# Integrated Lianhua-Qingwen and Western Medicine Versus Western Medicine-Only Therapies Against COVID-19: A Systematic Review and Meta-Analysis

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## Abstract

## Background

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome, has resulted in a global outbreak.

## Objective

To systematically review the therapeutic reports on COVID-19 treated with integrated herbal medicine "Lianhua-Qingwen"and Western medicine to evaluate the efficacy and safety of the treatment.

## Methods

PubMed, Embase, Web of Science, CNKI, CBM and other databases were searched to locate the clinical trials of integrated Lianhua-Qingwen and Western medicine treatment for COVID-19. The herbal medicine Lianhua-Qingwen reported in the treatments is in the form of capsules or granules. Two researchers of our team independently carried out data extraction and quality assessment of the collected literature according to the Cochrane systematic review methodology, calculated combined relative risk (RR) or weighted mean difference (MD)/standardized mean difference (SMD) .

## Results

This meta-analysis included 13 studies collected, a total of 1182 cases of patients with common type COVID-19. Comparison of integrated Lianhua-Qingwen and Western medicine treatment with conventional Western medicine treatment found that the effective combined RR value was 1.18 (95% CI: 1.09, 1.27; $I^2$ = 37%), and the RR value of CT image improvement rate was 1.12 (95% CI: 1.03, 1.23; $I^2$ = 38%). The rate of progressing to critical cases decreased by 50% (RR: 0.50; 95% CI: 0.35, 0.73; $I^2$ = 0%); the RR value of the fever disappearance rate was 1.43 (95% CI: 1.24, 1.65; $I^2$ = 0%); the RR value of the cough disappearance rate was 1.97 (95% CI: 1.45, 2.68; $I^2$ = 0%); the RR value of the rate of recovery from fatigue was 1.51 (95% CI: 1.15, 2.03; $I^2$ = 0%). Compared with conventional Western medicine treatment, the integrated therapy shortened the duration of fever by 1.33 days (95% CI: -1.92, -0.73; $I^2$ = 5%). The number of adverse reactions decreased by 49% (RR = 0.51; 95% CI: 0.14, 1.82; $I^2$ = 76%).

## Conclusion

Therapy of integrated Lianhua-Qingwen and Western medicine treatment is more effective for the treatment of patients with common type COVID-19, more effective in CT improvement rate, and more effective in reducing the rate of progressing to critical cases significantly and with fewer adverse reactions.

## Introduction

Corona virus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a disease with main clinical manifestations of fever, dry cough, fatigue, etc. In some patients, it involves the upper respiratory and digestive tracts with such clinical manifestations as nasal congestion, runny nose, diarrhea, etc. In severe cases, dyspnea usually occurs after one week. These severe cases rapidly develop into acute respiratory distress syndrome, septic shock, metabolic acidosis difficult to correct, coagulopathy, and multi-organ failure[1]. Globally, as of 11:09am CET, 16 January 2021, there have been 92,262,621 confirmed cases of COVID-19, including 1,995,037 deaths, reported to WHO (https://covid19.who.int/).

Western medicine treatment has played an important role in the prevention, diagnosis, and treatment of COVID-19. In *Diagnosis and Treatment Protocol for Coronavirus Pneumonia (Trial version7)* issued by China, Western medicines it recommends include the rational use of glucocorticoids, anti-infective medications, and antiviral medications[2]. Existing studies that have summarized the clinical results of several Western medicines suggest that Western medicines do have certain effects, but due to insufficient evidence, it is not yet possible to draw a definite conclusion, and some drugs such as ribavirin may cause side effects, such as more safety hazards, especially bradycardia, etc[3]

Traditional Chinese medicines have played an important role in treating many outbreaks of viral flu, especially the herbal medicine Lianhua-Qingwen capsules/granules has been used this year in the containment of COVID-19[4−18].The traditional Chinese medicine Lianhua-Qingwen capsules/granules develops from the following herbs: *forsythia suspensa, ephedra sinica, lonicera japonica, almonds, mint, Mianma Guanzhong, rhodiola crenulata, gypsum, pogostemon cablin*, etc, which possess broad-spectrum antiviral effects. Lianhua-Qingwen has been proven to be effective in inhibiting SARS virus[19], H1N1[20, 21] H3N2[22], H5N1[23], H9N2[24] and other influenza viruses. It is commonly used in the prevention and treatment of respiratory tract infection-related diseases. In March 2020, Lianhua-Qingwen capsules/granules was included in the "*Diagnosis and Treatment Protocol for Coronavirus Pneumonia (Trial version7)*" issued by the National Health Commission of China[25]; and in April 2020, Lianhua-Qingwen capsules/granules was approved for use in patients with novel coronavirus pneumonia.

Although Lianhua-Qingwen and other therapeutic regimens of integrated traditional Chinese and Western medicine have been included in COVID-19 clinical treatment guidelines in China, the number of current clinical research reports is small in sample size. Comparing two therapeutic regimens, we will find that there are uncertainties in the improvement of common symptoms and signs, and progressing to the critical cases, as well as the side effects in patients with COVID-19. To this end, our study assessed multiple clinical trials to compare the effects of the therapeutic regimens of Lianhua-Qingwen combined with Western medicine versus the use of only Western medicine, and analyzed the issues of safety and efficacy of different therapeutic regimens in the clinical treatment of COVID-19. Our study aims to provide evidence-based medical indications for the clinical practice of applying Lianhua-Qingwen and other traditional Chinese medicines in the treatment of COVID-19.

## Materials And Methods

### 1. Literature collection strategy

For the present study, we searched the following database: PubMed, Embase, Web of Science, CNKI, CBM, etc. with a literature search deadline of Jan 16, 2021. The key terms for literature search included Novel Coronavirus" OR "Novel Coronary Pneumonia" OR"2019-nCoV" OR "COVID-19" OR "SARS-CoV-2" OR "NCP" AND "Lianhua-Qingwen" OR "LHQW"

### 2. Inclusion and exclusion criteria

The inclusion criteria for trials to study include the following: 1) The type of research should be clinical based studies, including randomized controlled experiments and single-arm experiments; 2) It reports the relevant information before and after the treatment of the patients; 3) It studies the integrated use of traditional Chinese medicine Lianhua-Qingwen and Western medicine in the treatment vs. Western medicine-only treatment.

The exclusion criteria include the following: 1) News, reviews, comments, methodology report, letters, conference articles about COVID-19 treatment were excluded; 2) Literature with incomplete data or literature unable to be extracted was excluded.

### 3. Data extraction and quality assessment

Two reviewers independently conducted literature screening, data extraction and quality assessment, and cross-checks were applied. In case of disagreement, the third reviewer would resolve it through discussion or consultation.

Literature screening was conducted in preliminary to exclude those not qualified for our research by reading the title and abstract of a trial. Then the full text of the literature that meets the inclusion criteria was obtained. At that point the full text was read to check against the inclusion and exclusion criteria for further scrutiny. A self-made information extraction form was developed to collect information about the literature, including the title of the literature, the time of publication, the first author or corresponding author, the total number of patients, the number of cases, sex ratio, age, body temperature, and observation duration in each treatment group. For the assessment of the quality of literature, the Cochrane bias risk assessment scale was used and independently conducted by two reviewers.

### 4. Risk of bias

The evaluation of the quality was based on the "bias risk assessment" tool that adopts the Cochrane systematic review, including random allocation, allocation concealment, the presence or absence of blindness, data integrity, the existence of selection bias, and other sources of bias. In the statistical analysis, the quality assessment was classified by a score system: a score of 5 or higher means low-level bias risks; 3 to 4 standards for medium-level bias risks; 3 or less indicates high-level bias risks.

### 5. Statistical analysis

Meta-analysis was performed using RevMan 5.3 software. The integrated approach of adopting Chinese herbal medicine Lianhua-Qingwen and Western medicines to treat COVID-19 patients was compared with the therapy administering only Western medicines to recover the disease improvement rate, CT imaging improvement rate, main disease improvement rate, duration of fever, rate of progressing to critical cases and rate of adverse reactions of patients with novel coronavirus infection; and the relationship between the main indicators and other indicators was analyzed. The relative risk (RR) was used to express the effect quantity, and the weighted mean difference (MD) or standardized mean difference (SMD) was used to express the measurement data. The confidence interval (CI) is 95%. If the heterogeneity test result $P > 0.1$ or $I^2 \leq 50\%$ was included in the study, the fixed effect model would be used for Meta-analysis; if the heterogeneity test result showed $P \leq 0.1$ or $I^2 > 50\%$, the random effect model would be used for Meta-analysis.

## Results

### 1. Eligible studies

A total of 123 studies were retrieved in this study, and 62 studies were obtained after excluding the duplicate articles. Through further reading the literature titles and reading abstracts, and checking against the inclusion criteria and exclusion criteria, finally, 13 reports [4-6, 8-13, 15-18] were included in the present research, of which 11studies were randomized controlled experiments, 2 studies were single-arm experiments, and the patients studied were mainly from Hubei and Anhui provinces in mainland China. The test group was given Lianhua-Qingwen mainly combined with Western medicine treatment, and the control group was treated with conventional Western medicine treatment, with a total of 1,182 cases of COVID-19; the intervention time range was 5–20 days. The basic characteristics and patient information of the included literature are shown in Table 1.

| First author | Type of study | Location of study | N | | | Age | | Samples(male) | | Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Cont |
| Kaitao Yao[13] | Observational | Hubei | 42 | 21 | 21 | 57.1 ± 14.0 | 62.4 ± 12.3 | 16 (76. 2%) | 12 (57.1%) | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | Conv west treatı |
| Dezhong Cheng[10] | Observational | Hubei | 54 | 54 | - | 60.1 ± 16.98 | - | 29 (53.7% ) | - | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | Conv west treatı |
| Ruibing Lv[15] | Observational | Hubei | 101 | 63 | 38 | 59.12 ± 16.56 | 60.20 ± 17.01 | 28 (44.4%) | 18 (47.4%) | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | Conv west treatı |
| Ping Yu[6] | Observational | Hubei | 295 | 147 | 148 | 48.27 ± 9.56 | 47.25 ± 8.67 | 82 (56%) | 89 (60%) | Lianhua Qingwen, Arbidol combined with conventional western medicine treatment ,6 g / time ,3 times / day | Conv west treatı |
| Jia Shi[12] | Observational | Shanghai | 67 | 49 | 18 | 47.94 ± 14.46 | 46.72 ± 17.40 | 26 ( 38.81%) | 10( 14.93%) | Shufeng Jiedu Capsule, Lianhua Qingwen Granule, etc | Conv west treatı |
| Lili Liu[4] | Observational | Hubei | 32 | 18 | 14 | - | - | - | - | Lianhua Qingwen, combined with Arbidol | Lianh |
| Dezhong Cheng[9] | Observational | Hubei | 102 | 51 | 51 | 55.5 ± 12.3 | 55.8 ± 11.6 | 26 (51%) | 27 (52.9%) | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | Conv west treatı |

| First author | Type of study | Location of study | N | | | Age | | Samples(male) | | Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Cont |
| Ke Hu[11] | RCT | nine provinces throughout mainland China | 284 | 142 | 142 | 50.4 ± 15.2 | 51.8 ± 14.8 | 79 (55.6%) | 71 (50%) | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | Conv west treat |
| Wenguang Xia[16] | Observational | Hubei | 52 | 34 | 18 | 54. 18 ± 13. 08 | 53. 67 ± 12. 70 | 17 ( 50. 0%) | 6 ( 33. 3%) | Traditional Chinese Medicine Decoction, Traditional Chinese Medicine Injection | Antiv (Abid interf Lopir oselt infec (mox levof azith ceph penic drug: globu meth |
| Shengzao Wang[26] | Observational | Anhui | 60 | 30 | 30 | - | - | - | - | Lianhua Qingwen 4 tablets / times 3 times / day ;α- interferon :500 U,2 times / day; Lopinavir / ritonavir :2 tablets / times 2 times / r day | Lianl table times interf times |
| Facai Wang[27] | Observational | Anhui | 55 | 55 | - | - | - | - | - | Lianhua Qingwen Granule combined with conventional western medicine treatment ,1 bag / time ,3 times / day | - |
| Jiangjian Chen[18] | Observational | Guizhou | 70 | 35 | 35 | 44.75 ± 4.92 | 45.21 ± 4.68 | 18 (51.4%) | 20(57.1%) | Lianhua Qingwen, Granule combined with conventional western medicine treatment ,1.4 g / time ,2 times / day | Arbic with west treat |
| Fei Fang[17] | Observational | Hubei | 83 | 42 | 41 | 4.8 ± 3.7 | 3.9 ± 3.2 | 18 (42.9%) | 16 (39.1%) | Lianhua Qingwen Granule combined with conventional western medicine treatment | Conv west treat |

## 2. Overall improvement rate

Five studies report on the overall improvement rate, including 811 subjects (405 patients were in the group of treatment using Lianhua-Qingwen and Western medicine, and 406 patients treated with only conventional Western medicine). The data showed that the therapy using Lianhua-Qingwen combined with

Western medicine treatment improved the effectiveness of recovery of the patients with novel coronavirus by 18%, and the effective combined RR value was 1.18 (95% CI: 1.09, 1.21; $I^2$ = 37%, Fig. 2).

### 3. Chest CT imaging analysis

The rate of chest CT showing recovery was detected in 6 studies including 870 subjects (458 patients were in the group of taking Lianhua-Qingwen combined with Western medicine, and 412 patients were in the group taking conventional Western medicine). The data showed that Lianhua-Qingwen combined with Western medicine treatment showed a better chest CT result in patients with novel coronavirus. The RR value of CT image improvement rate was 1.12 (95% CI: 1.03, 1.23; $I^2$ = 38%, Fig. 3).

### 4. Disappearance rate of main symptoms

The main symptoms of patients with novel coronavirus pneumonia include fever, fatigue, and cough. We separately counted the effects of the two treatment methods on the disappearance rate of the main symptoms of fever, fatigue and cough, respectively.

**Fever**: 7 studies reported the fever disappearance rate, of which 5 studies adopted two-arm experiments and 2 studies adopted single-arm experiments, including 528 subjects (373 were in the group treated with Lianhua-Qingwen combined with Western medicine, and 155 were in the group receiving only conventional Western medicine treatment). The results of the two-arm studies were (RR = 1.43 (95% CI: 1.24, 1.65; $I^2$ = 0%); Fig. 4a1]; the single-arm studies results were (RD = 0.90 (95% CI: 0.73, 1.07; $I^2$ = 86 % ); Fig. 4a2).These results suggest that the combination of Lianhua-Qingwen and Western medicine more effectively improved the symptom of fever in patients with COVID-19 than the method of prescribing only Western medicines for the disease.

**Fatigue**: 5 studies reported the disappearance rate of fatigue, of which 3 studies used two-arm experiments, 2 studies used single-arm experiments, including a total of 269 subjects (192 patients received Lianhua-Qingwen combined with Western medicine, and 77 patients taking only conventional Western medicines). The results of the two-arm studies were (RR = 1.51 (95% CI: 1.15, 2.03; $I^2$ = 0%) ; Fig. 4b1); the results of single-arm studies were (RD = 0.80 (95% CI: 0.70, 0.90; $I^2$ = 0 % ); Fig. 4b2).These results suggest that Lianhua-Qingwen combined with Western medicine treatment better improved the symptom of fatigue in patients with COVID-19 than the approach of using only Western medicines for the disease.

**Cough**: There were 6 studies on the cough disappearance rate, of which 4 studies presented were of two-arm experiments, and 2 studies carried out single-arm experiments, including a total of 379 subjects (253 patients receiving the integrated approach, and 126 taking only conventional Western medicines). The results of the two-arm study were (RR = 1.97 (95% CI: 1.45, 2.68; $I^2$ = 0 % ); Fig. 4c1); the single-arm study results were (RD = 0.74 (95% CI: 0.64, 0.84; $I^2$ = 0 %); Fig. 4c2). They jointly illustrate that treatment with Lianhua-Qingwen combined with Western medicine better improved symptom of cough in patients with COVID-19.

### 5. Duration of fever

There were 3 studies on the duration of fever, including 155 subjects (91 patients were on treatment with both Chinese and Western medicine, and 64 were taking only conventional Western medicine). The data showed that treatment with Lianhua-Qingwen combined with Western medicine improved the symptom fever with shorter recovery time in patients with novel coronavirus. The recovery time was shortened by 1.33 days on average, (MD=-1.33, (95% CI: -1.92, -0.73; $I^2$ = 5%, Fig. 5)

### 6). The rate of progressing to severe cases

There were 7 studies on the rate of progressing to severe cases, including 936 subjects (490 cases were treated with both Chinese and Western medicine, and 446 were treated with only conventional Western medicine). The data suggest that the therapy using Lianhua-Qingwen combined with Western medicine reduced the rate of cases that progressed from mild to severe level when compared with the treatment approach by Western medicine alone (RR = 0.50 (95% CI: 0.35, 0.73; $I^2$ = 0%); Fig. 6)

### 7. Adverse reactions

Of the 13 studies included in our study, 11 studies reported treatment with Lianhua-Qingwen combined with Western medicine. Compared with the treatment by conventional Western medicine, no serious drug-related adverse reactions were seen in the group receiving Lianhua-Qingwen combined with Western medicine. Studies from [15] showed that in the group of conventional Western medicine, 38 cases complained of nausea, 5 cases of vomiting, and 3 cases of loss of appetite, the incidence of adverse reactions was 21.05%. However, in the group of Lianhua-Qingwen treatment with 63 patients, two cases complained of diarrhea, 1 case of loss of appetite, and the incidence of adverse reactions was only 4.76%, and the adverse reactions were improved in both groups after drug withdrawal. The research by Hu et al[11]. showed that the two groups of treatment showed abnormal liver function, renal dysfunction, headache, nausea, vomiting, diarrhea, loss of appetite and other adverse reactions, but there was no significant difference between the two groups[4]. Our analysis of the data also suggested that there was no significant difference in adverse reactions between the two groups: treatment with Lianhua-Qingwen combined with Western medicine vs. treatment with Western medicine treatment alone: (RR = 0.51 (95% CI: 0.14, 1.82; $I^2$ = 76%); Fig. 7).

# Discussions

The present study systematically reviewed the comparative studies of the integrated Lianhua-Qingwen and Western medications vs. Western medicine only approaches for the treatment of novel coronavirus pneumonia since the outbreak of COVID-19. We altogether analyzed 11 reports on the treatment of COVID-19 using therapies described above for a total number of 1,029 patients. It can be concluded that compared with Western medicine-only treatment method in the treatment of COVID-19, the method of adopting integrated Lianhua-Qingwen and Western medicine could significantly increase the improvement rate, the disappearance rate, and disappearance time of the main symptoms, improve the effect of chest CT on the patient, and reduce the risk of worsening of the disease. In addition, it has been found that there is no significant difference in adverse effects between the two treatment methods. The results of this study suggest that the treatment with Lianhua-Qingwen combined with Western medicine has a better synergistic effect on COVID-19.

The main symptoms of patients with COVID-19 are fever, fatigue and cough, and severe respiratory tract infections, and some patients also have a series of other symptoms such as diarrhea and nausea[28]. There is no special drug for the treatment of COVID-19. Recommendations for the treatment of COVID-19 in "*Diagnosis and Treatment Protocol for Coronavirus Pneumonia (Trial version7)*" released by the National Health Commission of China are mainly based on Western medicine treatment supplemented with Chinese medicine. Western medicine treatment has shown some effect non COVID-19, but it is not yet possible to draw a clear conclusion due to few clinical data,

However, clinical trials on COVID-19 treatment have shown that Chinese medicine has played an important role in dealing with the epidemic. The combination of Chinese and Western medicines can better improve the indicators of patients with novel coronavirus pneumonia[14], especially the administration of Lianhua-Qingwen capsules/ granules. Lianhua-Qingwen is a compound preparation of traditional Chinese herbal medicine. The main ingredients of Lianhua-Qingwen include extracts from *forsythia suspensa*, *lonicera japonica*, *Mianma Guanzhong*, *rhodiola crenulata*, etc., which have obvious antiviral effects. Other ingredients like *ephedra sinica*, *mint*, and *rhodiola crenulata* can relieve cough and fever, and clear lungs. In the research on COVID-19, it has been reported that ACE2 is the surface receptor of the COVID-19 and enters the host body by binding to ACE2[29−31], Chen et al.(Chen et al. 2020) used a combination of HRMS and non-targeted data mining methods to analyze the composition map of Lianhua Qingwen in human plasma and urine, and concluded that forsythin, etc. It has a high inhibitory effect on ACE2, and may target to reduce ACE2 related metabolic pathways to improve the COVID-19 pneumonia ; on the other hand, there is a "cytokine storm" in COVID-19[28], which will be produced in the body as the virus spreads accumulation of a large number of inflammatory factors, Lianhua Qingwen significantly inhibited the replication of SARS-COV-2 in VeroE6 cells at the mRNA level, and significantly reduced pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1 and CXCL) -10/IP-10), and the treatment of cells with Lianhua Qingwen will result in abnormal morphology of virus particles in the cells[32], Xia et al. [33] based on big data network analysis showed Lianhua Qingwen may improve the symptoms of patients with new coronary pneumonia by regulating immune response, cell apoptosis and viral infection. The current research results believe that Lianhua Qingwen contains ingredients that can target the treatment of new coronary pneumonia and has a good effect on improving COVID-19.

The results of our study suggest that Lianhua Qingwen combined with Western medicine showed a synergistic therapeutic effect. Up to now, a large number of literatures have analyzed the efficacy of Lianhua Qingwen in the treatment of new coronary pneumonia, and the analysis conclusions are consistent with the analysis conclusions of this article, confirming the treatment effect of Lianhua Qingwen on new coronary pneumonia, but there is no clear comparison with Lianhua Qingwen effects of combined Western medicine treatment and Western medicine alone, and the analysis time is earlier, and the included sample size is small. For example: Khan et al. [34] counted 122 patients taking Lianhua Qingwen combined with Arbidol hydrochloride treatment Effective, but the analysis lacks the control group; Liu [35]analyzed literature before June 2020 and believed that the overall efficiency of patients with Lianhua Qingwen combined with conventional treatment was higher, the CT recovery rate was better, and diarrhea occurred rate is low, but there is less analysis of the characteristic indicators of new coronary pneumonia, and only 4 articles include the conventional treatment group as a control; Zeng et al. [36] analyzed literature analysis as of May 2020 and found that: The combination of Lianhua Qingwen and traditional treatment is better than traditional treatment alone, but only 2 articles are included, and the data included is less; Fang et al.[37] analysis found that the combination of Lianhua Qingwen and Abido is more effective than using continuous treatment alone. Lianhua Qingwen has a good effect on the patient's recovery time, nucleic acid negative, improvement of chest CT time and hospital stay and other indicators, and there are no serious drug-related adverse events.

However, in this article, it should be noted that a large number of clinical trials were not published in time because the clinical trials had deficiencies in methodological design, such as randomization, hidden allocation, and insufficient reports on blinding, withdrawal, and sample size estimation. Therefore, subsequent reports of more randomized clinical trials will help to comprehensively analyze the effect of important preparations like Lianhua-Qingwen combined with Western medicine we have discussed above.

In summary, the conclusion of this systematic review is that Lianhua-Qingwen combined with Western medicine treatment has shown a better treatment efficiency and a more reassured clinical safety for patients with common type COVID-19, and has achieved well-demonstrated results in this anti-epidemic fight.

## Abbreviations

CCL-2, C-C motif chemokine ligand2; COVID-19, Coronavirus disease 2019; CT, Computed tomography; CXCL-10, CXC chemokine ligand-10, IL-6, Interleukin-6; IL-8, Interleukin-8; IP-10, interferon-gamma-induced protein; MCP-1, monocyteschemotacticprotein-1; NFκB, nuclear factor kappa-B; TNF-α, Tumor Necrosis Factor-α; COX-2, cyclooxygenase-2; ACE2, angiotensin-converting enzyme 2

## Declarations

### Declaration of Competing Interest

None.

Author contributions

Z.W., H.L., M.W., Y.P., L.M., J.L. drafted the manuscript. All authors contributed to the development of selection criteria, risk of a bias assessment strategy, and data extraction criteria. H.L., Z.Z., J.C., S.Z. developed the search strategy, Z.W., M.W., H.L. L.M. and J.L. provided statistical and methodological expertise. D.M. and J.L. contributed to interpretation of the data. All authors read, provided feedback, and approved the final manuscript.

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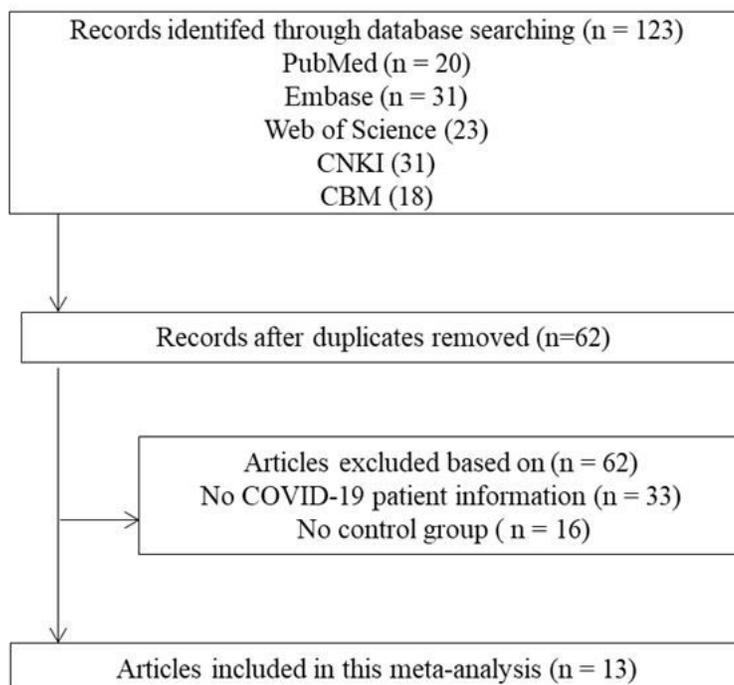
# Figures



Figure 1

Flow diagram of choosing the appropriated articles. After applying the inclusion and exclusion criteria, a total of 13 articles were included in the final meta-analysis with a total of 1182 COVID-19 cases

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Chen 2020 | 33 | 35 | 24 | 35 | 8.5% | 1.38 [1.08, 1.75] | |
| Cheng 2020 | 44 | 51 | 35 | 51 | 12.4% | 1.26 [1.01, 1.56] | |
| Hu 2020 | 130 | 142 | 117 | 142 | 41.4% | 1.11 [1.01, 1.22] | |
| Wang 2020 | 23 | 30 | 14 | 30 | 5.0% | 1.64 [1.07, 2.53] | |
| Yu 2020 | 102 | 147 | 93 | 148 | 32.8% | 1.10 [0.94, 1.30] | |
| **Total (95% CI)** | | 405 | | 406 | 100.0% | 1.18 [1.09, 1.27] | |
| Total events | 332 | | 283 | | | | |

Heterogeneity: Chi² = 6.39, df = 4 (P = 0.17); I² = 37%
Test for overall effect: Z = 4.12 (P < 0.0001)
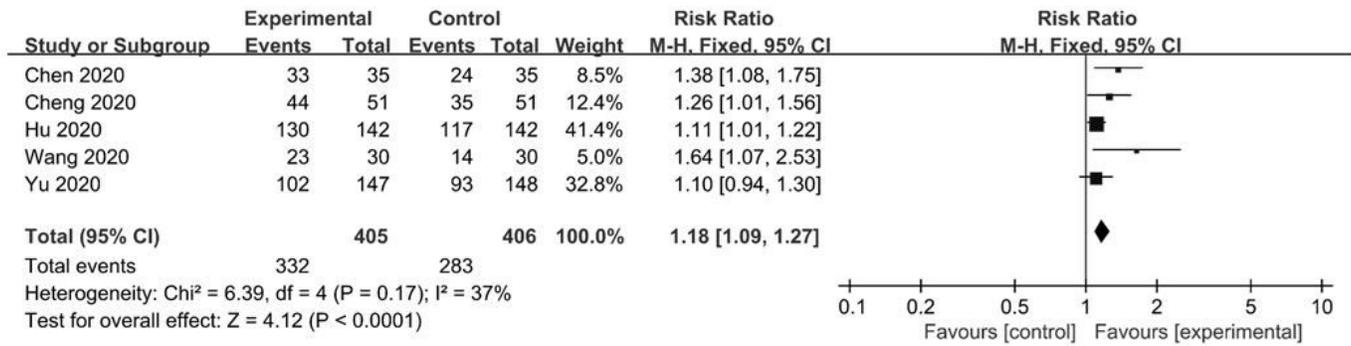
Favours [control]   Favours [experimental]

## Figure 2

Forest plot showing the effect of Lianhua-Qingwen combined with Western medicine vs Western medicine alone on virus clearness in SARS-CoV-2-infected patients.

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Chen 2020 | 30 | 35 | 22 | 35 | 7.9% | 1.36 [1.02, 1.82] | |
| Cheng 2020 | 28 | 51 | 23 | 51 | 8.2% | 1.22 [0.82, 1.80] | |
| Hu 2020 | 109 | 142 | 101 | 142 | 36.2% | 1.08 [0.94, 1.24] | |
| Shi 2020 | 44 | 49 | 17 | 18 | 8.9% | 0.95 [0.82, 1.10] | |
| Xia 2020 | 30 | 34 | 12 | 18 | 5.6% | 1.32 [0.93, 1.88] | |
| Yu 2020 | 102 | 147 | 93 | 148 | 33.2% | 1.10 [0.94, 1.30] | |
| **Total (95% CI)** | | 458 | | 412 | 100.0% | 1.12 [1.03, 1.23] | |
| Total events | 343 | | 268 | | | | |

Heterogeneity: Chi² = 8.10, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 2.61 (P = 0.009)
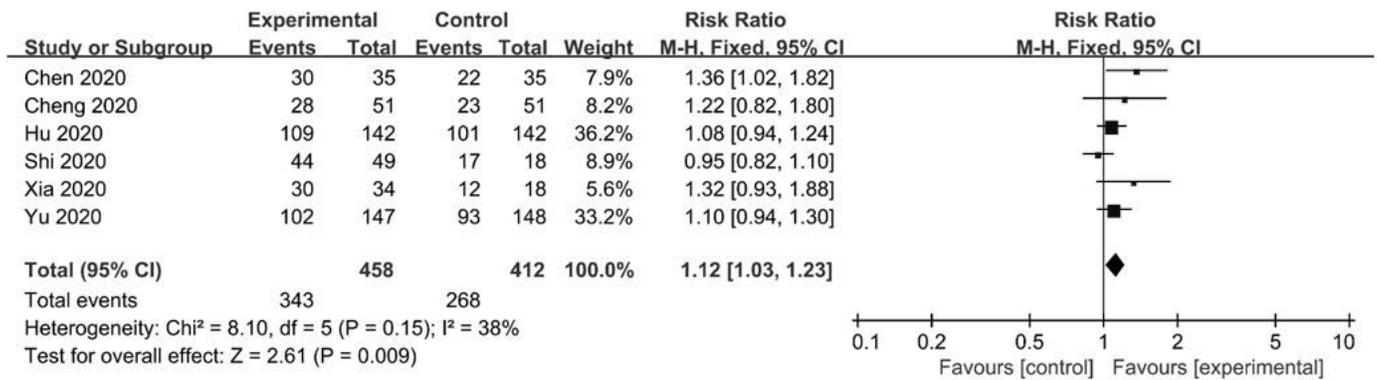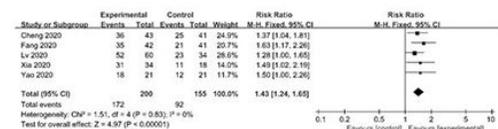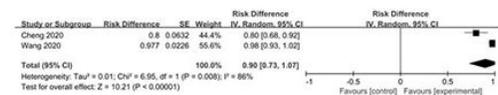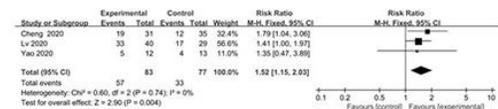
Favours [control]   Favours [experimental]

## Figure 3

Forest plot showing the effect of Lianhua-Qingwen combined with Western medicine vs Western medicine alone on the improvement of Chest CT imaging in SARS-CoV-2-infected patients.
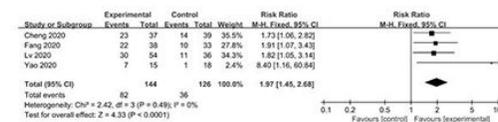
（a1）



（a2）



（b1）



（b2）



（c1）



（c2）

**Figure 4**

Forest plot showing the effect of Lianhua-Qingwen combined with Western medicine vs Western medicine alone on the recovery of main symptoms in SARS-CoV-2-infected patients.（a）Fever disappearance rate, b）Fatigue disappearance rate,（c）Coughing disappearance rate



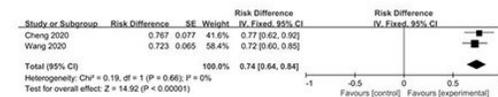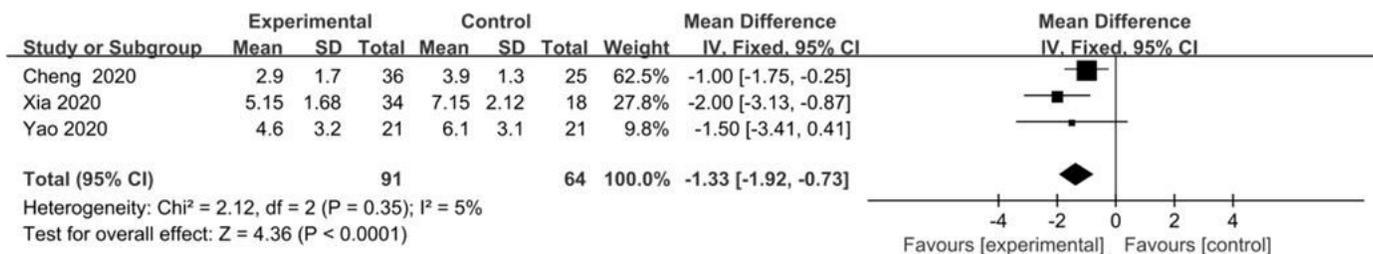**Figure 5**

Forest plot showing the effect of Lianhua-Qingwen combined with Western medicine vs Western medicine alone on the time to fever disappearance in SARS-CoV-2-infected patients.

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chen 2020 | 2 | 35 | 6 | 35 | 8.5% | 0.33 [0.07, 1.54] |
| Cheng 2020 | 4 | 51 | 11 | 51 | 15.6% | 0.36 [0.12, 1.07] |
| Hu 2020 | 3 | 142 | 6 | 142 | 8.5% | 0.50 [0.13, 1.96] |
| Liu 2020 | 1 | 18 | 1 | 14 | 1.6% | 0.78 [0.05, 11.37] |
| Lv 2020 | 21 | 147 | 35 | 148 | 49.5% | 0.60 [0.37, 0.99] |
| Xia 2020 | 2 | 34 | 3 | 18 | 5.6% | 0.35 [0.06, 1.92] |
| Yu 2020 | 4 | 63 | 6 | 38 | 10.6% | 0.40 [0.12, 1.33] |
| | | | | | | |
| Total (95% CI) | | 490 | | 446 | 100.0% | 0.50 [0.35, 0.73] |
| Total events | 37 | | 68 | | | |

Heterogeneity: Chi² = 1.57, df = 6 (P = 0.95); I² = 0%
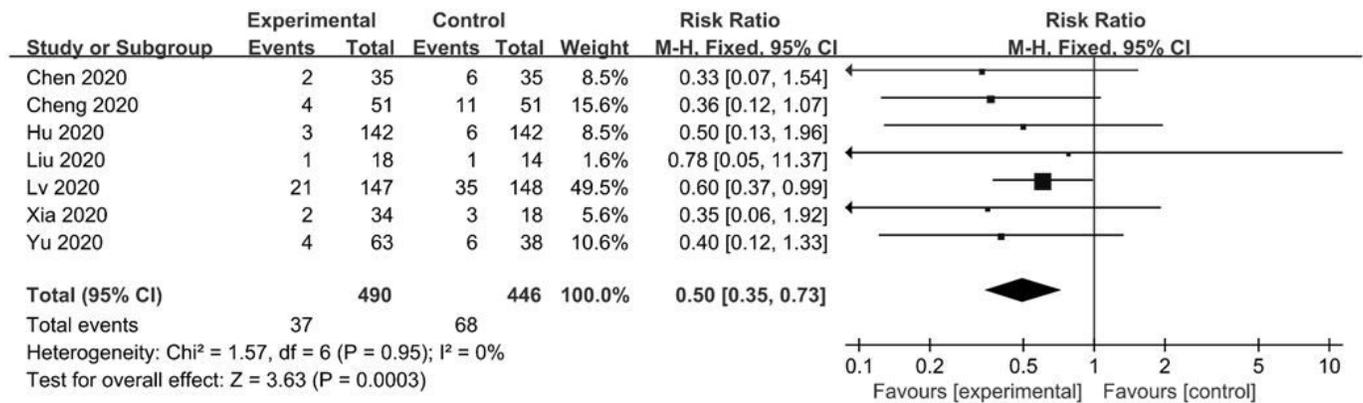Test for overall effect: Z = 3.63 (P = 0.0003)



Figure 6

Forest plot showing the impact of Lianhua-Qingwen combined with Western medicine vs Western medicine alone on the risk of severe COVID-19 in SARS-CoV-2-infected patients.
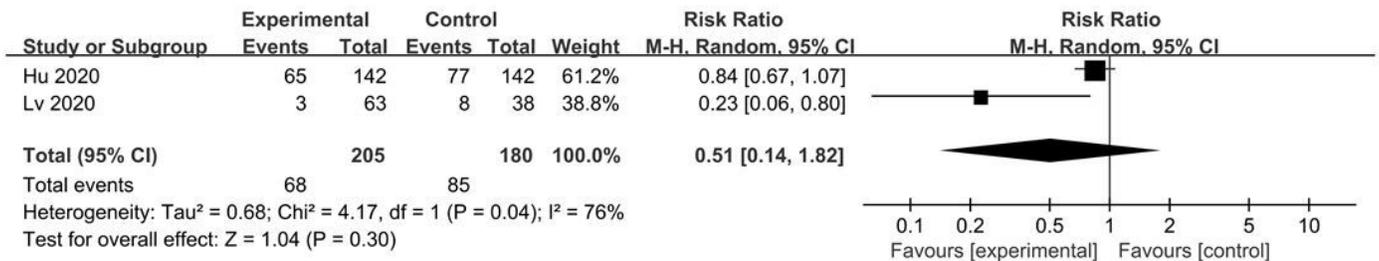
| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hu 2020 | 65 | 142 | 77 | 142 | 61.2% | 0.84 [0.67, 1.07] |
| Lv 2020 | 3 | 63 | 8 | 38 | 38.8% | 0.23 [0.06, 0.80] |
| | | | | | | |
| Total (95% CI) | | 205 | | 180 | 100.0% | 0.51 [0.14, 1.82] |
| Total events | 68 | | 85 | | | |

Heterogeneity: Tau² = 0.68; Chi² = 4.17, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 1.04 (P = 0.30)



Figure 7

Forest plot showing comparison of the adverse events

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Graphicalabstract.png