Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Among patients with COVID-19, should Lianhua be used as treatment?

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RECOMMENDATION

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)*

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.

PREVIOUS RECOMMENDATION

We recommend against the use of Lianhua as treatment in patients with mild to moderate COVID-19. *(Very low certainty of evidence; Strong recommendation)*

Previous consensus issues
The consensus panel considered the evidence from the presented trials to be of very low certainty, with only marginal benefit in terms of rate of recovery and time to symptom recovery and inconclusive evidence for harm due to imprecise confidence intervals. The accessibility issue and potential harm the drug might cause should be considered. Lianhua is currently a drug regulated by the Philippine Food and Drug Administration as it contains ephedra, a controlled substance. As a result, Lianhua could not be sold over-the-counter and may only be prescribed by physicians holding an S2 license. The ephedra content of Lianhua was reported by some physicians to be potentially harmful especially in patients with cardiovascular disease.

What's new in this version

This review includes 3 additional RCTs (total of 5 included studies).

Key Findings

Five (5) 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.

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

Databases 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 the date of the last search June 11, 2021 to October 28, 2021. For PubMed, the following search terms were used: coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, lianhua qingwen, lianhua, lianhua qingwen capsules, or lianhua capsules. 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.

Results

Characteristics of included studies

Five (5) RCTs were included in this review.[6,10-13] 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 5 studies included a total of 896 adult patients without severe COVID-19. 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 anti-virals, oxygen therapy, and/or symptomatic treatments. Four (4) studies used Lianhua Qingwen thrice daily: 2 as capsule and 2 as granules.[6,10-12] One study used Lianhua Qingke granules twice daily.[13] Outcomes reported were clinical deterioration, day-14 symptom improvement (fever, cough, and fatigue), improvement in chest CT scan, and serious drug-related adverse events. The characteristics of included studies are summarized in Appendix 3.

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 4 studies, issues with performance and detection bias in all 5 studies (4 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 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 with 295 participants reported on mortality.[12] Yu et al., reported 2 deaths in the comparator arm and 1 in the Lianhua arm yielding inconclusive results (RR 0.50, 95% CI 0.05-5.49).

Clinical deterioration

Data from 5 RCTs (N = 814) showed a significant benefit in preventing clinical deterioration or progression to severe disease in favor of Lianhua (RR 0.55, 95% CI 0.36 to 0.82; I^2 = 0%). Of the 5 studies, only one study with very serious risk of bias showed a significant decrease in the risk of clinical deterioration.

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

Pooled analysis from 2 studies with very low certainty of evidence on day-14 improvement of the following symptoms showed no significant difference between Lianhua arm and the control arm: cough (RR 1.09, 95% CI 0.65 to 1.81; I^2 = 86%), fatigue (RR 1.11, 95% CI 0.92 to 1.34; I^2 = 0%), and fever (RR 1.00, 95% CI 0.90 to 1.11; I^2 = 0%).[11,13] One study reported that day-14 total symptom recovery was slightly higher in the Lianhua arm (RR 1.11, 95% CI 1.01 to 1.22).[10]

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 to 1.16), nausea and vomiting (RR 0.80, 95% CI 0.62 to 1.03), diarrhea (RR 1.00, 95% CI 0.69 to 1.45), sore limbs (RR 1.26, 95% CI 0.88 to 1.81), and shortness of breath (RR 1.18, 95% CI 0.77 to 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 to 1.07), nausea and vomiting (RR 0.93, 95% CI 0.82 to 1.07), diarrhea (RR 1.00, 95% CI 1.00 to 1.00), sore limbs (RR 1.05, 95% CI 0.81 to 1.36), and chest tightness and shortness of breath (RR 0.97, 95% CI 0.73 to 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. There was significant improvement of sputum expectoration at day 14 among those given Lianhua compared to control (RR 1.66, 95% CI 1.04-2.64).[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]

One study showed significant shorter median time to recovery of total symptoms (HR 1.72, 95% CI 1.33 to 2.22), fatigue (HR 1.78, 95% CI 1.04 to 2.05), and cough (HR 1.71, 95% CI 1.3 to 2.23) in the Lianhua arm. There was no trend towards benefit in time to recovery for fever (HR 1.39, 95% CI 1.0 to 1.94),[10]

Improvement in chest CT scan

The pooled result from 3 studies [10,12,13] with low certainty of evidence showed significant improvement in chest CT scan in patients given Lianhua (RR 1.22, 95% CI 1.10 to 1.35; I^2 = 31%). 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]

Viral clearance

There was no significant difference in the conversion rate of SARS-CoV-2 viral assay (RR 1.08, 95% CI 0.94 to 1.24) and time to negative conversion (MD -0.42 days, 95% CI -1.51 to 0.67; p = 0.45).

Safety Outcomes

Pooled estimate from three studies with very low certainty of evidence reported no significant difference in total adverse events (RR 0.87, 95% CI 0.70-1.10; I^2 = 0%).[6,10,12] Adverse events

reported in both the Lianhua and control group included abnormal liver function, renal dysfunction, headache, nausea, vomiting, and loss of appetite.

Two studies with very low certainty of evidence reported zero serious adverse event in both experimental and control arms.[10,12]

Expected adverse effects from ephedra such as hypertension and tachycardia was not mentioned as an outcome to be measured in the methodology, nor reported in the results in any of the studies.

Recommendations from Other Groups

Table 1. Summary of Recommendation from Other Groups

Regulatory Agency	Recommendation
National Institutes of Health (as of October 19, 2021) [14]	No recommendations on the use of Lianhua for the treatment of COVID-19.
World Health Organization (as of September 24, 2021) [15]	
Infectious Diseases Society of America (as of October 15, 2021) [16]	
Australian Clinical Evidence Taskforce (as of October 21, 2021) [17]	
National Health Commision & State Administration of Traditional Chinese Medicine Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (as of March 4, 2020)	Recommend Lianhua Qingwen capsules to be used during medical observation as treatment of fatigue and fever. [18-20]
Diagnosis and Treatment Protocol for COVID-19 of the National Health Commission (as of August 18, 2020)	
Rapid Advice Guideline for the Diagnosis and Treatment of 2019-nCoV by the China International Exchange and Promotive Association for Medical and Healthcare (CPAM) (as of February 6, 2020)	
CPAM & Chinese Research Hospital Association (CRHA) (as of September 4, 2020)	Recommends the use of Lianhua to treat patients with mild or moderate COVID-19 with conventional therapy and suggested that Lianhua granules/capsules 6 g/1.4g be taken orally, thrice daily for 14 days.[21]
Expert Consensus on Guidance and Prevention Strategies for Hospital Pharmacists and Pharmacy Workfoce by the Chinese Pharmaceutical Association (CPA)	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] 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 Trusthworthy Traditional Chinese Medicine Recommendations (TCM	Suggests against the use of Lianhua Qingke granules in addition to western medicine for mild and moderate

Recs) Working Group (as of October 11, 2021)	COVID-19 patients. However, the guideline only based its recommendation on one RCT.[23]

Research Gaps

There are 5 ongoing registered RCTs (ChiCTR2000029433 for suspected cases, ChiCTR2100042066 for asymptomatic cases, NCT04433013 and ChiCTR2100042069 for mild COVID-19, and ChiCTR2100042068 for severe cases). Three are still ongoing recruitment while 2 are pending or no recruitment yet.

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Appendix 1: Evidence to Decision

Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate (2)	Small	Uncertain (3)			Lianhua had no significant effect in the mortality, however, it can prevent clinical deterioration or progression to severe disease among patients with non-severe COVID 19.
Harm	Large	Small (3)	Uncertain (2)				No significant differences in terms of adverse events or serious adverse events from the Lianhua group compared to standard of care.
Certainty of Evidence	High	Moderate (1)	Low (2)	Very low (2)			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 drug (1)	Does not favor drug	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost	Negligible cost or savings (4)	Moderate savings (1)	Large savings	Lianhua would cost P288.00/box with 24 capsules per box. Most recommended regimen (Lianhua cap TID for 14 days) will cost P504.00 (P36/day). On August 7, 2020, the FDA approved its use only for symptomatic relief but not for COVID-19 treatment
Certainty of evidence of required resources	No included studies (3)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced	Probably no impact	Increased (1)			
Acceptability	Uncertain (4)	No	Yes (1)				
Feasibility	Uncertain (3)	No	Yes (2)				

Appendix 2: Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	((“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))	10/28/21, 2:10 am	46	10
CENTRAL	“COVID-19” and “lianhua”	10/27/21, 11 pm	12	5
Cochrane COVID-19 Study Register	“COVID-19” and “lianhua”	10/27/21, 11:45 pm	12	2
COVID-NMA Initiative	Filter: “lianhua”	10/28/21, 1:12 am	0	0
LitCOVID	“COVID-19” and “lianhua”	10/28/2021, 12:15 am	10	4
China National Knowledge Infrastructure	“COVID-19” and “lianhua”	10/28/2021, 1: 37 am	40	8
HERDINPlus	“COVID-19” and “lianhua”	10/28/21, 12:10 am	0	0
ClinicalTrials.gov	Condition or disease: COVID-19 Other terms: Lianhua	10/27/21, 8 pm	1	1
Chinese Clinical Trial Registry	Target disease: COVID-19 Intervention: lianhua	10/27/21, 11:05 pm	3	0
EU Clinical Trials Register	“COVID-19” and “lianhua”	10/27/21, 11:17 pm	0	0
Republic of Korea – Clinical Research Information Service	“COVID-19” and “lianhua”	10/27/21, 11:42 pm	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	“COVID-19” and “lianhua”	10/28/2021, 1:03 am	0	0
CenterWatch	Filter: COVID-19 I am looking for: lianhua	10/27/21, 11:27 pm	0	0
WHO International Clinical Trials Registry Platform (ICTRP)	“COVID-19” and ‘lianhua”	10/27/21, 11:30 pm	5	3
chinaxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:04 am	0	0
Medrxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:05 am	10	0
Biorxiv.org	“COVID-19” and “lianhua”	10/28/21, 1:10 am	7	0
Google Scholar	“Clinical Study of Lianhua Qingwen Capsule in the Treatment of Corona Virus Disease 2019”	10/28/2021, 12:50 am	4	3
CiteSeerX	“Clinical Study of Lianhua Qingwen Capsule in the Treatment of Corona Virus Disease 2019”	10/28/2021, 12:53 am	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 (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) 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 (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 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

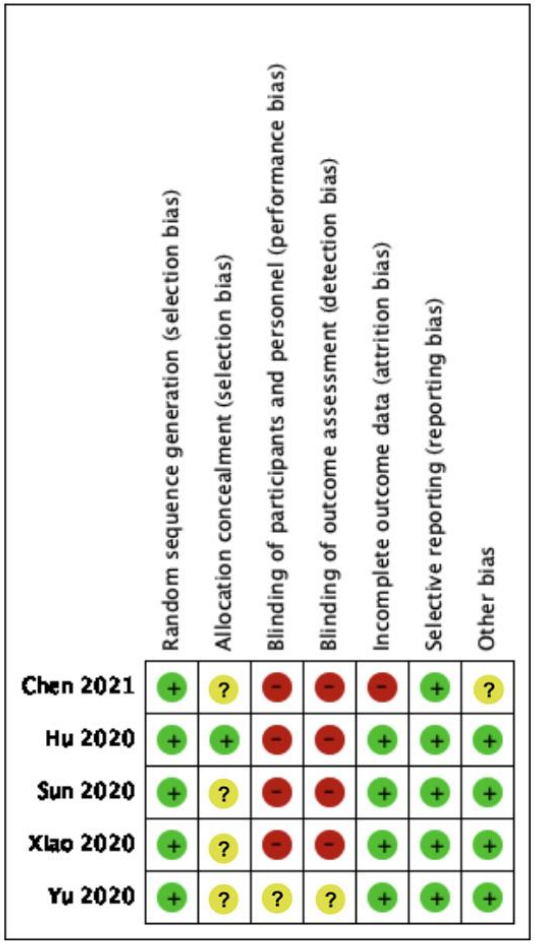
Xiao et al, 2020 [11]	Single site, randomized, controlled, non-blinded, three arms	Diagnosed cases of COVID-19 (n = 182)	Diagnosed cases of COVID-19 meeting the diagnostic criteria; 18–85 years old, regardless of sex; provided informed consent.	Clear evidence of bacterial infection; severe primary diseases, 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 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 (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); 2) 18 to 75 years old; 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 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) vs. conventional (lopinavir or ritona, interferon alfa plus symptomatic and supportive treatment	Aggravation rate, mortality rate, improvement of chest CT, 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	5 RCT (n = 814)	RR 0.55 (0.36-0.82)	**62 fewer per 1,000** (from 88 fewer to 25 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	1 RCT (n = 284)	HR 1.72 (1.33-2.22)	--	Benefit	Low
Total symptom recovery, Day 14	1 RCT (n = 284)	RR 1.11 (1.01-2.22)	**91 more per 1,000** (from 8 more to 181 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)	Equivalent	Very Low[1]
Cough Improvement, Day 14	2 RCT (n = 123)	RR 1.09 (0.65-1.81)	**72 more per 1,000** (from 64 fewer to 271 more)	Inconclusive	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	3 RCT (n = 636)	RR 1.22 (1.10-1.35)	**141 more per 1,000** (from 64 more to 224 more)	Benefit	Low
Negative conversion time	2 RCT (n = 341)	MD -0.42 day (-1.51 to 0.67)	**0.42 day lower** (1.51 lower to 0.67 higher)	Inconclusive	Low
Conversion rate of SARS-CoV 2 viral assay	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]
Adverse events	3 RCT (n = 456)	RR 0.87 (0.70-1.10)	**35 fewer per 1,000** (from 80 fewer to 27 more)	Inconclusive	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): Joey Tabula, Timothy Hudson David Culasino Carandang
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.

2. M. Xiao, J. Tian,Y. Zhou,et al.. Efficacy of Huoxiang Zhengqi dropping pills (藿香正气滴丸) and Lianhua Qingwen granules (连花清瘟颗粒) in treatment of COVID-19: a randomized controlled trial. Pharmacol Res.

3. H.M. Sun, F. Xu,L. Zhang,et al.. Study on clinical efficacy of Lianhua Qingke Granules (连花清瘟颗粒) in treatment of mild and ordinary COVID-19. Chin J Exp Tradit Med Form; 2020.

4. K. Hu, W.J. Guan,Y. Bi,et al.. Efficacy and safety of Lianhuaqingwen capsule (连花清瘟胶囊), a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine; 2020.

5. C. Chen, X. Li, Y. Liu, S. Chen. Clinical Study of Lianhua Qingwen capsule in the treatment of coronavirus disease 2019. Res Integr Tradit Chin West Med 13(1):1-4. Accessed 19 October 2020 at http://med.wanfangdata.com/cn/Paper/Detail?id=PeriodicalPaper_zxyjhy202101001

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												
5 [1,2,3,4,5]	randomised trials	very serious [a,b]	not serious	not serious	not serious	none	30/407 (7.4%)	56/407 (13.8%)	**RR 0.55** (0.36 to 0.82)	**62 fewer per 1,000** (from 88 fewer to 25 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												
1 [4]	randomised trials	very serious [b]	not serious	not serious	not serious	none	7 days vs 10 days, HR 1.72, (1.33 to 2.22), p<0.01				⊕⊕◯◯ LOW	CRITICAL
Total symptom recovery, Day 14												
1 [4]	randomised trials	very serious [b]	not serious	not serious	serious [d]	none	130/142 (91.5%)	117/142 (82.4%)	**RR 1.11** (1.01 to 1.22)	**91 more per 1,000** (from 8 more to 181 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

2 [1,3]	randomised trials	very serious [a,b]	Very serious [e,f]	not serious	serious [c]	none	54/64 (84.4%)	47/59 (79.7%)	**RR 1.09** (0.65 to 1.81)	**72 more per 1,000** (from 64 fewer to 271 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

3 [1,4,5]	randomised trials	very serious [a,b]	not serious	not serious	serious [c]	none	74/137 (23.3%)	85/319 (26.6%)	**RR 0.87** (0.70 to 1.1)	**35 fewer per 1,000** (from 80 fewer to 27 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

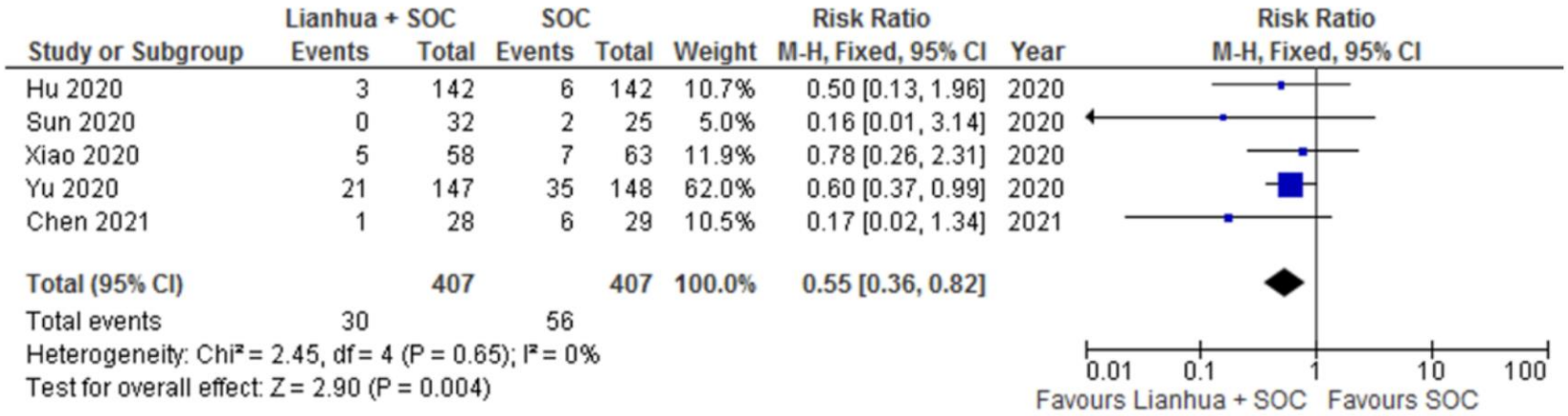


Figure 1. Clinical Deterioration

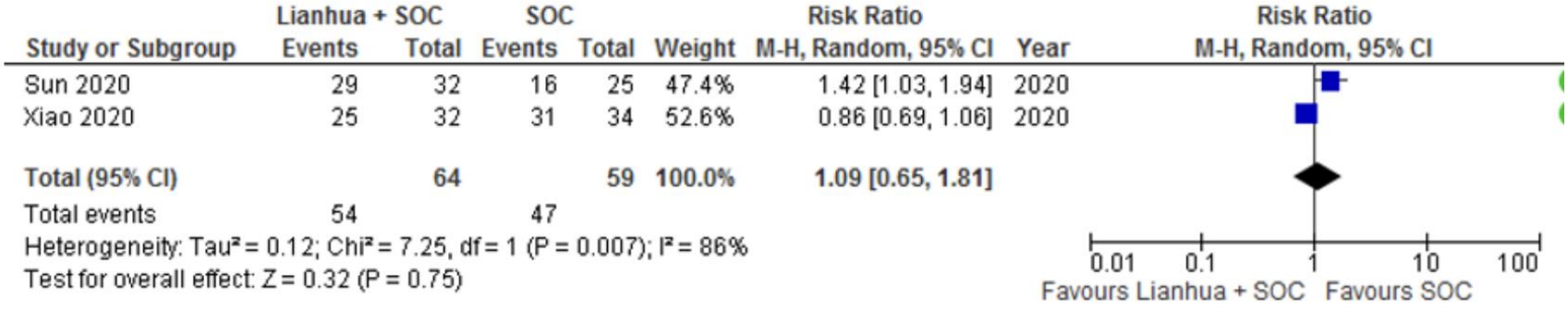


Figure 2. Day-14 cough improvement

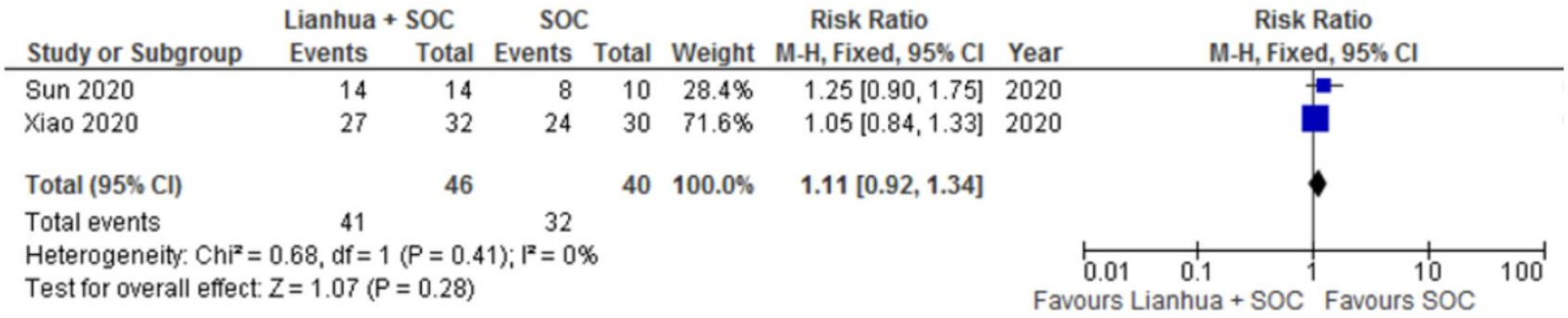


Figure 3. Day-14 fatigue improvement

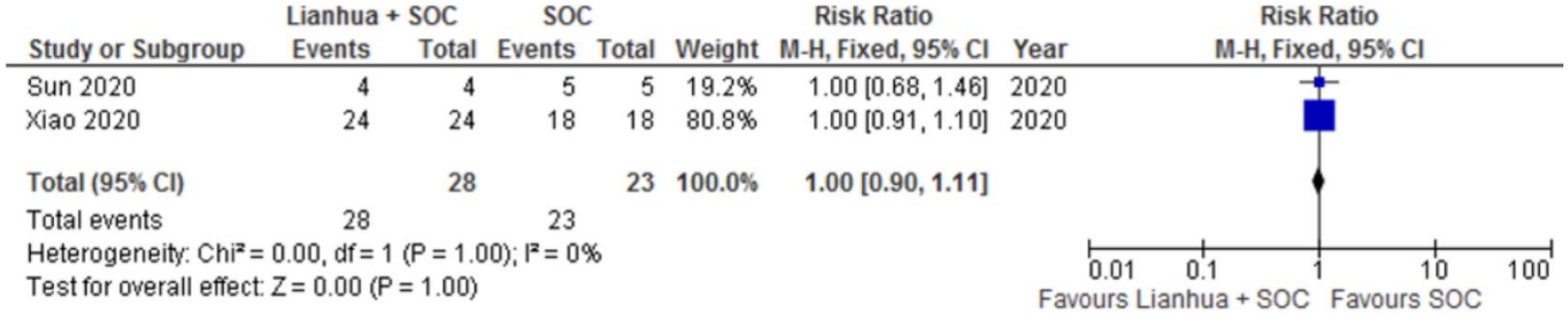


Figure 4. Day-14 fever improvement

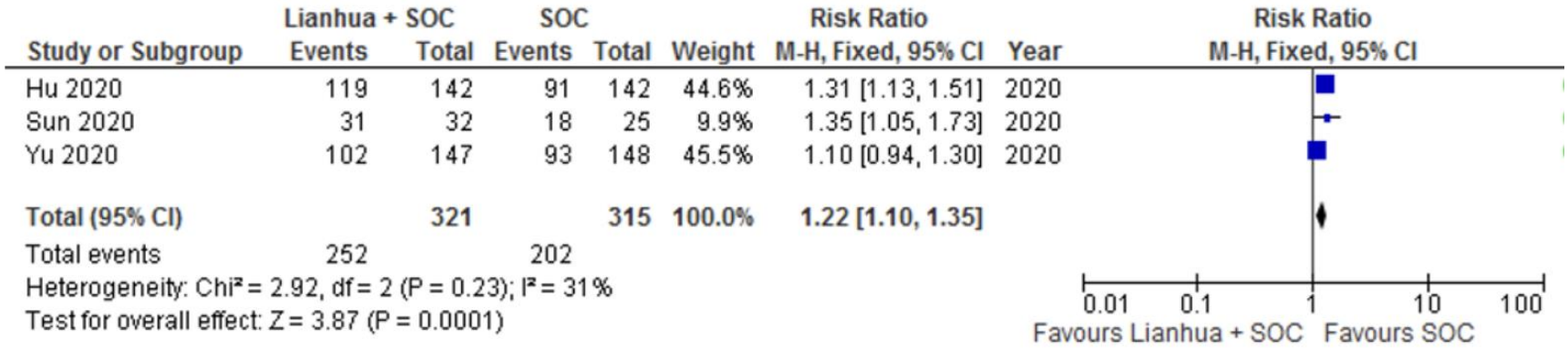


Figure 5. Chest CT improvement

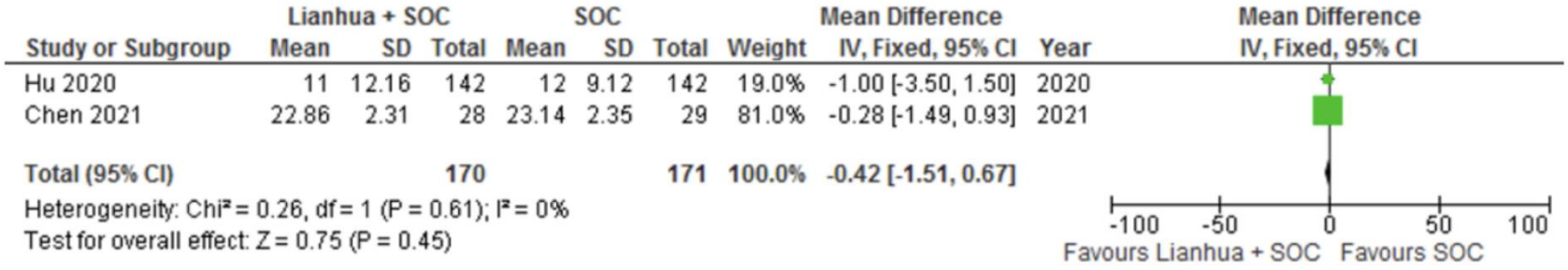


Figure 6. Negative Conversion Time

Study or Subgroup	Lianhua + SOC Events	Total	SOC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Yu 2020	0	147	0	148		Not estimable	2020
Hu 2020	65	142	77	142	90.7%	0.84 [0.67, 1.07]	2020
Chen 2021	9	28	8	29	9.3%	1.17 [0.52, 2.59]	2021
Total (95% CI)		**317**		**319**	**100.0%**	**0.87 [0.70, 1.10]**	
Total events	74		85				

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)

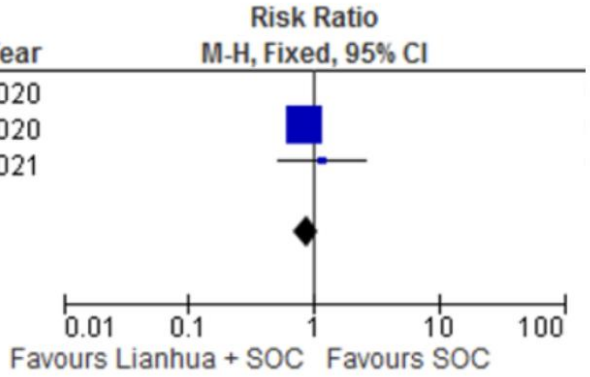


Figure 7. Adverse Events

Appendix 8: Characteristics of Ongoing Studies

Title	Population	Interventions	Characteristics	Outcome Measures
ChiCTR2000029433 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Wen Capsule/Granule in the treatment of suspected novel coronavirus pneumonia	Symptomatic (any of the ff: fever, cough, fatigue) patients ≥ 18 years old	Routine treatment + Lianhua Qingwen 4 caps/1 bag TID	N = 240 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: clinical symptoms recovery rate and recovery time Secondary: single symptom disappearance rate and main symptom disappearance time, proportion of aggravation during treatment, rate of CT improvement, disease recovery rate, routine blood test, biochemical indicators
ChiCTR2100042066 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	Asymptomatically infected patients discovered through pathogenic testing ≥ 18 years old	Lian-Hua Qing-Wen Capsule/Granule	N = 120 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: Time and rate of nucleic acid turning negative Secondary: clinical symptom and severity Clinical symptoms appearance time and proportion Proportion of mild and common cases diagnosed duting isolation/observation period
NCT04433013 A Randomized Controlled Trial Assessing the Efficacy of Lianhua Qingwen as an Adjuvant Treatment in Patients with Mild Symptoms of COVID-19	Symptomatic (≥1 symptom) patients ≥ 21 years old with confirmed COVID-19 by pathogenic testing	LHQW capsules 4 capsules, TID	N = 300 Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor	Primary: Proportion of participants who test negative for COVID-19 Secondary: Time taken in days for relief of clinical symptoms, proportion of participants with mild symptoms of COVID-19 progressing to moderate or severe illness, proportion of participants who test positive for COVID-19 with Ct value>30
ChiCTR2100042069 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	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 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: clinical symptoms recovery rate and recovery time 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 A randomized, open-label, blank-controlled, multi-center clinical study for Lian-Hua Qing-Ke Tablets in the treatment of severe novel coronavirus pneumonia	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 Equally divided to both arms Allocation: Randomized Intervention Model: Parallel Assignment Masking: none	Primary: time to clinical improvement (censored at Day 28) 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

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 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: improved clinical cure and the negativity of the SARS-CoV-2 nucleic acid test Secondary: 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 4) time to fever clearance, 5) duration of hospital stay, and 6) chest imaging improvement
Shi et al., 2021 IF: 3.885	China	No	Yes	Yes	19 RCTs 29 observational with control arm	2,696 – CHM 2,008 - SOC	Yes	CHM + standard pharmacotherapy.	standard pharmacotherapy alone or standard pharmaco-therapy plus placebo	Primary: GI symptom improvement and liver function Secondary: Sggravation of COVID-19, time to viral assay conversion
He et al., 2021 IF: N/A; preprint	China	No	No	Yes	6 RCTs 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