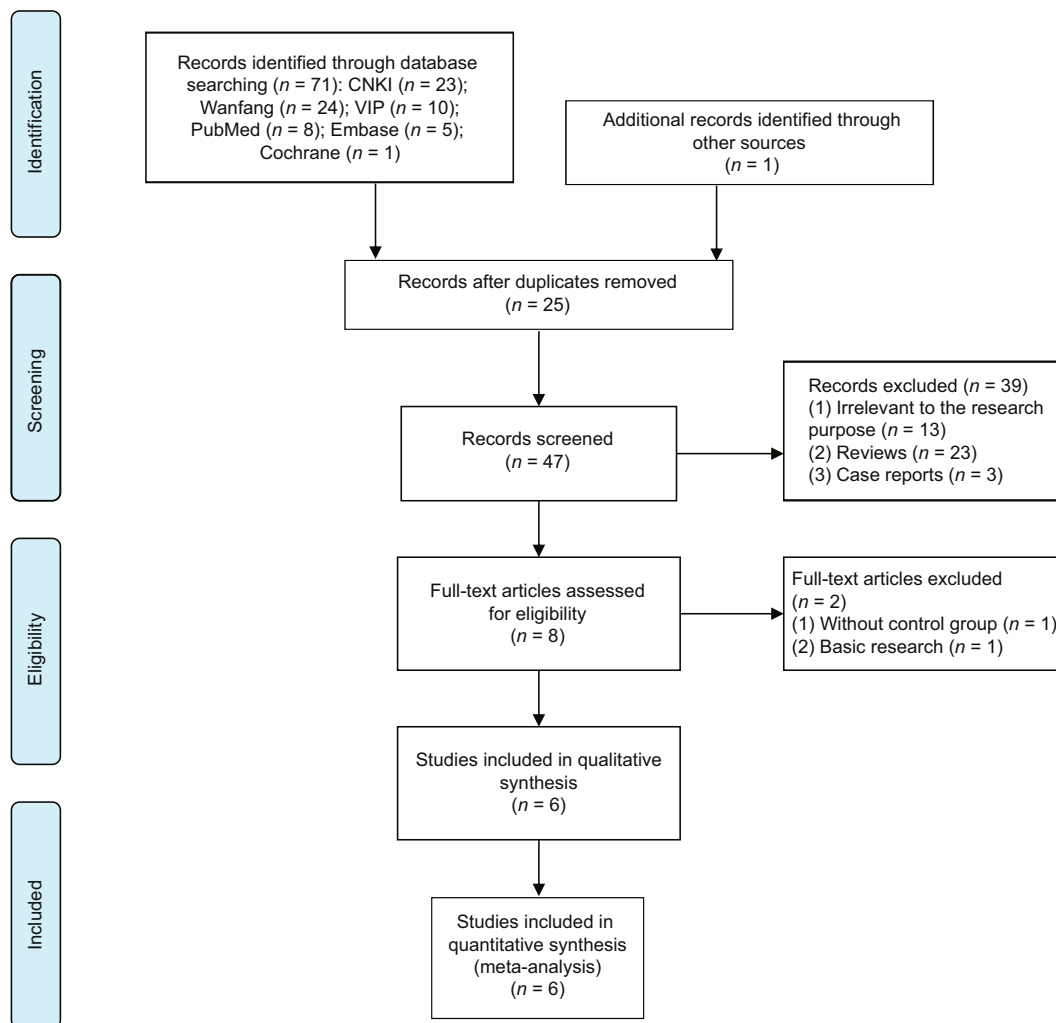


Fig. 1. Literature screening process. CNKI: China National Knowledge Infrastructure.V

Table 1 Characteristics of the studies included in this meta-analysis.

Study	Group	Sample size (M/F)	Age (year)	Body temperature (°C)	Course of treatment (d)	Type of treatment	Score (Jadad/NOS)
Chen et al. [15]	Experimental	26/25	55.5 ± 12.3	38.44 ± 0.63	7	L + W	7
	Control	27/24	55.8 ± 11.6	38.33 ± 0.64	7	W	
Hu et al. [16]	Experimental	79/63	50.4 ± 15.2	37.1 ± 0.7	14	L + W	6
	Control	71/71	51.8 ± 14.8	37.090 ± 0.668	14	W	
Liu et al. [17]	Experimental	11/7	44.06 ± 14.23	NA	NA	L + W	7
	Control	6/8	49.85 ± 17.10	NA	NA	L	
Lv et al. [18]	Experimental	28/35	59.12 ± 16.56	38.08 ± 0.63	10	L + W	7
	Control	18/20	60.20 ± 17.01	38.03 ± 0.67	10	W	
Yao et al. [19]	Experimental	16/5	57.1 ± 14.0	38.56 ± 0.68	NA	L + W	7
	Control	12/9	62.4 ± 12.3	38.38 ± 0.63	NA	W	
Yu et al. [20]	Experimental	82/65	48.27 ± 9.56	37.86 ± 0.65	7	L + W	4
	Control	89/59	47.25 ± 8.67	37.74 ± 0.57	7	W	

F: female; L: Lianhua Qingwen capsules; M: male; NA: not available; NOS: Newcastle-Ottawa Scale; RCT: randomized controlled trial; W: Western medicine.

than the single medication group in the treatment of COVID-19 (OR = 10.62, 95% CI [3.71, 30.40], $P < 0.0001$; Fig. 7).

3.4.5. Rate of recovery from fatigue

Three included studies [15,18,19] compared the rate of recovery from fatigue between the combination therapy group and the control group. The rates of recovery from fatigue in the combination group and the control group were 68.7% (57/83) and 42.8% (33/77), respectively. There was no statistical heterogeneity among

the studies ($P = 0.76, I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found that that the combination therapy group had a significantly higher rate of recovery from fatigue than the single medication group in the treatment of COVID-19 (OR = 2.82, 95% CI [1.44, 5.53], $P = 0.003$; Fig. 8).

3.4.6. Incidence of adverse reactions

Three included studies [16,18,20] compared adverse reactions to the treatment between the combination therapy group and

Table 2
Summary of results from the meta-analysis of clinical outcomes.

Outcome	Number of trials	Number of patients	L + W	C	P value	I ²	OR or MD	95% CI	P value for heterogeneity
Time to recovery from fever	4	419	217	202	0.78	0	-1.00	-1.04, 0.96	< 0.00001
Fever recovery rate	3	220	124	96	0.92	0	3.43	1.78, 6.59	0.0002
Cough recovery rate	3	209	106	93	0.39	0	3.39	1.85, 6.23	< 0.0001
Shortness of breath recovery rate	3	83	44	39	0.75	0	10.62	3.71, 30.40	< 0.0001
Fatigue recovery rate	3	160	83	77	0.76	0	2.82	1.44, 5.53	0.003
Adverse reaction rate	3	639	319	320	0.27	17	0.65	0.42, 1.01	0.06
Total effectiveness rate	4	741	370	371	0.87	0	2.51	1.73, 3.64	< 0.00001

C: control group; CI: confidence interval; L: Lianhua Qingwen capsules; MD: mean difference; OR: odds ratio; W: Western medicine.

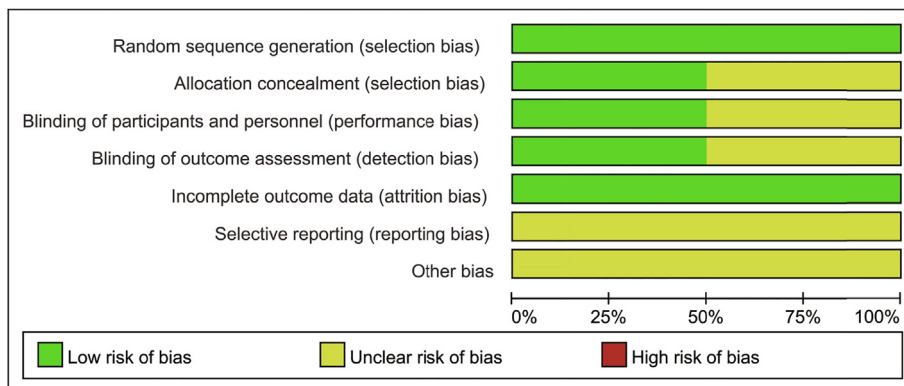


Fig. 2. Risk of bias graph for randomized controlled trials included in this study.

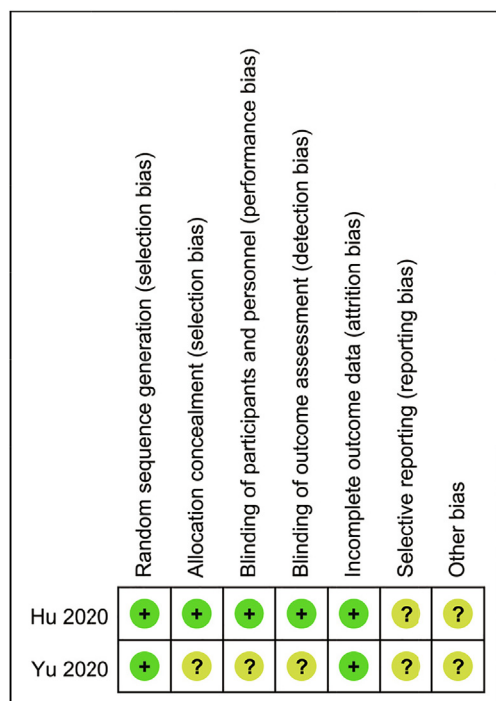


Fig. 3. Summary of the risk of bias analysis for the randomized controlled trials included in this study.

the control group. The incidences of adverse reactions in the combination therapy group and the control group were 21.3% (68/319) and 26.6% (85/320), respectively. No statistical heterogeneity could be seen between the studies ($P = 0.27$, $I^2 = 17\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found

that there was no significant difference in the incidence of adverse reactions between the combination therapy group and the single medication group in the treatment of COVID-19 (OR = 0.65, 95% CI [0.42, 1.01], $P = 0.06$; Fig. 9).

3.4.7. Total effectiveness rate

Four studies [15,16,18,20] compared the total effectiveness rate between the combination therapy group and the control group. The total effectiveness rates of the combination therapy group and the control group were 85.4% (316/370) and 70.6% (262/371), respectively. No statistical heterogeneity was seen between the different studies ($P = 0.87$, $I^2 = 0\%$), and a fixed effects model was used to combine the effect sizes for analysis. We found that the combination therapy group had a significantly higher total effectiveness rate in the treatment of COVID-19 than the control group (OR = 2.51, 95% CI [1.73, 3.64], $P < 0.00001$); Fig. 10).

4. Discussion

The global COVID-19 pandemic has become increasingly severe, and it has been listed by the World Health Organization as a “public health emergency of international concern” [21,22]. COVID-19 can be classified as an “epidemic” in Chinese medicine [23]. Lianhua Qingwen capsules contain a traditional Chinese medicine preparation. It is composed of 13 Chinese medicine extracts, namely, forsythia, honeysuckle, ephedra, wood fern, *Isatis* root, gypsum, menthol, patchouli, rhodiola, fishwort, rhubarb, sauteed bitter almonds, and licorice [24]. It clears toxins and plays a role in regulating lung function. The drug is widely used in modern applications to treat respiratory diseases caused by viral infections [25]. Pharmacological studies have shown that Lianhua Qingwen has inhibitory effects against the severe acute respiratory syndrome virus cultured *in vitro* [26], provides multistage resistance to influenza A viruses H1N1 and H3N2 [27] and inhibits avian influenza virus H7N9 [28]. Lianhua Qingwen inhibits the release

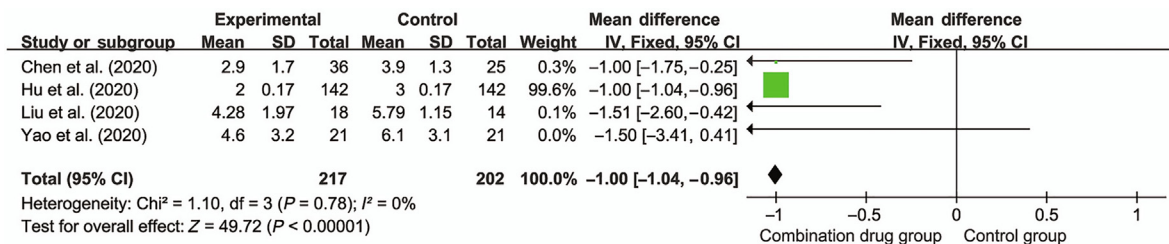


Fig. 4. Comparison of the time to recovery from fever between the two groups.

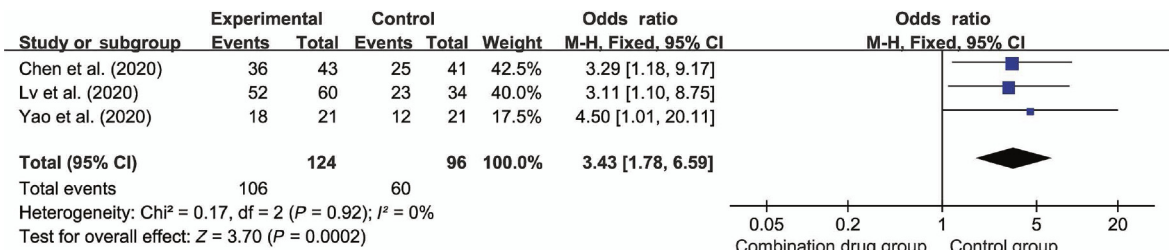


Fig. 5. Comparison of the rate of recovery from fever between the two groups.

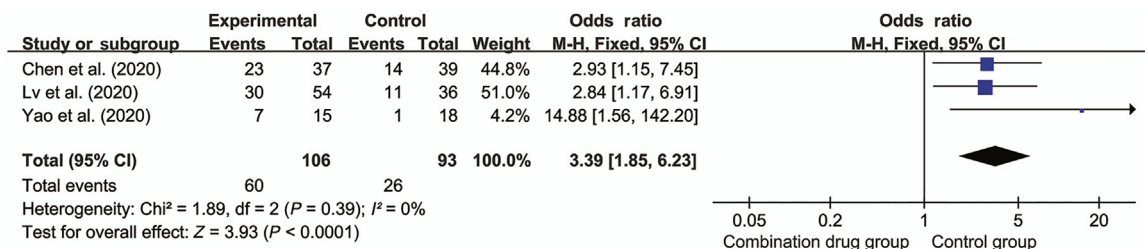


Fig. 6. Comparison of the rate of recovery from cough between the two groups.

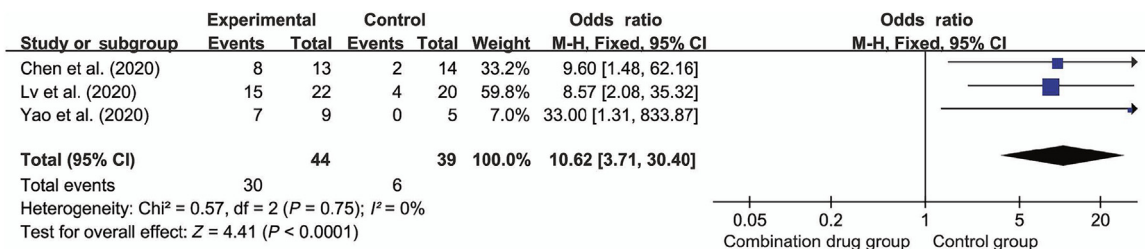


Fig. 7. Comparison of the rate of recovery from shortness of breath between the two groups.

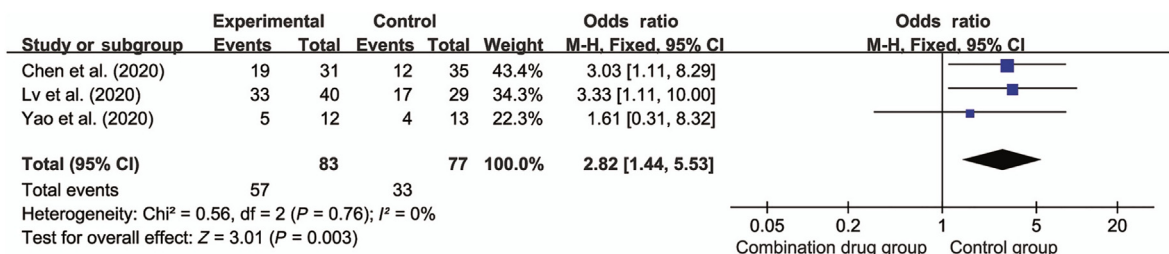


Fig. 8. Comparison of the rate of recovery from fatigue between the two groups.

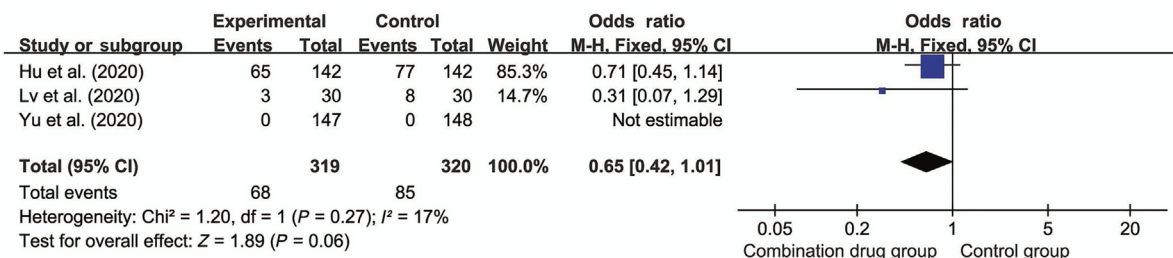


Fig. 9. Comparison of the incidence of adverse reactions between the two groups.

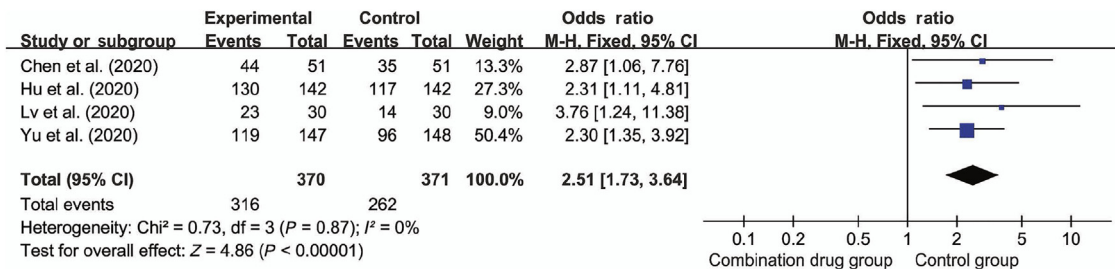


Fig. 10. Comparison of the total effectiveness rate of the two groups.

of inflammatory mediators in the body, thereby ameliorating the damage to lung tissue [29]. It has antibacterial effect against secondary bacterial infections after viral infections, reduces fever, and has anti-inflammatory properties [30–32], thereby promoting the relief of symptoms related to COVID-19. The latest network pharmacology research shows that Lianhua Qingwen can show its efficacy against coronavirus via multiple pathways, targets, and components. The active ingredients display a binding affinity to main protease and angiotensin-converting enzyme 2, and the mechanism encompasses a broad-spectrum antibacterial, antiviral and antipyretic effects, amelioration of phlegm and cough, immune regulation, suppression of virus-induced nuclear factor-κB activation and reduction in the expression of interleukin-6 (IL-6), IL-8, tumor necrosis factor-α, and interferon-inducible protein-10 genes [33,34].

In the present meta-analysis, 6 studies meeting the inclusion criteria were included. In total, there were 442 cases in the combination therapy group and 414 cases in the control (single medication) group. Five studies used Lianhua Qingwen in the form of granules, and one study used a capsule; 4 studies reported the course of treatment, and two studies did not report the course of treatment. The results showed that, the total effectiveness rate of combination therapy was greater than that of the single medication control (OR = 2.51, 95% CI [1.73, 3.64], P < 0.00001). The main symptoms (fever, cough, shortness of breath, and fatigue) was improved, and the time to recovery from fever was shortened (MD = -1.00, 95% CI [-1.04, 0.96], P < 0.00001). Thus, a combination of Lianhua Qingwen and Western medicine has positive clinical outcomes against COVID-19. This meta-analysis also compared the rates of adverse reactions between the combination therapy and the single medication treatment in the management of COVID-19, and the difference was not statistically significant (OR = 0.65, 95% CI [0.42, 1.01], P = 0.06). This suggests that the granular form of Lianhua Qingwen is safe for clinical application. However, in clinical treatment, it is still necessary to pay attention to the adverse reactions. Most of the adverse reactions to Lianhua Qingwen capsules occurred after the first use and involved the gastrointestinal system and skin, mainly manifesting as nausea, vom-

iting, abdominal distension, diarrhea, rash, or itching. In clinical practice, attention should be paid to the dosage and course of treatment, and adverse reactions should be closely monitored [35].

This study has several shortcomings. First, the number of included studies was small, and the studies were all conducted in China, so it is difficult to conduct subgroup analysis of other regions and races. Second, most of the studies were non-randomized double-blind studies, and high-quality, multicenter, large-sample-size, randomized, double-blind, controlled trials are still needed to verify the results. Third, some of the included studies did not report all of the important details, such as: there was no mention of blinding in the randomized study, and in two studies, the course of treatment was unknown.

5. Conclusion

This meta-analysis confirmed that Lianhua Qingwen, taken in combination with Western medicine can significantly improve the main symptoms of patients with COVID-19; this treatment approach is able to shorten the time to recovery from fever, has significant clinical efficacy and causes few adverse reactions. Combination therapy with Lianhua Qingwen and Western medicine was effective in patients with mild to moderate COVID-19. However, due to the few studies available, the present analysis had a small sample size, and multicenter, large-sample-size RCTs are still needed to verify the therapeutic advantages of including Chinese medicine in treatment of COVID-19.

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Author contributions

DCW and MY designed this study, and WXX executed the search strategy; JW and YHL collected the data, and DCW and MY re-checked the data; JW and YHL performed the analysis, and

DCW re-checked the analysis; JW and YHL assessed the quality of the studies, and DCW and MY re-checked the quality of the studies; DCW wrote the manuscript, and JW edited the manuscript. All listed authors reviewed and revised the manuscript. DCW and MY contributed equally to this work.

Declaration of competing interest

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

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