**Philippine COVID-19 Living Clinical Practice Guidelines**
*Institute of Clinical Epidemiology, National Institutes of Health, UP Manila*
*In cooperation with the Philippine Society for Microbiology and Infectious Diseases*
*Funded by the Department of Health*

# EVIDENCE SUMMARY

**RESEARCH QUESTION**: **Among COVID-19 patients, should Lianhua be used as treatment?**

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## RECOMMENDATIONS

| Recommendations | Certainty of Evidence | Strength of Recommendation |
|---|---|---|
| We suggest the use of Lianhua in the symptomatic relief of adult patients with non-severe COVID-19. | Very low | Weak |
| We suggest against the use of Lianhua in children with COVID-19. | Very low | Weak |

***Consensus Issues***

This recommendation agrees with the FDA's approval for use of Lianhua only for symptomatic relief but not for COVID-19 treatment. The consensus panel suggests the use of Lianhua for the symptomatic relief among adults with non-severe COVID-19, based on a very low certainty evidence that it has benefit in time to symptom recovery and reduction in clinical deterioration. Current evidence in terms of harm remains inconclusive, based on both direct evidence (randomized controlled trials among patients with COVID-19) and indirect evidence (meta-analysis on use of Lianhua on selected non-COVID-19 disease like influenza, Mycoplasma pneumonia and hand-foot-mouth disease). The panel also recognized that the Dangerous Drug Board Committee on Reclassification issued provisional removal of Lianhua Qingwen capsules from the list of dangerous drugs, due to its minimal Ephedra content (9.14mg Ephedra per capsule), posing low or negligible risk of abuse. The dose used in the RCTs were similar to the manufacturer's dose recommendation of 4 capsules 3x/day, however the duration varied across studies, ranging from 7 to 14 days.

On the other hand, the panel unanimously suggested against the use of Lianhua among children with COVID-19 due to lack of good-quality evidence, with only one retrospective non-randomized controlled study available as of writing. The panel also emphasized the potential harm of Lianhua, due to risk of hemolysis among patients with G6PD deficiency and cardiac toxicity due to its Ephedra content, amount of which may not be negligible particularly in young children.

## KEY FINDINGS

- Seven (7) randomized controlled trials investigated the effect of Lianhua compared to standard of care as treatment for patients with COVID-19.
- Lianhua showed significant benefit in preventing clinical deterioration or progression to severe disease among patients with non-severe COVID 19.
- There was no significant benefit in mortality, and day-14 improvement in fever, cough and fatigue.
- There was no significant difference in adverse events or serious adverse events between the Lianhua and control group.
- The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes.
- One retrospective non-randomized controlled study involving children aged 2 months to 13 years with suspected COVID-19 showed that Lianhua increased the disappearance rates of fever, cough,

and expectoration. No significant difference in the disappearance rates of shortness of breath, digestive tract symptoms, nasal obstruction, runny nose was observed.

## WHAT'S NEW IN THIS VERSION?

This review includes 2 additional RCTs (total of 7 included RCTs), evidence about the safety of Lianhua, and evidence about the use of Lianhua for pediatric patients.

**PREVIOUS RECOMMENDATION**
*As of 06 December 2021*

**There is insufficient evidence to recommend the use of Lianhua in the treatment of patients with non-severe COVID-19.** *(Very low certainty of evidence)*

*Previous Consensus Issues*
Although the recent review showed some benefit on the symptomatic treatment (clinical deterioration), the panel considered that the uncertainties on the quality of the evidence outweigh the trend in benefit. First, the subset of patients (percentage of mild and moderate cases) were not clearly stated in the included studies. This may actually affect the trend towards benefit since patients with mild COVID are expected to improve and have shorter time to recovery. Second, the definition of outcomes, particularly total symptom recovery may be too lax as it accounted only for at least one of the major symptoms. The panel also considered that since this is a regulated drug, there are uncertainties about the reported harm (expected adverse effects from ephedra such as hypertension and tachycardia was not assessed in the study procedures or reported in the results) and serious adverse events (unclear if the reported events were transient nor how severe the cases were). There are also inconsistencies in the direction of the clinical outcomes. While there is some benefit seen in reducing clinical deterioration, no definite benefit was seen in terms of clinical improvement of individual symptoms.

## INTRODUCTION

Since COVID-19 was declared a pandemic in early March 2020, various potential pharmacologic therapies including traditional Chinese medicine (TCM) have been extensively explored. Lianhua Qingwen (LHQW), a classical Chinese medical preparation officially recorded in the 2015 edition of the *Chinese Pharmacopoeia*, has been used in the SARS outbreak of 2002-2003 in China [1]. Recent *in vitro* studies have shown its effectiveness against SARS-CoV-2 through inhibition of replication, modification of viral morphology, and exertion of anti-inflammatory activity [2]. Specifically, a network pharmacologic analysis has shown that it regulates TFs or miRNAs of ACE2 [3]. Furthermore, blocking of SARS-CoV-2 binding with ACE2 receptors were observed in vitro in *Lonicera japonica*, *Forsythia suspensa*, and *Rheum palmatum*, which are some of the plant components of Lianhua [4].

A systematic review and meta-analysis of five studies published in September 2020 (including RCTs and observational studies) on the use of Lianhua against COVID-19 pneumonia showed benefit in terms of improvement of flu-like symptoms, shortness of breath, pulmonary imaging, shorter healing period, and lesser conversion to severe cases [5]. This review presents clinical studies on the efficacy and safety of Lianhua against COVID-19.

## REVIEW METHODS

This review is an update of the previously completed review done on October 28, 2021. Databases and registries including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane COVID-19 Study Register, LitCOVID, CenterWatch, China National Knowledge Infrastructure (CNKI), ChinaXiv.org, MedRxiv.org, BioRxiv.org, clinicaltrials.gov, Japan Primary Registries Network/ NIPH Clinical Trials Search, Republic of Korea - Clinical Research Information Service (CRIS), Chinese Clinical Trial Registry (ChiCTR), LitCOVID, WHO Clinical Trials International Clinical Trials Registry Platform (ICTRP), COVID-NMA Initiative COVID-19 Open Living Evidence Synthesis, EU Clinical Trials Register, WHO Therapeutics and COVID-19 Living Guideline, COVID-19 Local Evidence Database, and HERDIN Plus were searched for studies from October 29, 2021 to December 1, 2022. A separate search for the use of

Lianhua as treatment for COVID-19 in pediatric patients was done using the same databases and registries. Only randomized controlled trials were included. There is no language restriction in the included studies. The reference list of systematic reviews, meta-analyses, and clinical practice guidelines were reviewed for possible additional studies. Review articles and other study designs were excluded. The methodological quality of included studies were assessed using the Cochrane Risk of Bias tool and Newcastle-Ottawa Quality Assessment Scale. RevMan 5.3 software was used to conduct meta-analyses for selected outcomes. Quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

## RESULTS

### Characteristics of included studies

Seven (7) RCTs were included in this review [6,10-13,24,31]. All RCTs were conducted in China. One RCT [6] was identified in the CNKI database, but only the abstract can be retrieved despite maximal efforts. Data from this study was obtained from three systematic reviews [7-9], with 2 reviews appraised to be of high certainty and one to be of moderate certainty using the AMSTAR 2 tool.

The 7 studies included a total of 1,160 adult patients without severe COVID-19. Only one study investigated asymptomatic patients [31]. The standard of care used in these studies was based on the recommendations on the “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)”, which included antivirals, oxygen therapy, and/or symptomatic treatments. Five (5) studies used Lianhua Qingwen thrice daily: 3 as capsule and 2 as granules [6,10-12,31]. Two studies used Lianhua Qingke: one as granules twice daily and another as tablets, 4 pieces thrice daily [13,24]. Outcomes reported were clinical deterioration, day-14 symptom improvement (fever, cough, and fatigue), improvement in chest CT scan, and serious drug-related adverse events.

For children and adolescents, no RCTs were identified through the online search (Appendix 2b). However, one retrospective non-randomized controlled study with good methodological quality involving children aged 2 months to 13 years with suspected COVID-19 was retrieved (Appendix 11) [30]. The regimen used was dependent on the age but are all administered thrice daily: 2g for <3 years old, 3g for 3-6 years old, and 6g for 6-13 years old [30]. In this study, the treatment group consisted of 42 children receiving routine treatment combined with Lianhua Qingwen granules while the control group of 41 patients received routine treatment only. The clinical outcomes were recorded after 5 days of treatment. Outcomes included disappearance rates of fever, cough, shortness of breath, nasal obstruction, runny nose, and expectoration.

### Certainty of evidence

The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes. The very serious risk of bias was due to unclear treatment allocation in 5 studies, issues with performance and detection bias in all 7 studies (5 studies were open-label, 1 study did not report if it was blinded), and issues with incomplete outcome data in 1 study [6]. One study has an issue with selective reporting since some of the pre-specified outcomes (clinical deterioration, time to negative conversion) were not reported in the analysis [24]. One study also had some concerns for other bias due to lack of description on how the outcomes were measured [6]. The risk of bias summary is in Appendix 5. The GRADE evidence profile is in Appendix 6.

### Effectiveness Outcomes

**Mortality**
Only one study with very low certainty of evidence (n=295) reported on mortality [12]. Yu et al. reported two deaths in the comparator arm and one in the Lianhua arm yielding inconclusive results (RR 0.50, 95% CI 0.05-5.49).

**Clinical deterioration**
Data from 6 RCTs (n=934) showed significant benefit in preventing clinical deterioration or progression to more severe disease in favor of Lianhua (RR 0.54, 95% CI 0.40-0.72; $I^2$=0%) (Figure 1) [6,10-13,31].

One study (n=120) with moderate certainty of evidence reported on the clinical deterioration of previously asymptomatic patients [31]. Symptoms took longer to appear in previously asymptomatic patients treated with Lianhua compared to control (MD 4.00, 95% CI 2.05-5.95). Furthermore, fewer asymptomatic patients treated with Lianhua progressed to moderate COVID-19 (RR 0.49, 95% CI 0.31-0.77), though no significant difference was observed in the proportion of asymptomatic patients worsening to mild COVID-19 (RR 0.80, 95% CI 0.23-2.83). The incidence of fever (RR 0.22, 95% CI 0.08-0.62), fatigue (RR 0.33, 95% CI 0.11-0.98), cough (RR 0.50, 95% CI 0.29-0.85), and expectoration (RR 0.36, 95% CI 0.14-0.93) was lower in previously asymptomatic patients treated with Lianhua compared to placebo. However, the incidence of shortness of breath (RR 0.50, 95% CI 0.13-1.91), chest tightness (RR 0.45, 95% CI 0.17-1.23), headache (RR 0.67, 95% CI 0.12-3.85), and diarrhea (RR 3.00, 95% CI 0.12-72.20) did not differ between the two groups.

**Cure rate**

Only one study (n=284) with low certainty of evidence reported on cure rate [10]. In the study, cure rate is defined as having met all of the following criteria: recovery of body temperature for more than 3 days, symptom recovery, marked improvement in the chest CT images, and two consecutive negative SARS-CoV-2 RNA tests (at least one day apart). This study reported that Lianhua compared to standard care resulted in a slight increase in cure rate (RR 1.19, 95% CI 1.03-1.38).

**Symptom improvement**

There were 4 studies that reported symptom improvement using various outcomes. Only cough were similarly reported in 3 studies [11,13,24] while fatigue and fever improvement on day 14 were similarly reported in 2 studies [11,13]. The rest of the outcomes could not be pooled.

Pooled analysis from 3 studies with very low certainty of evidence on day-14 improvement of the cough showed no significant difference between Lianhua arm and the control arm (RR 1.10, 95% CI 0.87-1.41; $I^2$=77%), but with significant heterogeneity (Figure 2) [11,13,24]. Two studies reported no significant difference in the day-14 improvement of fatigue (RR 1.11, 95% CI 0.92-1.34; $I^2$=0%) and fever (RR 1.00, 95% CI 0.90-1.11; $I^2$=0%) [11,13], however, two studies also reported significant improvement of sputum expectoration at day 14 among those given Lianhua compared to control (RR 1.19, 95% CI 1.05-1.34) (Figures 3-5) [13,24].

One study reported improvement of other symptoms such as loss of appetite, nausea and vomiting, diarrhea, sore limbs, chest tightness, and shortness of breath at day 7 and day 14 [11]. At day 7, there was no significant benefit in loss of appetite (RR 0.86, 95% CI 0.64-1.16), nausea and vomiting (RR 0.80, 95% CI 0.62-1.03), diarrhea (RR 1.00, 95% CI 0.69-1.45), sore limbs (RR 1.26, 95% CI 0.88-1.81), and shortness of breath (RR 1.18, 95% CI 0.77-1.82), among those given Lianhua and control. Similarly, there was no significant benefit at day 14 in loss of appetite (RR 0.95, 95% CI 0.87-1.07), nausea and vomiting (RR 0.93, 95% CI 0.82-1.07), diarrhea (RR 1.00, 95% CI 1.00-1.00), sore limbs (RR 1.05, 95% CI 0.81-1.36), and chest tightness and shortness of breath (RR 0.97, 95% CI 0.73-1.29) [11]. Based on one study, there was no significant improvement in day 14 hoarseness (RR 1.31, 95% CI 0.62-2.80) and sore throat (RR 1.00, 95% CI 1.00-1.00) among those given Lianhua and control [13].

One study reported symptom improvement as a continuous variable (mean difference for symptom scores), with the symptom score ranging from 1 (no symptom) to 4 (severe symptoms). Results showed statistically significant improvement in symptom scores for fever (MD -0.48, 95% CI -0.61 to -0.35), fatigue (MD -0.28, 95% CI -0.39 to -0.17), cough (MD -1.10, 95% CI -1.26 to -0.94), sore throat (MD -1.40, 95% CI -1.54 to -1.26) and chest pain (MD -0.37, 95% CI -0.55 to -0.19) [12].

Three studies reported that the total symptom recovery was higher in the Lianhua arm (RR 1.17, 95% CI 1.09-1.25, $I^2$=3%) (Figure 6) [10,12,24] while one study reported that day-28 symptom resolution rate is slightly higher in the Lianhua arm (RR 1.22, 95% CI 1.01-1.48) [24].

Two studies [10,24] showed significant shorter median time to total symptom recovery (HR 0.54, 95% CI 0.44-0.67) (Figure 7) and time to recovery from cough (HR 0.54, 95% CI 0.44-0.66) (Figure 8) while one

study mentioned about shorter median time to recovery of fatigue[10] (HR 1.78, 95% CI 1.04-2.05) and sputum expectoration (HR 0.49, 95% CI 0.22-0.70) in the Lianhua arm [24]. There was no significant benefit in time to recovery for fever (HR 1.39, 95% CI 1.0-1.94) [10].

### Other outcomes

**Improvement in chest CT scan**

The pooled result from 4 studies [10,12,13,24] with low certainty of evidence showed significant improvement in chest CT scan in patients given Lianhua (RR 1.21, 95% CI 1.11-1.32; $I^2$=0%) (Figure 9). One [12] out of the 3 studies defined improvement as a minimum of 30% decrease in lesion size while the rest defined it as reduction of infiltration, lesion site, or density of ground glass opacities in chest CT scan [12,13,24].

**Viral clearance**

There was significantly higher negative conversion rate of SARS-CoV-2 viral assay (RR 1.33, 95% CI 0.78-2.27; $I^2$=78%) in the treatment arm (Figure 12) but no significant difference in the time to negative conversion (MD -1.46 days, 95% CI -3.89 to 0.97 day; $I^2$=61%] (Figure 10) [6,10,31]. Subgroup analysis was done due to high level of heterogeneity in both outcomes.

*Asymptomatic COVID-19*

Based on one study, there was a significantly higher negative conversion rate of SARS-CoV-2 viral assay (RR 1.81, 95% CI 1.11-2.97) and shorter time to negative conversion (MD -7 days, 95% CI -12.72 to -1.28 days] in asymptomatic patients treated with Lianhua [31].

*Mild to moderate COVID-19*

Based on one study, there was no significant difference in the negative conversion rate of SARS-CoV-2 viral assay (RR 1.08, 95% CI 0.94-1.24) [10]. There was also no significant difference in time to negative conversion (2 studies, n=341, MD -0.42 days, 95% CI -1.51 to 0.67; p=0.45) in patients with mild to moderate COVID-19 (Figure 11) [6,10].

### Safety Outcomes

Pooled estimate from five studies with very low certainty of evidence reported no significant difference in total adverse events (RR 0.84, 95% CI 0.67-1.05; $I^2$=0%) (Figure 13) [6,10,12,24,31]. Adverse events reported in both the Lianhua and control group included abnormal liver function, renal dysfunction, headache, nausea, vomiting, eye disease, and loss of appetite. Two studies with very low certainty of evidence reported zero serious adverse event in both experimental and control arms (RR 1.00, 95% CI 0.14-7.97) [10,12].

Expected adverse effects from ephedra such as hypertension and tachycardia were not mentioned as an outcome to be measured in the methodology, nor reported in the results in any of the studies, though a study mentioned that heart dysfunction is not observed in the treatment group [24].

## Lianhua for children

Based on one study (n=42), among children 2 months to 13 years old with suspected COVID-19, the disappearance rates of fever (RR=1.63, 95% CI 1.17-2.26), cough (RR=1.91, 95% CI 1.07-3.43), and expectoration (RR=3.33, 95% CI 1.32-8.42) are significantly higher in the treatment group (p<0.05) [30]. No significant difference in the disappearance rates of shortness of breath (RR=1.62, 95% CI 0.98-2.69), digestive tract symptoms (RR=3.06, 95% CI 0.92-0.17), nasal obstruction (RR=1.31, 95% CI 0.70-2.44), runny nose (RR=1.33, 95% CI 0.54-3.32) was observed [30].

## RECOMMENDATIONS FROM OTHER GROUPS

| Group or Agency | Recommendation |
|---|---|
| National Institutes of Health (accessed January 24, 2023) [14] | No recommendations on the use of Lianhua for the treatment of COVID-19. |
| World Health Organization (accessed January 24, 2023) [15] | |
| Infectious Diseases Society of America (accessed January 24, 2023) [16] | |
| Australian Clinical Evidence Taskforce (accessed January 24, 2023) [17] | |
| National Health Commission & State Administration of Traditional Chinese Medicine Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (accessed January 24, 2023) | Recommend Lianhua Qingwen capsules to be used during medical observation as treatment of fatigue and fever [18,20]. |
| Rapid Advice Guideline for the Diagnosis and Treatment of 2019-nCoV by the China International Exchange and Promotive Association for Medical and Healthcare (CPAM) (accessed January 24, 2023) | |
| Diagnosis and Treatment Protocol for COVID-19 Patients of the National Health Commission (Tentative 9th Version) (June 29, 2022 version; accessed January 24, 2023) | Recommend Lianhua Qingwen capsules to be used during:<br>1. medical observation which manifests as fatigue and gastrointestinal discomfort<br>2. mild confirmed cases<br>3. moderate cases (plague poison and dryness syndrome phase) [19] |
| CPAM & Chinese Research Hospital Association (CRHA) (accessed January 24, 2023) | Recommends the use of Lianhua to treat patients with mild or moderate COVID-19 with conventional therapy and suggested that Lianhua granules/capsules 6g/1.4g be taken orally, thrice daily for 14 days [21]. |
| Expert Consensus on Guidance and Prevention Strategies for Hospital Pharmacists and Pharmacy Workforce by the Chinese Pharmaceutical Association (CPA) (accessed January 24, 2023) | Recommends the use of Lianhua capsule, 4 capsules orally, thrice daily or Lianhua granules, 1 packet orally, thrice daily to detoxify and remove lung hotness [22].<br><br>CPA mentioned common adverse reactions such as gastrointestinal symptoms, rash, and pruritus and advised patients with hypertension and heart disease, patients with severe chronic diseases such as liver disease, diabetes, and kidney disease, patients with spleen deficiency and loose stools, children, pregnant women, lactating women, elderly to take Lianhua with caution and under physician guidance of physicians. Long term use is discouraged [22]. |
| International Trustworthy Traditional Chinese Medicine Recommendations (TCM Recs) Working Group (accessed January 24, 2023) | Suggests against the use of Lianhua Qingke granules in addition to western medicine for mild and moderate COVID-19 patients. However, the guideline only based its recommendation on one RCT [23]. |

### ONGOING STUDIES AND RESEARCH GAPS

There are 8 ongoing registered RCTs investigating the use of Lianhua as treatment for COVID-19 (ChiCTR2200058079 and ChiCTR2100042066 for asymptomatic cases, ChiCTR2100045647 and ChiCTR2100042069 for mild COVID-19, CHICTR2200058639 for asymptomatic and mild cases, ChiCTR2200064767 for mild to moderate cases, ChiCTR2100042068 for severe cases, and ChiCTR2200059739 for cases with nucleic acid that did not turn negative 8 days after initial treatment). Five are still ongoing recruitment and three are not recruiting or pending recruitment.

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST

Lianhua would cost ₱288.00/box with 24 capsules per box. Most recommended regimen (Lianhua Qingwen 4 cap TID for a maximum of 7 days, with warm water) will cost ₱1,008.00 (₱144/day) [32].

### PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

On August 7, 2020, the Food and Drug Administration (FDA) approved its use only for symptomatic relief but not for COVID-19 treatment; this was further emphasized on April 5, 2021 by the Department of Health (DOH) and FDA [33]. The Dangerous Drugs Board's Committee on Reclassification has removed Lianhua Qingwen capsules from the list of dangerous drugs last March 12, 2021. S2 prescription is therefore not needed for it to be purchased and is readily available in local drug stores [34]. On September 12, 2021, FDA has warned against the purchase and use of unregistered Lianhua products [35].

A meta-analysis of five studies about the use of Lianhua on selected non-COVID disease (common pneumonia, influenza, mycoplasma pneumonia, hand-foot-mouth disease) explored the cardiac effects of Lianhua. There was no statistically significant difference in the incidence of heart rate and arrhythmia between the Lianhua group and the conventional drug group (RR=0.67, 95% CI 0.23-1.93) [25-29].

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Appendix 1: Preliminary Evidence to Decision

**Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)**

| FACTORS | JUDGEMENT | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|---|---|---|
| **Problem** | No | Yes (7) | Varies (1) | | | | Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity. |
| **Benefits** | Large | Moderate (2) | Small (1) | Trivial (2) | Varies (3) | Uncertain | Lianhua had no significant effect in the mortality RR 0.50 (95% CI 0.05-5.49).<br><br>Evidence showed benefit on clinical deterioration RR 0.54 (95% CI 0.40 to 0.72) among patients with non-severe COVID-19. |
| **Harm** | Large | Moderate | Small (1) | Trivial (3) | Varies (3) | Uncertain (1) | No significant differences in terms of adverse events or serious adverse events RR 1.00 (95% CI 0.14-7.07) from the Lianhua group compared to standard of care. |
| **Certainty of Evidence** | High | Moderate | Low (1) | Very low (7) | | | The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes. |
| **Balance of effects** | Favors intervention | Probably favors intervention (2) | Does not favor intervention or no intervention (1) | Probably favors no intervention (1) | Favors no intervention (1) | Varies (3) | |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability (6) | Probably no important uncertainty or variability (2) | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost (1) | Moderate Cost | Negligible cost or savings (5) | Moderate savings (1) | Varies (1) | Lianhua would cost ₱288.00/box with 24 capsules per box. Most recommended regimen (Lianhua cap TID for 14 days) will cost ₱504.00 (₱36/day). |
| **Certainty of evidence of required resources** | No included studies (4) | Very low (1) | Low (2) | Moderate | High | | |
| **Cost effectiveness** | No included studies (4) | Favors using the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison (1) | Probably favors the invention | Varies (3) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Equity** | Uncertain | Varies (4) | Probably reduced (1) | Probably no impact (3) | Probably increased | Increased | |
| **Acceptability** | Uncertain | Varies (6) | No | Probably no | Probably yes (2) | Yes | |
| **Feasibility** | Uncertain | Varies (3) | No | Probably no (1) | Probably yes (4) | Yes | On August 7, 2020, the FDA approved its use only for symptomatic relief but not for COVID-19 treatment. |
| **Recommendation** | For (3) | Against (5) | | | | | |
| **Strength** | Weak (8) | Strong | | | | | |

**Additional considerations from the panelist:**

- What is the evidence for asymptomatic COVID-19?
- Use as previously indicated

Appendix 2a: Search Yield and Results

| DATABASE | SEARCH STRATEGY / SEARCH TERMS | DATE AND TIME OF SEARCH | RESULTS | |
|---|---|---|---|---|
| | | | Yield | Eligible |
| **MEDLINE** | ((“COVID-19”) OR (“severe acute respiratory syndrome coronavirus 2”) OR (“2019-nCoV”) OR (“SARS-CoV-2”) OR (“corona virus disease 2019”)) AND ((lianhua) OR (lianhua qingwen) OR (lianhua capsule) OR (lianhua qingwen capsule))<br><br>Filters applied: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review<br>Custom range: 2021/10/28 - 2022/11/2 | 12/01/22, 1:50 pm | 16 | 6 |
| **CENTRAL** | “COVID-19” and “lianhua”<br>Custom Range: 2021 - 2022 | 11/02/22, 1:56 pm | 13 | 5 |
| **Cochrane COVID-19 Study Register** | “lianhua” | 11/02/22, 2:00 pm | 33 | 10 |
| **COVID-NMA Initiative RCTs on Treatment** | Filter: “lianhua” | 11/02/22, 2:08 pm | 0 | 0 |
| **LitCOVID** | “lianhua” | 11/02/22, 2:10 pm | 82 | 4 |
| China National Knowledge Infrastructure | “COVID-19” and “lianhua”; “coronavirus” AND “lianhua” | 12/01/22, 4:35 pm | 36 | 4 |
| **HERDINPlus** | “COVID-19” and “lianhua” | 11/02/22, 1:56 pm | 0 | 0 |
| | | | | |
| **ClinicalTrials.gov** | Condition or disease: COVID-19<br>Other terms: Lianhua | 11/02/22, 3:50 pm | 2 | 0 |
| **Chinese Clinical Trial Registry** | Target disease: COVID-19<br>Intervention: lianhua | 11/02/22, 4:15 pm | 11 | 6 |
| **EU Clinical Trials Register** | “COVID-19” and “lianhua” | 11/02/22, 3:11 pm | 0 | 0 |
| **Republic of Korea – Clinical Research Information Service** | “COVID-19” and “lianhua” | 11/02/22, 3:15 pm | 0 | 0 |
| **Japan Primary Registries Network/ NIPH Clinical Trials Search** | Name of the target (disease): “COVID-19”<br>Intervention: “lianhua” | 11/02/22, 3:20 pm | 0 | 0 |
| **CenterWatch** | Filter: COVID-19<br>I am looking for: lianhua | 11/02/22, 3:25 pm | 1 | 0 |
| **WHO International Clinical Trials Registry Platform (ICTRP)** | Lianhua, marked option labelled “restrict to COVID-19” | 11/02/22, 3:30 pm | 9 | 3 |
| | | | | |
| **chinaxiv.org** | “COVID-19” and “lianhua” | 11/02/22, 3:00 pm | 0 | 0 |
| **Medrxiv.org** | “COVID-19” and “lianhua” | 11/02/22, 3:03 pm | 11 | 0 |
| **Biorxiv.org** | “COVID-19” and “lianhua” | 11/02/22, 3:09 pm | 9 | 0 |

Appendix 2b: Search Yield and Results (Lianhua for Children)

| DATABASE | SEARCH STRATEGY / SEARCH TERMS | DATE AND TIME OF SEARCH | RESULTS | |
|---|---|---|---|---|
| | | | Yield | Eligible |
| MEDLINE | ((“COVID-19”) OR (“severe acute respiratory syndrome coronavirus 2”) OR (“2019-nCoV”) OR (“SARS-CoV-2”) OR (“corona virus disease 2019”)) AND ((lianhua) OR (lianhua qingwen) OR (lianhua capsule) OR (lianhua qingwen capsule)) AND ((child) OR (pediatric) OR (infant) OR (newborn))<br><br>Filters applied: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review | 11/02/2022, 6:00 pm | 2 | 0 |
| CENTRAL | lianhua and ((child) or (pediatric) or (infant) or (newborn)) | 11/02/2022, 6:00 pm | 0 | 0 |
| Cochrane COVID-19 Study Register | lianhua and ((child) or (pediatric) or (infant) or (newborn)) | 11/02/2022, 6:00 pm | 1 | 1 |
| COVID-NMA Initiative RCTs on Treatment | Filter: “lianhua” | 11/02/2022, 6:00 pm | 0 | 0 |
| LitCOVID | lianhua AND (child OR pediatric OR newborn OR infant) | 11/02/2022, 6:00 pm | 0 | 0 |
| China National Knowledge Infrastructure | Lianhua AND children | 11/02/2022, 6:00 pm | 26 | 1 |
| HERDINPlus | lianhua AND (child OR pediatric OR newborn OR infant) | 11/02/2022, 6:00 pm | 0 | 0 |
| | | | | |
| ClinicalTrials.gov | Condition or disease: COVID-19<br>Other terms: Lianhua, children | 11/02/2022, 6:00 pm | 0 | 0 |
| Chinese Clinical Trial Registry | Target disease: COVID-19<br>Intervention: lianhua | 11/03/2022, 8:11 pm | 11 | 0 |
| EU Clinical Trials Register | “COVID-19” and “lianhua” | 11/02/2022, 6:00 pm | 0 | 0 |
| Republic of Korea – Clinical Research Information Service | “COVID-19” and “lianhua” | 11/02/2022, 6:00 pm | 0 | 0 |
| Japan Primary Registries Network/ NIPH Clinical Trials Search | Name of the target (disease): “COVID-19”<br>Intervention: “lianhua” | 11/02/2022, 6:00 pm | 0 | 0 |
| CenterWatch | Filter: COVID-19<br>I am looking for: lianhua<br>Advance Filter: Pediatric | 11/03/2022, 8:00 pm | 0 | 0 |
| WHO International Clinical Trials Registry Platform (ICTRP) | “COVID-19” and ‘lianhua”, marked option labelled “search for clinical trials in children” | 11/02/2022, 6:00 pm | 0 | 0 |
| | | | | |
| chinaxiv.org | “COVID-19” and “lianhua” | 11/02/2022, 6:00 pm | 0 | 0 |
| Medrxiv.org | COVID-19 AND lianhua AND child* | 11/02/2022, 6:00 pm | 3 | 0 |
| Biorxiv.org | “COVID-19” and “lianhua” | 06/29/22, 6:36 pm | 2 | 0 |

## Appendix 3: Characteristics of Included Studies

| Author | Study design | Population (n) | Inclusion criteria | Exclusion criteria | Intervention | Outcomes |
|---|---|---|---|---|---|---|
| Chen et al, 2021 [6] | Single site, randomized, controlled, two arms | Diagnosed cases of COVID-19<br><br>(n = 60) | Mild COVID-19 cases and ordinary cases of new COVID-19 pneumonia | Severe or critically ill patients | Control group: conventional treatment (symptomatic and supportive treatment plus interferon alfa, lopinavir or ritonavir)<br><br>Experimental: conventional treatment + Lianhua Qingwen capsule, 4 caps thrice a day for 10 days | Clinical deterioration rate, nucleic acid conversion time, adverse events |
| Hu K et al 2020 [10] | Multicenter, randomized controlled, open-label | Patients more than 18 years old. with COVID-19<br><br>(n = 284) | Laboratory-confirmed cases with COVID-19; being symptomatic (either having fever, coughing, or fatigue) plus radiologic abnormalities consistent with pneumonia; patients aged 18 years or greater of either sex. | Respiratory tract bacterial infections due to primary or secondary immunodeficiency, congenital respiratory malformation, congenital heart disease, gastroesophageal reflux, and lung malformation; asthma or other chronic airway diseases needing maintenance therapy, acute respiratory tract bacterial infection (i.e., bronchiectasis, tonsillitis, bronchitis, rhinosinusitis, otitis media), severe pulmonary interstitial diseases; severe pneumonia needing mechanical ventilation; severe systemic diseases (i.e., malignancy, autoimmune diseases, liver or renal diseases) or surgeries (splenectomy, organ transplantation) that in the judgement of the investigators could affect the assessment of efficacy; women during pregnancy or lactation; participation in clinical trials within 3 months; known allergies to the investigational medications; other conditions judged by the investigators. | Routine treatment; Lianhua (4 capsules, thrice daily) plus routine treatment (oxygen therapy, antiviral medications, symptomatic therapies) | Primary endpoint: rate of symptom recovery<br><br>Secondary endpoint: time to symptom recovery, rate of and time to recovery of individual symptoms, proportion of patients with improvement on chest CT, proportion of patients with clinical cure, timing and rate of conversion of SARS-CoV-2 RNA assay, adverse events |

| | | | | | | |
|---|---|---|---|---|---|---|
| Xiao et al, 2020 [11] | Single site, randomized, controlled, non-blinded, three arms | Diagnosed cases of COVID-19<br><br>(n = 182) | Diagnosed cases of COVID-19 meeting the diagnostic criteria; 18–85 years old, regardless of sex; provided informed consent. | Clear evidence of bacterial infection; severe primary diseases, such as heart, kidney, lung, endocrine, blood, metabolism, or gastrointestinal tract diseases, which may affect the patient's participation in the trial or affect the outcome of the study; family history of mental illness or previous mental illness; allergies or multiple drug allergies; pregnant or lactating women | 6g of Lianhua Qingwen granules thrice a day + Western medicine; one bag of Huoxiang Zhengqi dropping pills twice a day + one bag of Lianhua Qingwen granules thrice a day + Western medicine; Western medicine | Main outcome measure: clinical symptom improvement and disappearance rates after 14 days of treatment<br><br>secondary outcome: proportion of patients who progressed to severe status |
| Yu et al, 2020 [12] | Single site randomized, controlled | Diagnosed COVID-19 adult inpatients from February 17 to March 6, 2020<br><br>(n = 295) | 1) All meet the diagnostic criteria of COVID-19 in the "Diagnosis and Treatment Plan for Pneumonia of Novel Coronavirus Infection (Sixth Edition)", and are either mild (with mild symptoms and no pneumonia on imaging) or common (with Symptoms such as fever and respiratory tract, and imaging shows the presence of pneumonia);<br>2) 18 to 75 years old;<br>3) voluntarily signed the informed consent form | Severe or critically ill patients; Severe heart, liver and kidney dysfunction; Severe diseases that may affect the outcome of the patient; Pregnant or breastfeeding women; HIV infection | Control group: arbidol + moxifloxacin + ambroxol<br><br>Experimental group: Lianhua Qingwen Granules (6 g, thrice daily, for 7 days) + arbidol + moxifloxacin + ambroxol | Aggravation rate, mortality rate, improvement of chest CT, adverse events |
| Sun et al 2020 [13] | Randomized, controlled two arms | COVID-19 patients over 18 years of age | Patients over 18 years of age diagnosed with new coronavirus pneumonia with cough symptoms | | Lianhua Qingke granules (twice daily) + conventional vs. conventional (lopinavir or ritona, interferon alfa plus symptomatic and supportive treatment | Aggravation rate, mortality rate, improvement of chest CT, adverse events |
| Zhang et al (2022) [24] | Multicenter, randomized controlled, open-label | COVID-19 patients over 18 years of age | confirmed COVID-19 by virus testing; ≥18 years of age; fever, cough, expectoration, chest tightness, polypnea, and/or dyspnea at enrollment; and informed consent provided. | bacterial respiratory infection resulting from common pathologies (immunodeficiency diseases, congenital respiratory and heart disease, GERD); asthma treated daily, chronic airway disease, acute tracheobronchitis, sinusitis, otitis media; chest CT confirmed pulmonary diseases; ventilator-requiring pneumonia; pregnant or lactating; clinical study patient(past 3 | Lianhua Qingke tablets (4 pcs thrice daily) + conventional vs. conventional (oxygen therapy, antivirals, and symptomatic therapies) | Primary outcomes: total symptom recovery rate within 14 days, time to symptom recovery<br><br>Secondary outcomes: single symptom disappearance rate, time to major symptom disappearance, changes in color, sputum quality and amount (cases w/ expectoration), changes in oxygenation index (OI), aggravation rate, CT improvement rate, disease |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | months); allergy to ≥2 drugs/foods or allergy to the drug's constituents | | recovery rate, time to and rate of negative conversion, adverse events |
| Zhang et al (Nov 2022) [31] | Multicenter, randomized controlled | COVID-19 patients over 18 years of age | patients asymptomatically infected COVID-19 discovered through pathogenic testing; ≥18 years of age; informed consent provided | patients with new coronavirus pneumonia confirmed by pathogenic testing; patients with serious diseases such as malignant disease, autoimmune disease, liver and kidney disease, blood disease, neurological disease, and endocrine disease; pregnant or lactating women; patients who participated in other clinical trials within the last 3 months; allergy to ≥2 drugs/foods or allergy to the drug's constituents | Lianhua Qingwen capsules (4 pcs thrice daily for 14 days) + conventional vs. conventional (isolation) | Primary outcomes: time and rate of nucleic acid turning negative during the isolation<br><br>Secondary outcomes: clinical symptoms and severity, clinical symptoms appearance time and proportion, proportion of mild and common cases of novel coronavirus pneumonia diagnosed during the isolation, routine blood test, and biochemical indicators; adverse events |

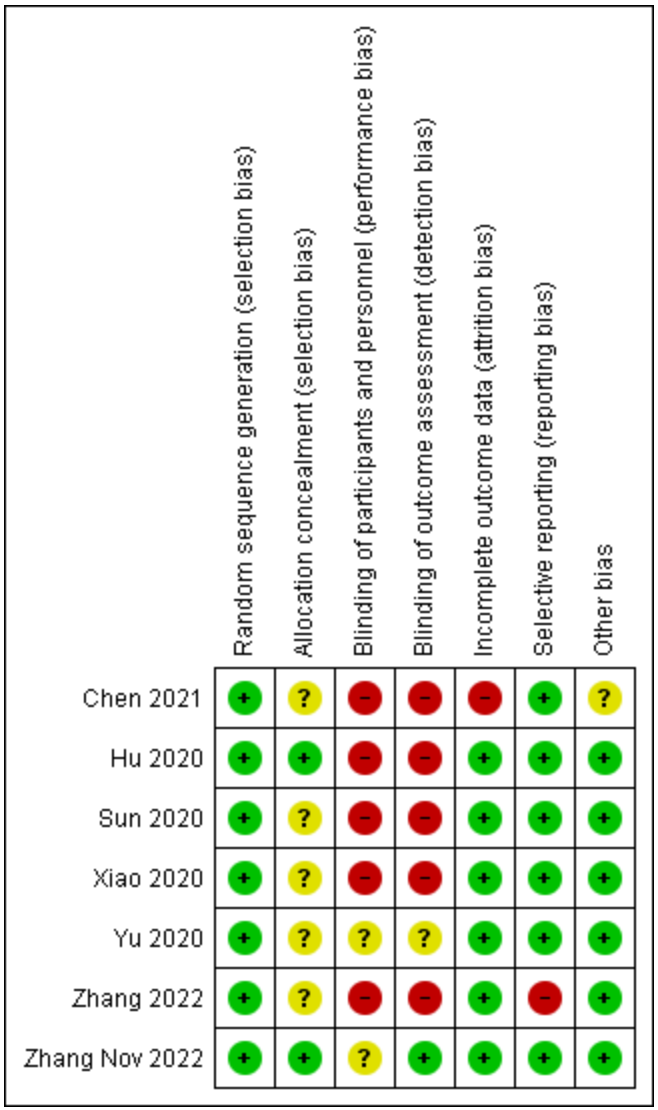
Appendix 4: Summary of Evidence

| Outcomes | Basis | Relative Effect (95% CI) | Difference (95% CI) | Interpretation | Overall Certainty of Evidence |
|---|---|---|---|---|---|
| **CRITICAL OUTCOMES** | | | | | |
| Mortality | 1 RCT (n = 295) | RR 0.50 (0.05-5.49) | **7 fewer per 1,000** (from 13 fewer to 61 more) | Inconclusive | Very Low[1] |
| Clinical Deterioration | 6 RCT (n = 937) | **RR 0.54** (0.40 to 0.72) | **95 fewer per 1,000** (from 123 fewer to 58 fewer) | Benefit | Low |
| Clinical cure | 1 RCT (n = 284) | RR 1.19 (1.03 – 1.38) | **126 more per 1,000** (from 20 more to 252 more) | Tendency towards benefit | Low |
| Time to symptom recovery | 2 RCT (n = 428) | HR 0.54 (0.44-0.67) | -- | Benefit | Low |
| Time to cough recovery | 2 RCT (n = 428) | HR 0.54 (0.44-0.66) | -- | Benefit | Low |
| Time to recovery from sputum expectoration | 1 RCT (n = 144) | HR 0.49 (0.22-0.70) | -- | Benefit | Low |
| Total symptom recovery, Day 14 | 3 RCT (n = 723) | RR 1.17 (1.09-1.25) | **129 more per 1,000** (from 68 more to 189 more) | Tendency towards benefit | Very Low[1] |
| Fever Improvement, Day 14 | 2 RCT (n = 51) | RR 1.00 (0.90-1.11) | **0 fewer per 1,000** (from 100 fewer to 110 more) | No difference | Very Low[1] |
| Cough Improvement, Day 14 | 3 RCT (n = 267) | RR 1.10 (0.87-1.41) | **82 more per 1,000** (from 107 fewer to 338 more) | Inconclusive | Very Low[1] |
| Sputum expectoration improvement. Day 14 | 2 RCT (n = 201) | RR 1.19 (1.05-1.34) | **143 more per 1,000** (from 38 more to 256 more) | Tendency towards benefit | Very Low[1] |
| Fatigue Improvement, Day 14 | 2 RCT (n = 86) | RR 1.11 (0.92-1.34) | **88 more per 1,000** (from 280 fewer to 648 more) | Inconclusive | Very Low[1] |
| Serious adverse events | 2 RCT (n = 579) | RR 1.00 (0.14-7.07) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | Inconclusive | Very Low[2] |
| **OTHER NON-CRITICAL OUTCOMES** | | | | | |
| Chest CT scan improvement | 4 RCT (n = 780) | RR 1.21 (1.11-1.32) | **138 more per 1,000** (from 72 more to 210 more) | Benefit | Low |
| Negative conversion time, overall | 3 RCT (n = 461) | RR -1.46 (-3.89 – 0.97) | MD 1.47 days lower (from 3.89 lower to 0.97 day higher) | Inconclusive | Low |
| Conversion rate of SARS-CoV 2 viral assay, overall | 2 RCT (n = 404) | RR 1.18 (1.02 to 1.36) | 91 more per 1,000 (from 10 more to 183 more) | Tendency towards benefit | Low |
| Negative conversion time, | 2 RCT (n= 341) | - | **0.42 day lower** | Inconclusive | Low |

| | | | | | |
|---|---|---|---|---|---|
| mild to moderate COVID-19 | | | (1.51 lower to 0.67 higher) | | |
| Conversion rate of SARS-CoV 2 viral assay, mild to moderate COVID-19 | 1 RCT (n= 284) | RR 1.08 (0.94-1.24) | **57 more per 1,000** (from 43 fewer to 171 more) | No difference | Very Low[1] |
| Negative conversion time, asymptomatic COVID-19 | 1 RCT (n = 120) | - | MD **7 days lower** (12.72 lower to 1.28 lower) | Benefit | Moderate |
| Conversion rate of SARS-CoV 2 viral assay, asymptomatic COVID-19 | 1 RCT (n = 120) | **RR 1.81** (1.11 to 2.97) | **216 more per 1,000** (from 29 more to 525 more) | Benefit | Moderate |
| Adverse events | 5 RCT (n = 900) | **RR 0.84** (0.67 to 1.05) | **35 fewer per 1,000** (from 72 fewer to 11 more) | No difference | Very Low[1] |

[1]very serious risk of bias, serious imprecision
[2]very serious risk of bias, very serious imprecision

Appendix 5: Methodological Assessment of Included Studies



## Appendix 6: GRADE Evidence Profile

**Author(s):** Timothy Hudson David Culasino Carandang, Joey Tabula
**Question:** Lianhua plus SOC compared to SOC for COVID-19

**Bibliography:** 1. P. Yu, Y.Z. Li,S.B. Wan,et al.. Effects of Lianhua Qingwen granules (连花清瘟颗粒) plus arbidol on treatment of mild corona virus disease-19. Chin Pharm J; 2020.

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| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Lianhua plus SOC | SOC | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 1 [1] | randomised trials | very serious [a,b] | not serious | not serious | serious [c] | none | 1/147 (0.7%) | 2/148 (1.4%) | **RR 0.50** (0.05 to 5.49) | **7 fewer per 1,000** (from 13 fewer to 61 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Clinical deterioration** | | | | | | | | | | | | |
| 6 [1,2,3,4,5,7] | randomised trials | very serious [a,b] | not serious | not serious | not serious | none | 51/467 (10.9%) | 96/467 (20.6%) | **RR 0.54** (0.40 to 0.72) | **95 fewer per 1,000** (from 123 fewer to 58 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **Clinical cure** | | | | | | | | | | | | |
| 1 [4] | randomised trials | very serious [b] | not serious | not serious | not serious | none | 112/142 (78.9%) | 94/142 (66.2%) | **RR 1.19** (1.03 to 1.38) | **126 more per 1,000** (from 20 more to 252 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Time to symptom recovery** | | | | | | | | | | | | |
| 2 [4,6] | randomised trials | very serious [b] | not serious | not serious | not serious | none | HR 0.54 (0.44 to 0.67) | | | | ⊕⊕◯◯ LOW | CRITICAL |
| **Total symptom recovery, Day 14** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 [1,4,6] | randomised trials | very serious [b] | not serious | not serious | serious [d] | none | 320/361 (88.6%) | 274/362 (75.7%) | **RR 1.17** (1.09 to 1.25) | **129 more per 1,000** (from 68 more to 189 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Fever improvement, Day 14** | | | | | | | | | | | | |
| 2 [1,3] | randomised trials | very serious [a,b] | not serious | not serious | serious [c] | none | 28/28 (100%) | 23/23 (100%) | **RR 1.00** (0.90 to 1.11) | **0 fewer per 1,000** (from 100 fewer to 110 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Cough improvement, Day 14** | | | | | | | | | | | | |
| 3 [2,3,6] | randomised trials | very serious [a,b] | Very serious [e,f] | not serious | serious [c] | none | 125/136 (91.9%) | 108/131 (82.4%) | **RR 1.10** (0.87 to 1.41) | **82 more per 1,000** (from 107 fewer to 338 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Sputum expectoration improvement, Day 14** | | | | | | | | | | | | |
| 2 [3,6] | randomised trials | very serious [b] | not serious | not serious | not serious | none | 91/104 (87.5%) | 73/97 (75.3%) | **RR 1.19** (1.05 to 1.34) | **143 more per 1,000** (from 38 more to 256 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Fatigue improvement, Day 14** | | | | | | | | | | | | |
| 2 [1,3] | randomised trials | very serious [a,b] | Not serious | not serious | serious [c] | none | 41/46 (89.1%) | 32/40 (80.0%) | **RR 1.11** (0.92 to 1.34) | **88 more per 1,000** | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Adverse effects** | | | | | | | | | | | | |
| 5 [1,4,5,6,7] | randomised trials | very serious [a,b] | not serious | not serious | serious [c] | none | 82/449 (18.3%) | 98/451 (21.7%) | **RR 0.84** (0.67 to 1.05) | **35 fewer per 1,000** (from 72 fewer to 11 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |
| **Serious adverse effects** | | | | | | | | | | | | |
| 2 [1,4] | randomised trials | very serious [a,b] | not serious | not serious | very serious [c,g] | none | 0/289 (0.0%) | 0/290 (0.0%) | **RR 1.00** (0.14 to 7.07)[h] | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

***Explanations***

a. Unclear allocation concealment
b. Lack of blinding
c. CI is not on the same side
d. Lower or upper limit of CI very close to 1
e. Minimal or no overlap of confidence intervals
f. Substantial heterogeneity
g. No event rate
h. Computed via imputing values

Appendix 7: Forest Plots

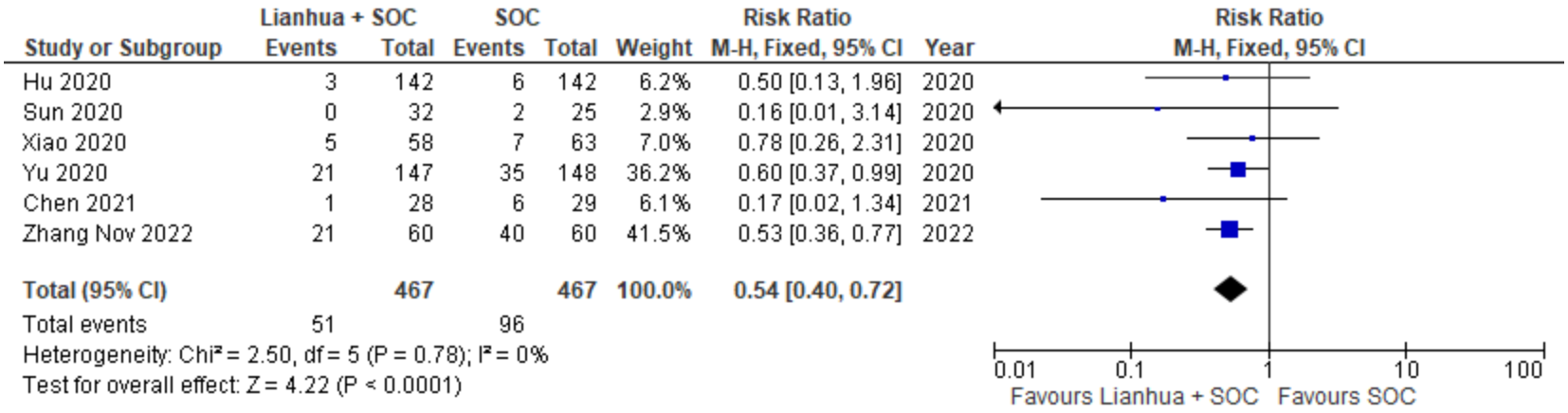


**Figure 1.** Clinical Deterioration

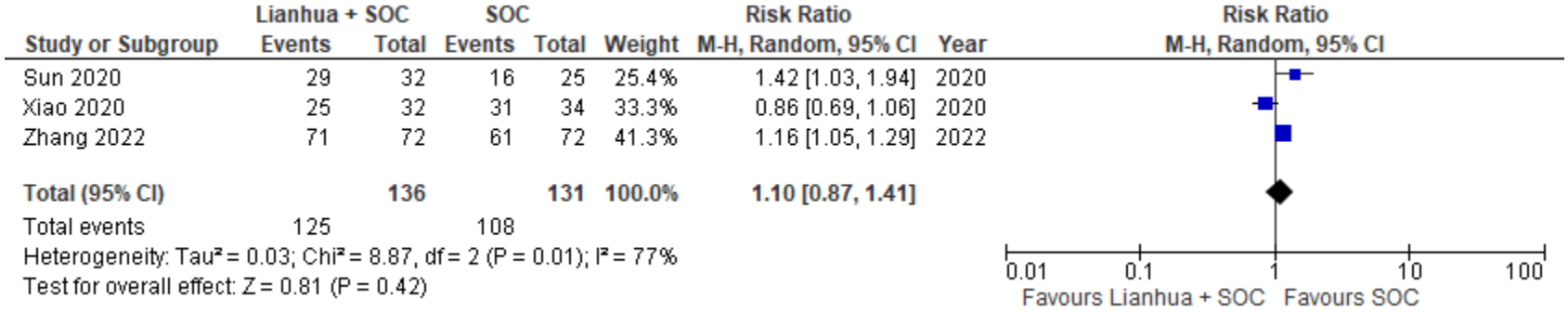


**Figure 2**. Day-14 cough improvement

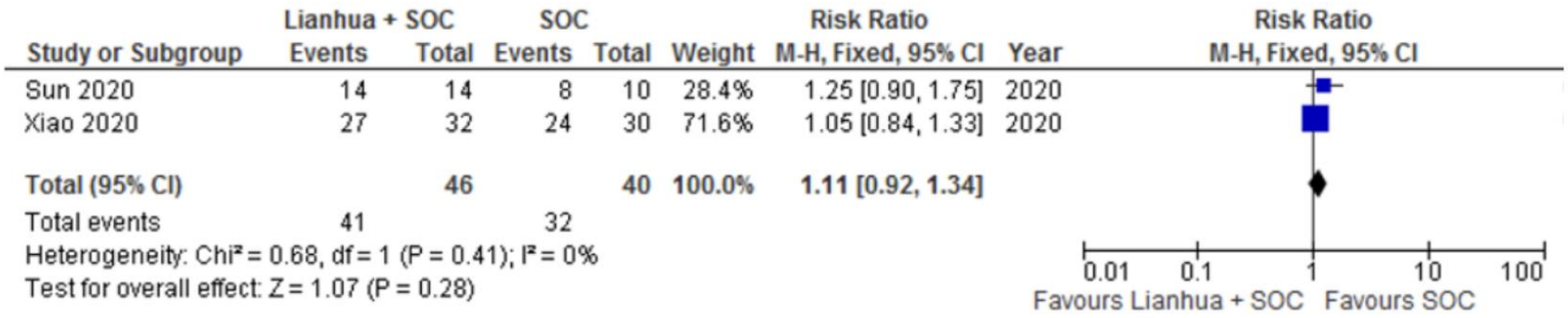


**Figure 3.** Day-14 fatigue improvement

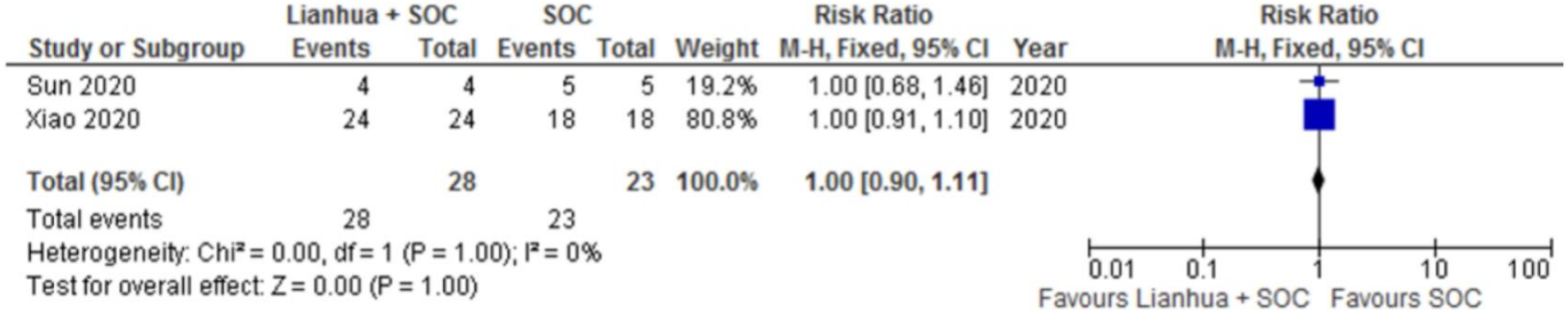


**Figure 4.** Day-14 fever improvement

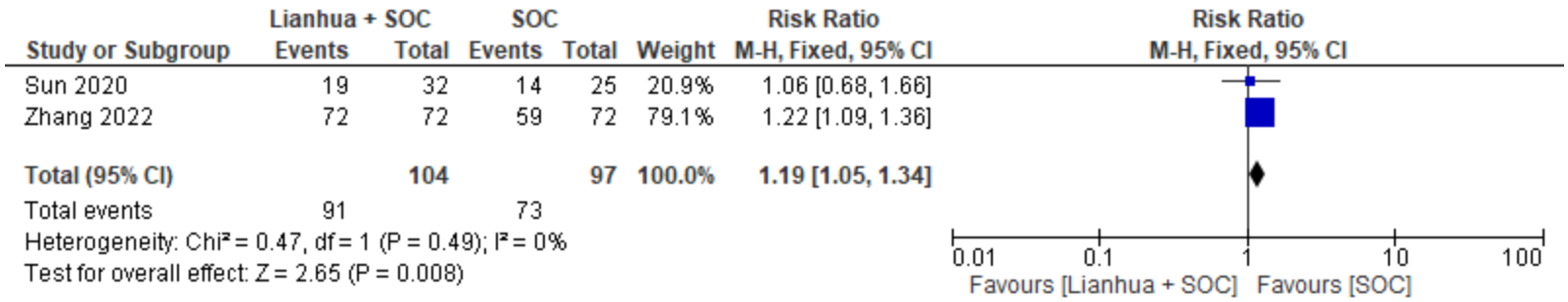


**Figure 5.** Day-14 sputum expectoration recovery rate

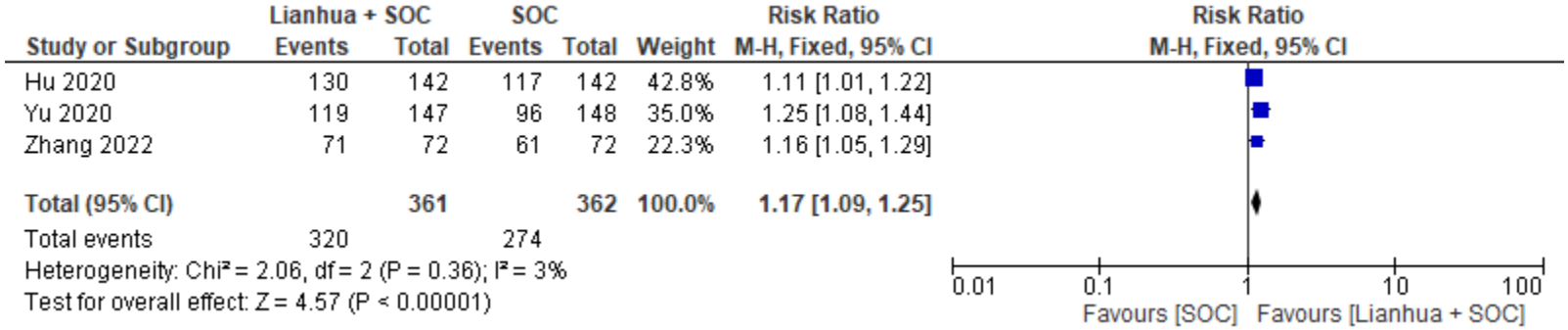


**Figure 6.** Total symptom recovery rate

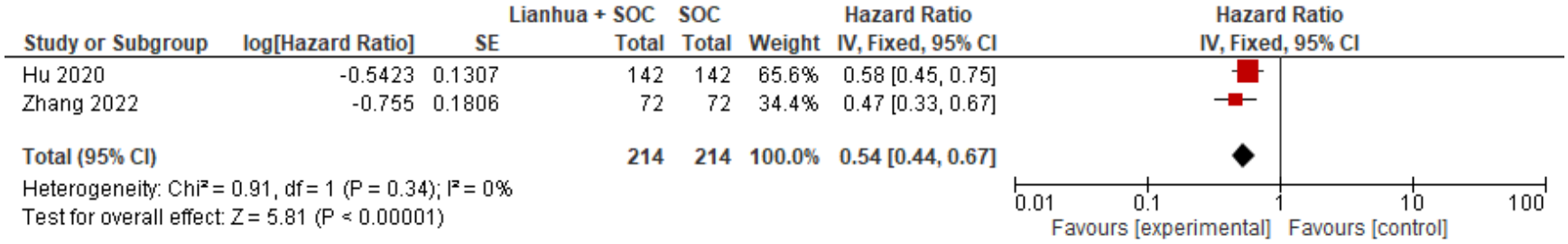


**Figure 7.** Time to total symptom recovery

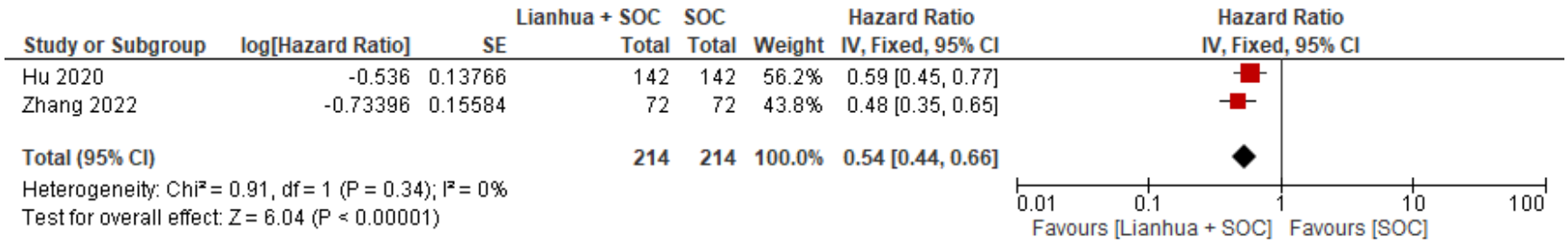


**Figure 8.** Time to Recovery from Cough

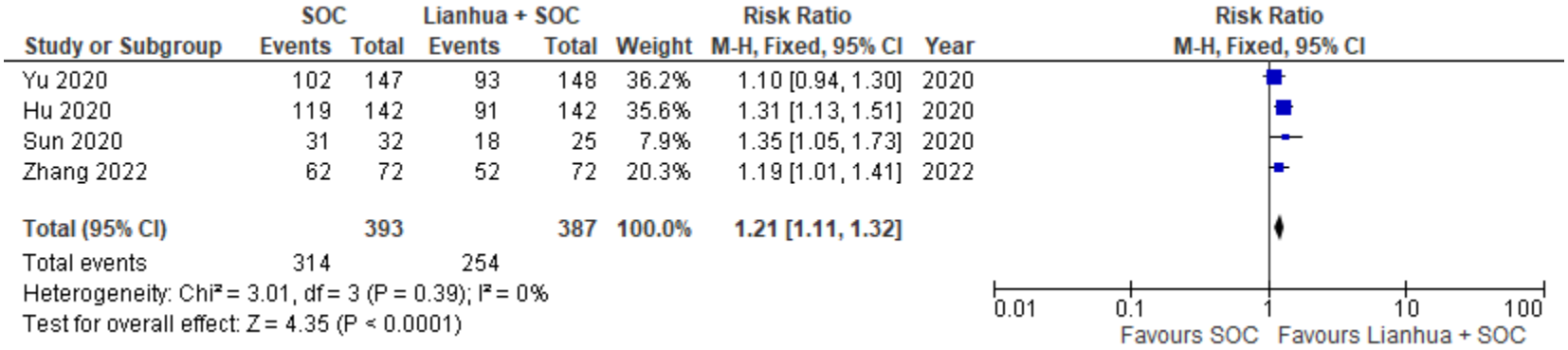


**Figure 9.** Chest CT improvement

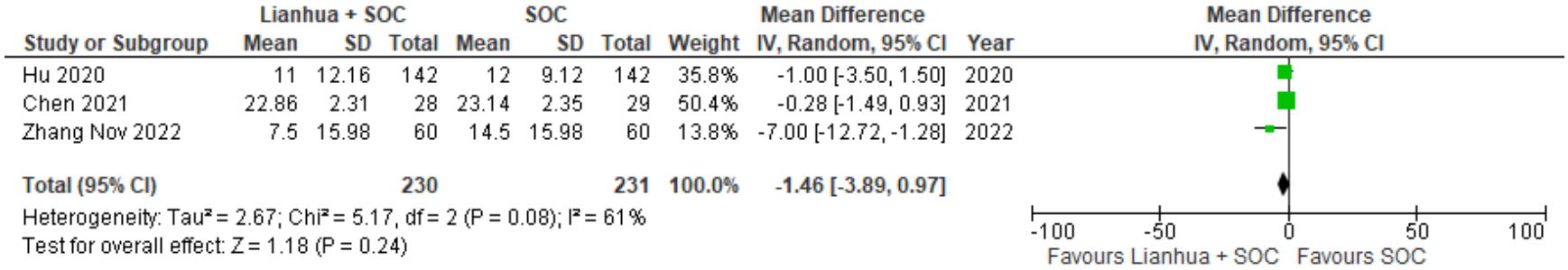


**Figure 10.** Negative Conversion Time, overall

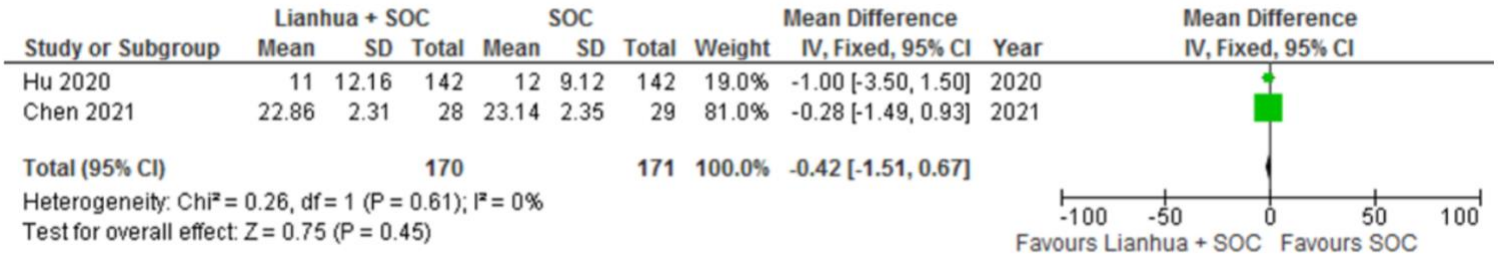


**Figure 11.** Negative Conversion Time, mild to moderate COVID-19

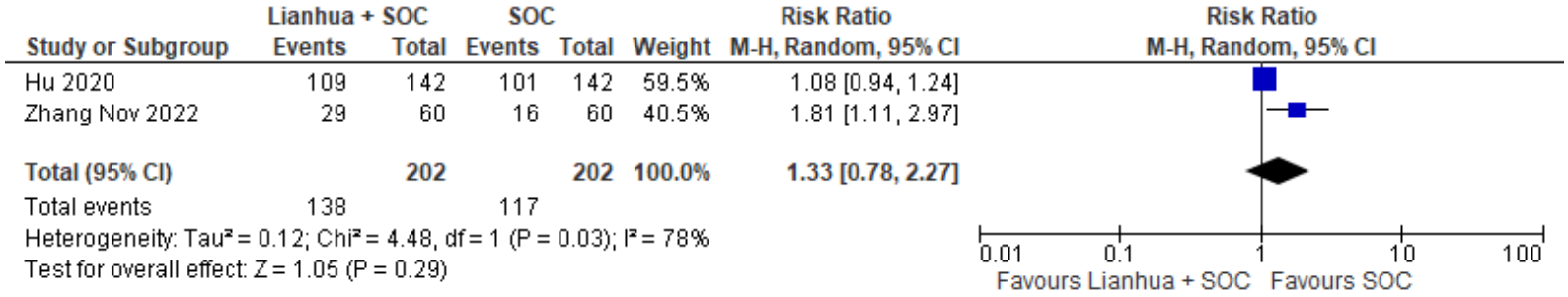


**Figure 12.** Negative Conversion Rate, overall

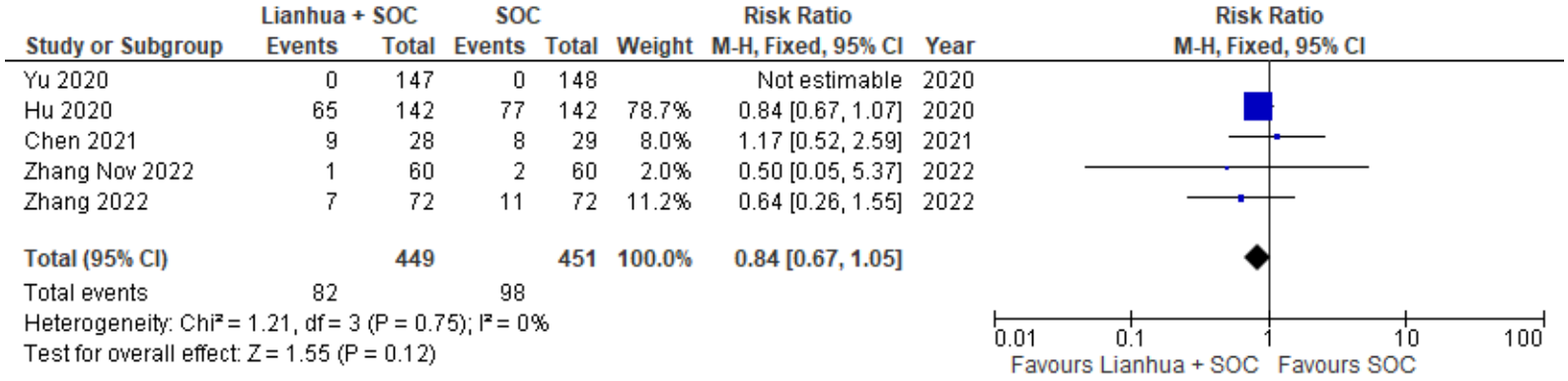


**Figure 13.** Total Adverse Events

## Appendix 8: Characteristics and Current Status (as of November 2, 2022) of Ongoing Studies

| Title | Population | Interventions | Characteristics | Outcome Measures |
|---|---|---|---|---|
| ChiCTR2100042066<br>A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Wen Capsule/Granule in the treatment of asymptomatic patients with novel coronavirus pneumonia<br>Status: Recruiting | Asymptomatically infected patients discovered through pathogenic testing ≥ 18 years old | Lian-Hua Qing-Wen Capsule/Granule | N = 120<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: none | Primary: Time and rate of nucleic acid turning negative<br>Secondary: clinical symptom and severity<br>Clinical symptoms appearance time and proportion<br>Proportion of mild and common cases diagnosed during isolation/observation period |
| ChiCTR2100042069<br>A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Ke Tablets in the treatment of COVID-19 patients with mild and common-type<br>Status: Recruiting | Symptomatic (any of the ff: fever, cough, fatigue) patients ≥ 18 years old with confirmed COVID-19 by pathogenic testing | Routine treatment + Lian-Hua Qing-Ke tablets | N = 120<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: none | Primary: clinical symptoms recovery rate and recovery time<br>Secondary: single symptom disappearance rate and main symptom disappearance time, changes in color, quality, and quantity of sputum in patients with expectoration, proportion of aggravation during treatment, rate of CT improvement, disease recovery rate, time and rate of coronavirus becoming negative |
| ChiCTR2100042068<br>A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Ke Tablets in the treatment of severe novel coronavirus pneumonia<br>Status: Recruiting | Patients ≥18 years old with confirmed COVID-19 by pathogenic testing and severe COVID-19 pneumonia | Routine treatment + Lian-Hua Qing-Ke tablets | N = 20<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: none | Primary: time to clinical improvement (censored at Day 28)<br>Secondary: improvement time of clinical symptoms, changes of oxygenation index in blood gas analysis, duration of mechanical ventilation, duration of supplemental oxygen, time to RT-PCR negativity, all-cause mortality |
| ChiCTR2200058639<br>Effective cluster randomized controlled study of Lianhua Qingwen in the treatment of asymptomatic infections and mild confirmed cases of novel coronavirus<br>Status: Pending recruitment | Patients ≥18 years old with asymptomatic infections and mild confirmed cases | Lianhua Qingwen 4 capsules/time or Lianhua Qingwen Granules 1 bag/time, TID | N = 20, 000 (Lianhua); 15,000 (negative control)<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: not stated | Primary: total negative rate of nucleic acid test within 7 days |
| ChiCTR2200059739<br>A single center, prospective, randomized controlled study of paxlovid compared to Lianhua Qingwen in shortening the negative time of novel coronavirus positive patients<br>Status: Not yet recruiting | Patients 18-90 years with RTPCR confirmed COVID-19 and 1.) nucleic acid did not turn negative 8 days after initial treatment; 2)ECoG activity status score was 0 or 1. 3) sufficient baseline organ function and hematological function | Lianhua Qingwen granule 6G / bag, 1 bag TID; Lianhua Qingwen capsule 4 caps TID | N = 220<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: not stated | Primary: Nucleic acid negative conversion time and negative conversion rate |
| ChiCTR2200058079<br>A randomized, double-blind, placebo-controlled clinical study of Lianhua Qingwen capsule in the treatment of asymptomatic patients with novel coronavirus pneumonia<br>Status: Recruiting | Patients ≥18 years old with asymptomatic infection | Lianhua Qingwen Capsule (dosage not stated) | N = 1600<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: double-blind | Primary: Nucleic acid negative conversion time and negative conversion rate during the isolation observation period |
| ChiCTR2100045647<br>To evaluate the clinical mechanism of Lianhua Qingwen Capsule on the systemic immune regulation of patients with new coronavirus pneumonia<br>Status: Recruiting | Patient 18 to 59 years; with confirmed mild COVID-19 infection; subjects must be >=50 kg, and female >=45kg; BMI: 19 - 26 | Lianhua Qingwen 4 capsules/time TID | N = 20<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: none | Primary: inflammatory factors; immune cell genus |

| | | | | |
|---|---|---|---|---|
| ChiCTR2200064767<br>To evaluate the clinical mechanism of Lianhua Qingke tablets in alleviating symptoms, reducing the incidence of common and severe types, and nucleic acid negative rate in COVID-19 positive patients admitted to the shelter hospital<br>Status: Not yet recruiting | Patients > 18 years old with COVID-19 diagnosed by etiology test, presenting with fever, cough, expectoration, sore throat, dry throat at the time of admission | Lianhua Qingke tablets, 4 tablets/time TID | N = 600<br>Equally divided to both arms<br>Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: not stated | Primary: disappearance rate and median time of clinical symptoms<br>Secondary: Single symptom disappearance rate and main symptom disappearance time, proportion of converting to ordinary type, proportion of aggravation during treatment, nucleic acid negative conversion time and negative conversion rate |

Appendix 9: Characteristics of the Systematic Reviews retrieved through Citation Search

| Study and Impact Factor | Country of authors | Cochrane review or not? | Is funding present? | Is there prospective registration or protocol publication? | Number of included studies in the review | Total sample size (number of participants included) | Are meta-analyses done? | Intervention | Comparison | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al., 2021<br><br>IF: 4.4 | China | No | No | Yes | 25 RCTs | 2,222 | Yes | Chinese medicine interventions alone or combined with other treatments | Placebo, standard medication treatment, and usual care | Primary:<br>improved clinical cure and the negativity of the SARS-CoV-2 nucleic acid test<br><br>Secondary:<br>1) clinical deterioration, 2) incidence of unfavorable clinical events of acute respiratory distress syndrome (ARDS), mechanical ventilation, and intensive care unit (ICU) admission, 3) death<br>4) time to fever clearance,<br>5) duration of hospital stay, and<br>6) chest imaging improvement |
| Shi et al., 2021<br><br>IF: 3.885 | China | No | Yes | Yes | 19 RCTs<br>29 observational with control arm | 2,696 – CHM<br>2,008 - SOC | Yes | CHM + standard pharmacotherapy. | standard pharmacotherapy alone or standard pharmaco-therapy plus placebo | Primary:<br>GI symptom improvement and liver function<br><br>Secondary:<br>Aggravation of COVID-19, time to viral assay conversion |
| He et al., 2021<br><br>IF: N/A; preprint | China | No | No | Yes | 6 RCTs<br>3 case control | 1,163 | Yes | Lianhua Qingwen + western medicine | Western medicine alone | Clinical effective rate, chest CT disappearance rate of fever, cough, and fatigue, duration of fever; progress into severe clinical disease; adverse events. |

*CHM – Chinese herbal medicine

*Chinese medicine interventions include Chinese medicine formulas (e.g., Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu formula), Chinese patented medicine (e.g., Jinhua Qinggan granule and Lianhua Qingwen capsule), and Chinese medicine injections (e.g., Xuebijing and Xiyanping injections)

* Frontiers in Pharmacology

* International Union of Biochemistry and Molecular Biology (IUBMB) Life

Appendix 10: Evaluation of the systematic reviews retrieved using AMSTAR-2 tool

| AMSTAR 2 Questions | Wang et al., 2021 | Shi et al., 2021 | He et al., 2021 |
|---|---|---|---|
| *1. Did the research questions and inclusion criteria for the review include the components of PICO?* | Y | Y | Y |
| ***2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*** | Y | Y | Y |
| *3. Did the review authors explain their selection of the study designs for inclusion in the review?* | Y | Y | N |
| ***4. Did the review authors use a comprehensive literature search strategy?*** | Y | Y | PY |
| *5. Did the review authors perform study selection in duplicate?* | Y | Y | Y |
| *6. Did the review authors perform data extraction in duplicate?* | Y | Y | Y |
| ***7. Did the review authors provide a list of excluded studies and justify the exclusions?*** | PY | PY | PY |
| *8. Did the review authors describe the included studies in adequate detail?* | Y | Y | Y |
| ***9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*** | Y | PY | Y |
| *10. Did the review authors report on the sources of funding for the studies included in the review?* | N | N | N |
| ***11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?*** | Y | Y | Y |
| *12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?* | Y | Y | N |
| ***13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?*** | Y | Y | Y |
| *14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?* | Y | Y | Y |
| ***15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*** | Y | Y | Y |
| *16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?* | Y | Y | Y |
| ***Rate of overall confidence*** | High | High | Moderate |

## Appendix 11: Evaluation of the retrospective cohort study using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies

**Research Title: Fang, F., Yang, L., Qin, S. C., Jiao, R. (2020). Clinical efficacy of traditional Chinese medicine Lianhua Qingwen Granules in 42 suspected cases of children with Corona Virus Disease 2019. Chinese Journal of New Drugs ; 29(24):2809-2812.**

Overall Evaluation: Good Quality

A. Selection - 3 stars

1) Representativeness of the exposed cohort - somewhat representative (one star)
2) Selection of the non-exposed cohort - drawn from the same community as the exposed cohort (one star)
3) Ascertainment of exposure – no description
4) Demonstration that outcome of interest was not present at start of study – Yes (one star)

B. Comparability – 2 stars

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
a) The study controls for age, sex (one star)
b) Study controls for other factors (list): body temperature, heart rate, respiratory rate, CRP levels, procalcitonin levels, heating time/day, antibiotic use/case, phlegm medicine/case (one star)
c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

C. Outcome – 2 stars

1) Assessment of outcome – no description
2) Was follow-up long enough for outcomes to occur – Yes, 5 days; this is close to the usual outcomes measured in adult studies (Day 7 resolution of symptoms) (one star)
3) Adequacy of follow-up of cohorts: Complete follow up- all subject accounted for (one star)