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Evidence-Based Integrative Medicine

Efficacy and Safety of Lianhua Qingwen for Patients with COVID-19: A Systematic Review and Meta-Analysis*

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ABSTRACT **Background**: Corona virus disease 2019 (COVID-19) has spread around the world since its outbreak, and there is no ascertained effective drug up to now. Lianhua Qingwen (LHQW) has been widely used in China and overseas Chinese, which had some advantages in the treatment of COVID-19. **Objective**: To evaluate the efficacy and safety of LHQW for COVID-19 by conducting a systematic review with meta-analysis. **Methods**: A comprehensive literature search was conducted in 12 electronic databases from their establishment to October 30, 2021. Note Express 3.2.0 was used for screening of trials, and the data was independently extracted in duplicate by 2 researchers. The risk of bias of randomized controlled trials (RCTs) and retrospective studies were assessed by using the Cochrane collaboration tool and Newcastle Ottawa Scale, respectively, followed by data analysis using RevMan 5.3. The RCTs or retrospective studies to treat COVID-19 using LHQW were included. The intervention measures in the experimental group were LHQW alone or combined with chemical drugs (LCWC), and that in the control group were chemical drugs (CDs). Outcome measures included computed tomography (CT) recovery rate, disappearance rates of primary (fever, cough, fatigue), respiratory, gastrointestinal and other symptoms, exacerbation rate and adverse reaction. Subgroup analysis was conducted according to whether LHQW was combined with CDs and the different treatment methods in the control group. **Results**: Nine trials with 1,152 participants with COVID-19 were included. The CT recovery rates of LHQW and LCWC were 1.36 and 1.32 times of CDs, respectively (P<0.05). Compared with CDs, LCWC remarkably increased the disappearance rates of fever, cough, fatigue, expectoration, shortness of breath, and muscle soreness (P<0.05). LHQW also obviously decreased the exacerbation rate, which was 0.45 times of CDs alone (P<0.05). There was no obvious difference between LCWC and CDs in adverse reaction (P>0.05). **Conclusions**: LHQW was more suitable for treating COVID-19 patients with obvious expectoration, shortness of breath and muscle soreness. LHQW had advantages in treating COVID-19 with no obvious exacerbation. (PROSPERO No. CRD42021235937)

KEYWORDS Lianhua Qingwen, COVID-19, 2019-nCoV, systematic review, meta-analysis, Chinese medicine

Corona virus disease 2019 (COVID-19) is a severe respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is highly contagious and deadly[1] and is listed by the World Health Organization (WHO) as a public health emergency of international concern. Since its outbreak, COVID-19 has spread almost around the world rapidly.[2] Until March 24, 2022, COVID-19 has caused 475,741,597 confirmed infections and 6,128,383 deaths worldwide.[3] The number is still rising, presenting a huge challenge for medical workers. In addition to its health effects, COVID-19 has caused social, economic and political damage. Although there have been many drugs to treat COVID-19 in clinic, no treatment can completely

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treat or prevent SARS-CoV-2 infection up to now.[4] And most trials were retrospective and observational designs with insufficient sample sizes, making it difficult to assess the effectiveness of specific interventions. Therefore, it is in urgent need to seek effective drugs for the treatment of COVID-19.

Chinese medicine (CM) has favorable experience in the prevention and treatment of infectious diseases, which has shown to be effective in patients with influenza.[5] In addition, compared with the methods of killing or inactivating pathogens directly in modern medicine, CM has a wider range of application sites in the human body.[6] In the prevention and treatment of COVID-19, it focuses on improving human immunity,[7] so it has been widely used and shown some advantages.[8] The combination of CM and chemical drugs (CDs) seems to be more effective in treating COVID-19 than using CDs alone.[9]

Lianhua Qingwen (连花清瘟, LHQW) granule or capsule has been widely accepted as a broad-spectrum antiviral agent in the clinic, and it is a representative CM for the treatment of respiratory infectious diseases, which has been used in the prevention of SARS and shown some advantages.[10] LHQW is composed of 12 kinds of herbs, including *Fructus Forsythiae*, *Flos Lonicerae*, *Herba Ephedrae*, *Semen Armeniacae Amarum*, *Radix Isatidis*, *Rhizoma Dryopteris Crassirhizomae*, *Herba Houttuyniae*, *Herba Agastaches*, *Radix et Rhizoma Rhei*, *Herba Rhodiolae sacrae*, *Herba Menthae*, *Radix Glycyrrhizae*, and a mineral drug *Gypsum firosum*, furthermore, the ratio of the ingredients in the formulation is 255:255:85:85:255:255:255:85:51:85:7.5:85:255. The National Health Commission of the People's Republic of China published "Guidelines for the diagnosis and treatment of COVID-19 pneumonia" (trial version from the fourth/fifth/sixth/seventh editions) and recommended LHQW as a CM treatment for COVID-19 in China.[11] Therefore, this study aimed to systematically evaluate the efficacy and safety of LHQW for COVID-19 from a variety of clinical symptoms by using systematic review and meta-analysis, hoping that it could provide information for the treatment of COVID-19.

METHODS

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) with Cochrane methodology,[12] and it has been registered with the PROSPERO No. CRD42021235937, but there was no protocol published.

Search Strategy

An electronic search of 12 electronic databases, including Cochrane Library, EMBASE, MEDLINE, PubMed, Springerlink, Web of Science, Clinicaltrials.gov, Chinese Biomedical Literature Database, the Chinese National Knowledge Infrastructure, Wanfang Database, Weipu Database, and Chinese Biomedical Literature Database, was performed from their establishment to October 30, 2021. Forward and backward citation searching was conducted for all eligible trials. MeSH and keyword terms were used in searching, including: ("COVID-19" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus" OR "SARS-CoV-2" OR "novel corona virus" OR "novel coronavirus" OR "2019-nCoV" OR "nCoV-2019") AND ("lianhuaqingwen" OR "lianhua qingwen" OR "lian hua qing wen") AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial" OR "lin chuang yan jiu" OR "lin chuang shi yan"). The language and status of publications in our literature search were not be specified. And the bibliographies of included trials and related reviews were manually searched for additional references.

Inclusion Criteria

Types of Studies

This study included randomized controlled trials (RCTs) or retrospective studies to treat COVID-19 using LHQW.

Types of Participants

Patients diagnosed with COVID-19[11] who were not restricted by age, gender or nationality were eligible for inclusion in this study.

Types of Interventions

The intervention measures in the experimental group should contain LHQW, and that in the control group should be CDs alone.

Outcome Measures

The trials should include at least one of the following outcomes: computed tomography (CT) recovery rate, disappearance rates of primary symptoms (fever, cough, fatigue), respiratory symptoms (expectoration,

shortness of breath, dyspnea, chest distress, rhinobyon, rhinorrhea, sore throat), gastrointestinal symptoms (inappetence, nausea, emesis, diarrhea) and other symptoms (muscular soreness, headache), exacerbation rate and adverse reaction.

Exclusion Criteria

Types of Studies

(1) Trials on effective analysis data cannot be obtained; (2) reviews, conference paper, case reports, experience sharing, animal experiments, etc.; (3) repeatedly published articles and plagiarized work.

Types of Interventions

LHQW combined with other CM formula in experimental group.

Outcome Measures

There was no data to extract in the outcome measures.

Study Selection and Data Extraction

According to the inclusion and exclusion criteria mentioned above, 2 researchers (Sun XH and Zhang Sh) independently screened the titles and abstracts of potential eligible trials that were in duplicate, then they retrieved independently and reviewed the full text of the possible trials in duplicate based on the inclusion and exclusion criteria and compared their results. The screening process was conducted in Note Express 3.2.0 (Beijing Aegean Software Co., Ltd., China).

We conducted various forms of calibration exercises and pilots before the data extraction process. Two researchers (Zhang Sh and Chen ZL) used standardized tables to independently extract data in duplicate from all eligible trials. In case of disagreement, they agreed through discussion, or submitted it to a third party for evaluation. And before the screening process, the third party used a standardized screening form and performed calibration exercises.

For all eligible trials, the researchers extracted data on the following characteristics: the basic information of the study (author's name, title of the study, year of publication, country/region and publication status), study characteristics (sample size, source of cases, age, diagnostic criteria, inclusion and exclusion criteria), intervention and control measures (dosage form, dose and duration), research methodology (random scheme generation, allocation hiding, blind method, incomplete result data, selective reporting, other biases and loss of follow-up), and outcome measures.

Assessment of Risk of Bias

The methodological quality of each included study was assessed independently by 2 reviewers (Sun XH and Chen ZL) according to 2 tools. The Cochrane collaboration tool is used to assess the quality of RCTs, and it comprises the following 7 aspects: random sequence generation, allocation concealment, blind method, incomplete result data, selective reporting and other biases. The quality assessment results of each item can be divided into 3 grades: "low risk", "high risk" and "unclear". As the design is more rigorous and the methodological quality of each RCT is higher, the risk coefficient is lower. Newcastle Ottawa Scale (NOS)[13] is used to assess the quality of retrospective studies. This method includes 3 aspects of evaluation: the selection method, comparability and contact exposure assessment method of case group and control group. The higher the score is, the greater the quality of the study is. When necessary, the consensus on this issue was studied with the help of a third party.

Data Analysis

Statistical analysis was performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, UK). The results of a single study were first described. The binomial variables were described by using relative risk (RR) and 95% confidence interval (CI), and the continuous variables were described by mean difference (MD) and 95% CI to describe the effect value of the inter-group comparison. Heterogeneity was judged on the basis of I^2 test results. I^2>50% indicated significant heterogeneity of inter-study, and the random effect model was adopted. The fixed effect model was adopted when I^2<50%,[14] however, if the clinical or methodological heterogeneity between trials is large, random effect model was still considered. Subgroup analysis was conducted according to whether the experimental group was combined with CDs and the different treatment methods in the control group. Inverted funnel plots was used to determine publication bias when the number of included trials exceeded 10 in the meta-analysis.[15]

RESULTS

Study Selection

Based on the above retrieval strategy, a total of 1,039 potentially relevant trials were retrieved from 12 electronic databases, and 187 trials were retrieved after deleting duplicates. After reviewing the titles and abstracts, 171 trials were excluded because they did not comply with the inclusion criteria, and 16 trials initially met the predetermined requirements and their full texts were read for detailed assessment. Finally, 9 trials[16-24] were included for meta-analysis. The PRISMA flow diagram of literature retrieval process is shown in Appendix 1. All included trials have been published as full article.

Study Characteristics

Appendix 2 summarizes the basic characteristics of the eligible 9 trials, all of which were conducted in China. A total of 1,152 patients with COVID-19 were analyzed. Sample sizes ranged from 42 to 295. Three trials[16,19,23] were RCTs, and 6[17,18,20-22,24] were retrospective studies. In the included trials, LHQW combined with CDs (LCWC) *vs*. CDs was used in 7 trials,[17-23] while LHQW *vs*. CDs was used in 2 trials.[16,24] CT recovery rate was reported in 5 trials,[16,17,19,21,23] while disappearance rates of fever,[17,18,20,21] cough,[17,18,20,22] expectoration,[17,18,20,22] shortness of breath,[17,18,20,22] muscular soreness[17,18,20,22] and exacerbation rate[17,20,23,24] were reported in 4 trials, and disappearance rates of fatigue,[17,20,22] dyspnea,[17,20,22] chest distress,[17,20,22] rhinobyon,[18,20,22] rhinorrhea,[18,20,22] inappetence,[17,20,22] and nausea[17,20,22] were reported in 3 trials, moreover, disappearance rates of sore throat, emesis, diarrhea and headache were reported in 2 trials.[20,22] Duration of treatment was reported in 7 trials,[16-21,23] ranging from 5 to 15 days, and duration in 1 trial[24] was tailored to the patient's condition.

Risk of Bias in Included Trials

The methodological quality of 3 RCTs[16,19,23] is summarized in Figure 1. Although randomization was announced in all 3 trials, 2 trials[19,23] used random number table, and 1[16] did not report the adequate sequence generation. Additionally, all of the 3 trials did not report allocation concealment and blind method. Appendix 3 summarizes the NOS scores of 6 retrospective studies,[17,18,20-22,24] all of which were of fair quality. Appendix 4 provides the funnel plot of the trials for disappearance rate of primary symptoms, and it revealed that there was no publication bias in the trials.

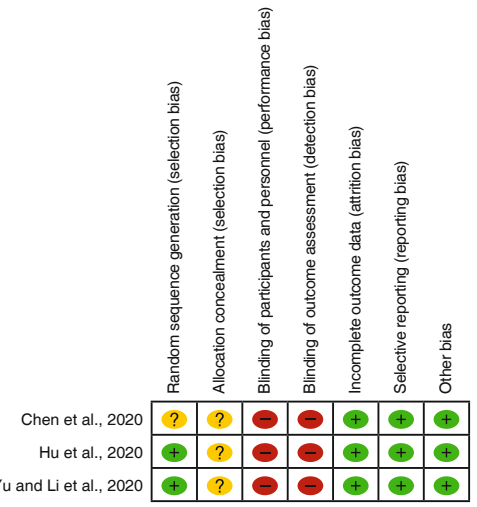

Figure 1. Methodological Quality Assessment Results for Three RCTs

Outcomes

CT Recovery Rate

A total of 5 trials[16,17,19,21,23] reported the CT recovery of patients after treatment, in which 4[17,19,21,23] used LCWC *vs*. CDs and 1 trial[16] used LHQW *vs*. CDs. Meta-analysis showed that using LHQW to treat COVID-19 could obviously enhance CT recovery rate (5 trials; *n*=803; RR: 1.33; 95% CI, 1.18 to 1.49; *P*<0.00001; Figure 2), and the recovery rates of LHQW and LCWC were 1.36 (1 trial; *n*=70; RR: 1.36; 95% CI, 1.02 to 1.82; *P*=0.04) and 1.32 (4 trials; *n*=733; RR: 1.32; 95% CI, 1.16 to 1.49; *P*<0.0001) times higher than that of CDs alone, respectively.

Disappearance Rate of Primary Symptoms

Four trials[17,18,20,22] reported the improvement of fever and cough after treatment, and 3[18,20,22] reported fatigue. All of the trials used LCWC *vs*. CDs. The results showed that LCWC could obviously improve primary symptoms of patients with COVID-19 (RR: 1.56; 95% CI, 1.36 to 1.79; *P*<0.00001; Figure 3). Meta-analysis revealed a significant improvement by LCWC in fever, cough and fatigue, with the disappearance rates of 1.48 (4 trials; *n*=295; RR: 1.48; 95% CI, 1.23 to 1.79; *P*<0.0001), 1.88 (4 trials; *n*=270; RR: 1.88; 95% CI, 1.38 to 2.55; *P*<0.0001) and 1.49 (3 trials; *n*=160; RR: 1.49; 95% CI, 1.13 to 1.97; *P*=0.004) times higher than that of CDs alone, respectively.

Disappearance Rate of Respiratory Symptoms

Expectoration and shortness of breath were reported in 4 trials,[17,18,20,22] in addition, dyspnea,[17,20,22] chest distress,[17,20,22] rhinobyon[18,20,22] and rhinorrhea[18,20,22]

were reported in 3 trials, and sore throat was reported in 2 trials.[20,22] LCWC was used to compare with CDs in all trials. Meta-analysis showed that LCWC could remarkably improve respiratory symptoms of patients (RR: 1.79; 95% CI, 1.33 to 2.40; *P*=0.0001; Figure 4). Compared with CDs, the disappearance rate of

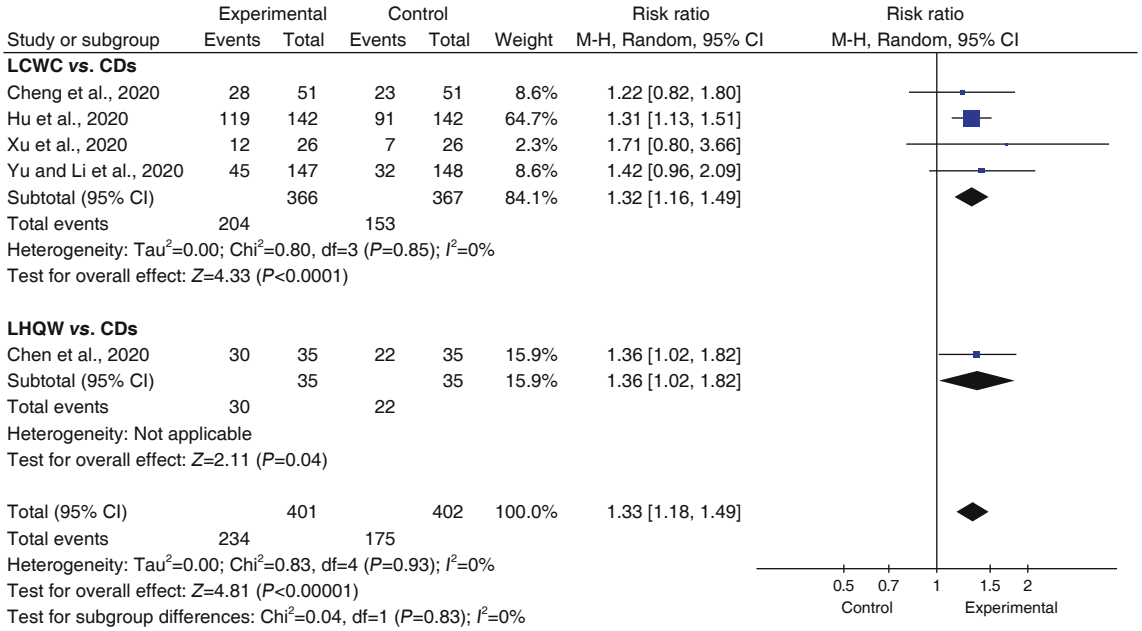

Figure 2. Forest Plot of the Trials Showing CT Recovery Rate in Different Interventions

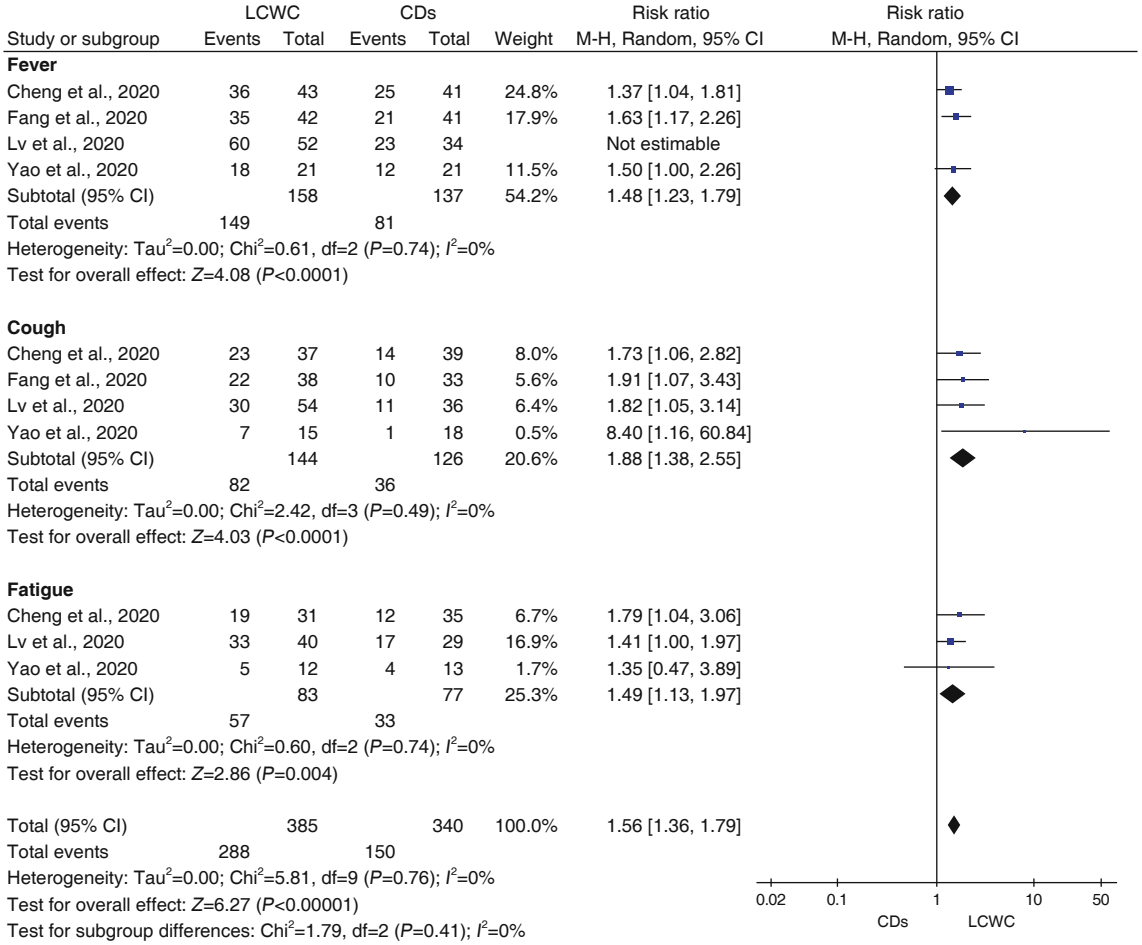

Figure 3. Forest Plot of the Trials Showing Disappearance Rate of Primary Symptoms in LCWC *vs*. CDs

expectoration and shortness of breath were significantly improved in the LCWC group, the effects of which were 2.57 (4 trials; *n*=170; RR: 2.57; 95% CI, 1.12 to 5.87; *P*=0.03) and 2.79 (4 trials; *n*=104; RR: 2.79; 95% CI, 1.29 to 6.02; *P*=0.009) times than that of CDs alone, respectively. However, there was no remarkable difference between LCWC and CDs on dyspnea (3 trials; *n*=35; RR: 2.23; 95% CI, 0.83 to 6.00; *P*=0.11), chest distress (3 trials; *n*=89; RR: 2.00; 95% CI, 0.81 to 4.96; *P*=0.13), rhinobyon (3 trials; *n*=19; RR: 1.17; 95% CI, 0.69 to 1.98; *P*=0.55), rhinorrhea (3 trials; *n*=17; RR: 0.99; 95% CI, 0.63 to 1.58; *P*=0.98) and sore throat (2 trials; *n*=12; RR: 1.53; 95% CI, 0.38 to 6.23; *P*=0.55).

Disappearance Rate of Gastrointestinal Symptoms

Three trials[17,20,22] reported inappetence and nausea, and 2[20,22] reported emesis and diarrhea. The results showed that LCWC could obviously improve the gastrointestinal symptoms of patients (RR: 1.65; 95% CI, 1.01 to 2.67; *P*=0.04; Figure 5). However, LCWC did not show obvious advantages in the improvement of inappetence (3 trials; *n*=135; RR: 2.80; 95% CI, 0.64 to 12.31; *P*=0.17), nausea (3 trials; *n*=36; RR: 1.41; 95% CI, 0.77 to 2.57; *P*=0.27), emesis (2 trials; *n*=11; RR: 2.25; 95% CI, 0.41 to 12.28; *P*=0.35) and diarrhea (2 trials; *n*=19; RR: 1.04; 95% CI, 0.42 to 2.58; *P*=0.94).

Disappearance Rate of Other Symptoms

Four trials[17,18,20,22] reported muscle soreness before and after treatment, and 2[20,22] reported headache. LCWC significantly increased the disappearance rate of muscle soreness compared with CDs, and its effect was 1.83 higher than that of CDs (4 trials; *n*=50; RR: 1.83; 95% CI, 1.02 to 3.27; *P*=0.04; Figure 6). However, there was no significant difference in headache between the two groups (2 trials; *n*=17; RR: 1.29; 95% CI, 0.67 to 2.46; *P*=0.44).

Exacerbation Rate

Exacerbation after treatment was reported in 4 trials, in which 3[17,20,23] used LCWC *vs*. CDs and 1[24] used LHQW *vs*. CDs. Meta-analysis exhibited that using LHQW to treat COVID-19 could significantly reduce the exacerbation rate of patients (4 trials; *n*=621; RR: 0.50; 95% CI, 0.36 to 0.70; *P*<0.0001; Figure 7). The exacerbation rates of LHQW and LCWC were 0.45 (1 trial; *n*=123; RR: 0.45; 95% CI, 0.25 to 0.80; *P*=0.006) and 0.53 (3 trials; *n*=498; RR: 0.53; 95% CI, 0.35 to 0.81; *P*=0.003) times than that of CDs alone, respectively.

Adverse Reaction

Adverse reaction after treatment was reported in 2 trials,[19,20] both of which used LCWC *vs*. CDs. The adverse reaction included abnormal liver function, renal dysfunction, headache, nausea, vomiting, diarrhea and loss of appetite. The meta-analysis showed that there was no obvious difference between LCWC and CDs [2 trials; *n*=385; RR: 0.51; 95% CI, 0.14 to 1.82; *P*=0.30; Appendix 5].

DISCUSSION

The efficacy and safety of LHQW for COVID-19 were evaluated by meta-analysis on the basis of 9 trials and 1,152 participants. The results showed that LHQW alone or LCWC both significantly improved CT recovery rate at 1.36 and 1.32 times higher than that of CDs alone, respectively. At the same time, LHQW also obviously decreased exacerbation rate, and the rates of LHQW and LCWC were 0.45 and 0.53 times of CDs alone, respectively. Combining LHQW with CDs, the disappearance rates of fever, cough, fatigue, expectoration and shortness of breath were 1.48, 1.88, 1.49, 2.57, and 2.79 times than that of CDs alone, respectively. However, there was no remarkable difference between LCWC and CDs on the disappearance rates of dyspnea, chest distress, rhinobyon, rhinorrhea, sore throat, inappetence, nausea, emesis, diarrhea and headache. Therefore, LHQW could improve some symptoms in patients with COVID-19 and increase the clinical effect.

Although some meta-analyses had also studied the efficacy of LHQW in the treatment of COVID-19, the inclusion and exclusion criteria of trials in these studies were not strict enough,[25-27] and their results were not consistent. Comparing with our findings, these meta-analyses also found LHQW can relieve fever, cough, expectoration, fatigue and muscle soreness, but they showed obvious relief of dyspnea and chest pain, which not reached in our study. This may be related to the small number of included trials and the insufficient inclusion criteria in these meta-analyses, and the included trials had a high risk of bias. Therefore, these studies could not reflect the exact efficacy of LHQW for treating COVID-19. This study had a more rigorous standard of inclusion and exclusion criteria, and evaluated the efficacy of LHQW on various systemic symptoms of patients with

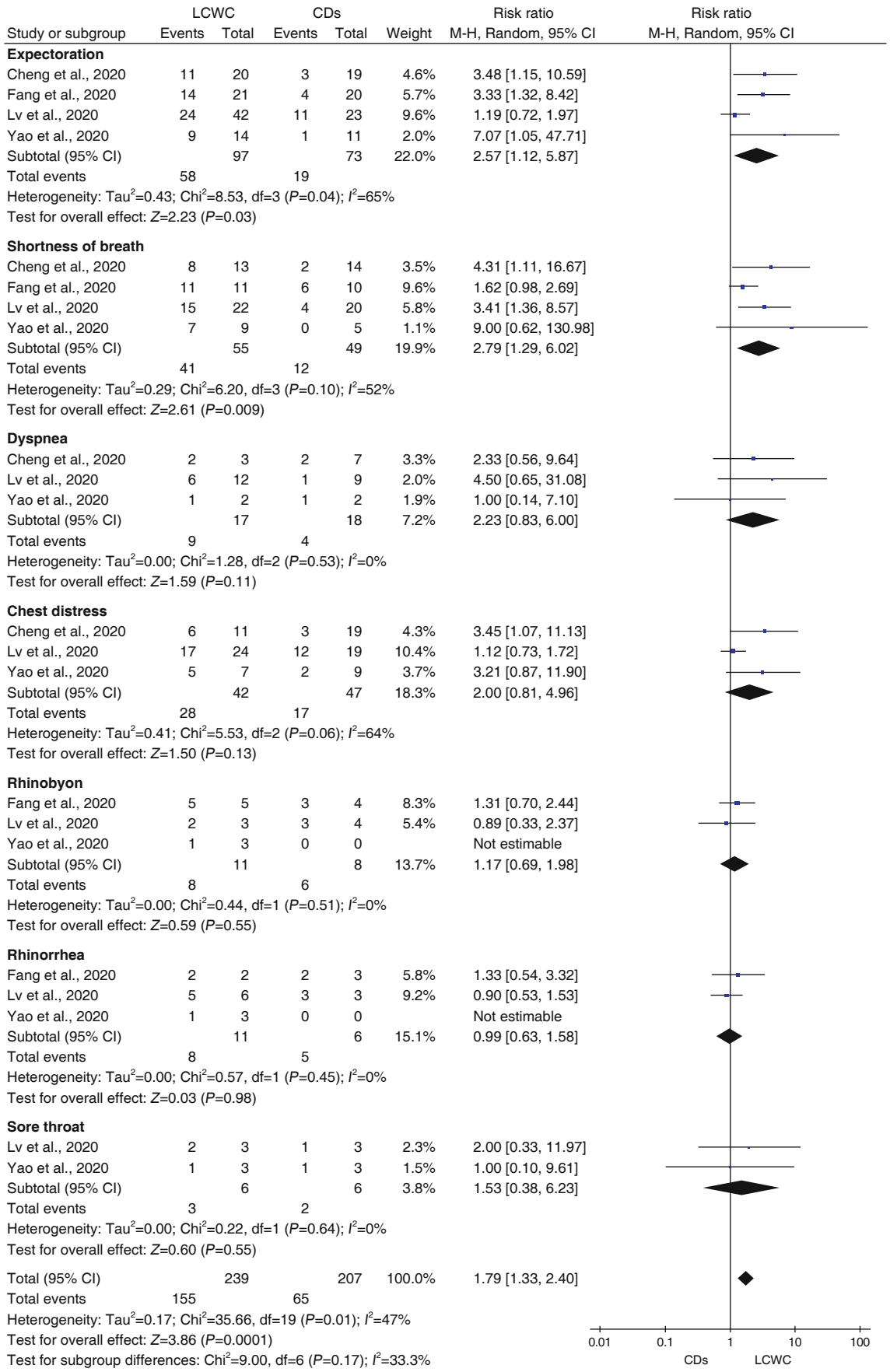

Figure 4. Forest Plot of the Trials Showing Disappearance Rate of Respiratory Symptoms in LCWC *vs*. CDs

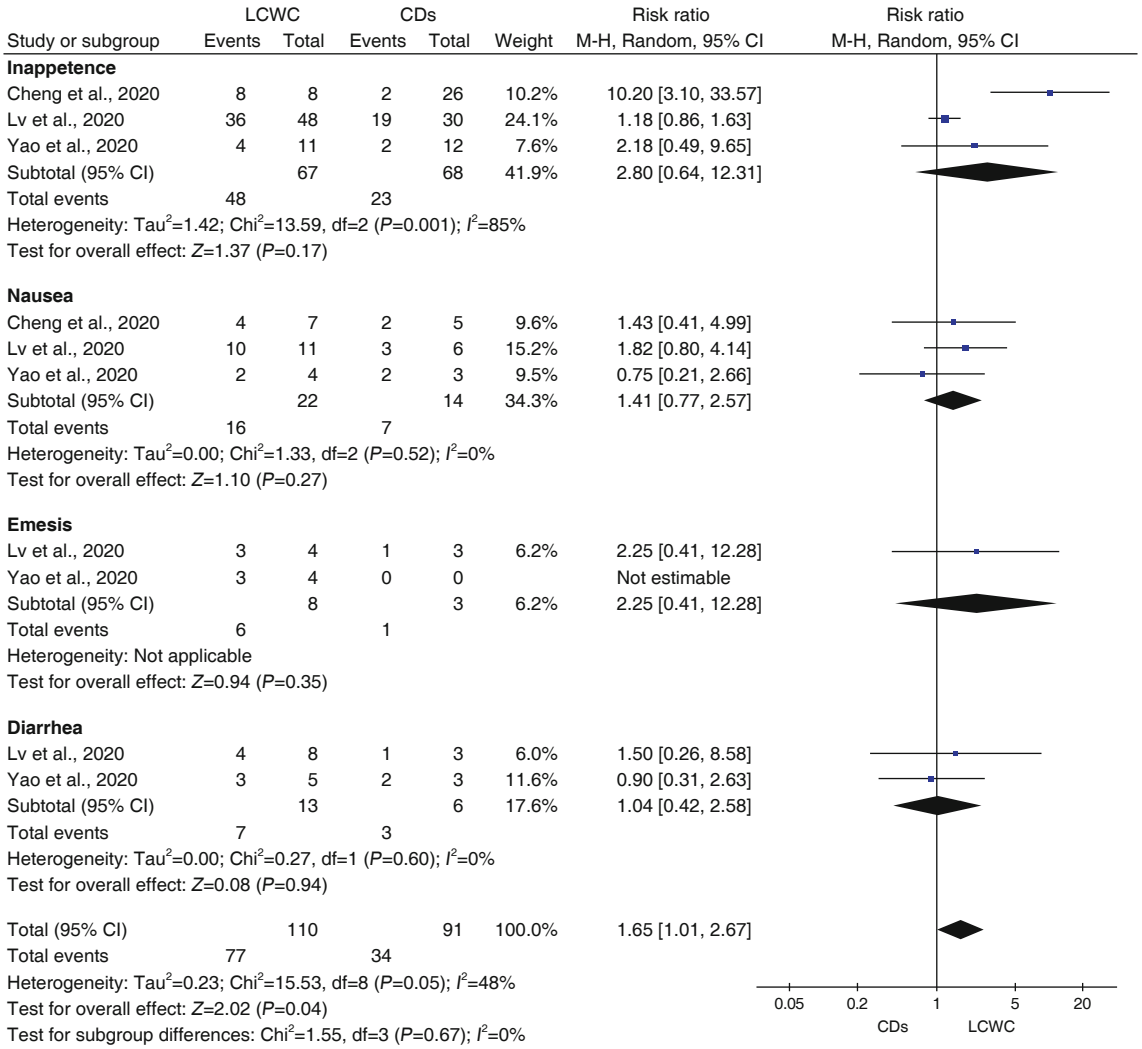

Figure 5. Forest Plot of the Trials Showing Disappearance Rate of Gastrointestinal Symptoms in LCWC *vs*. CDs

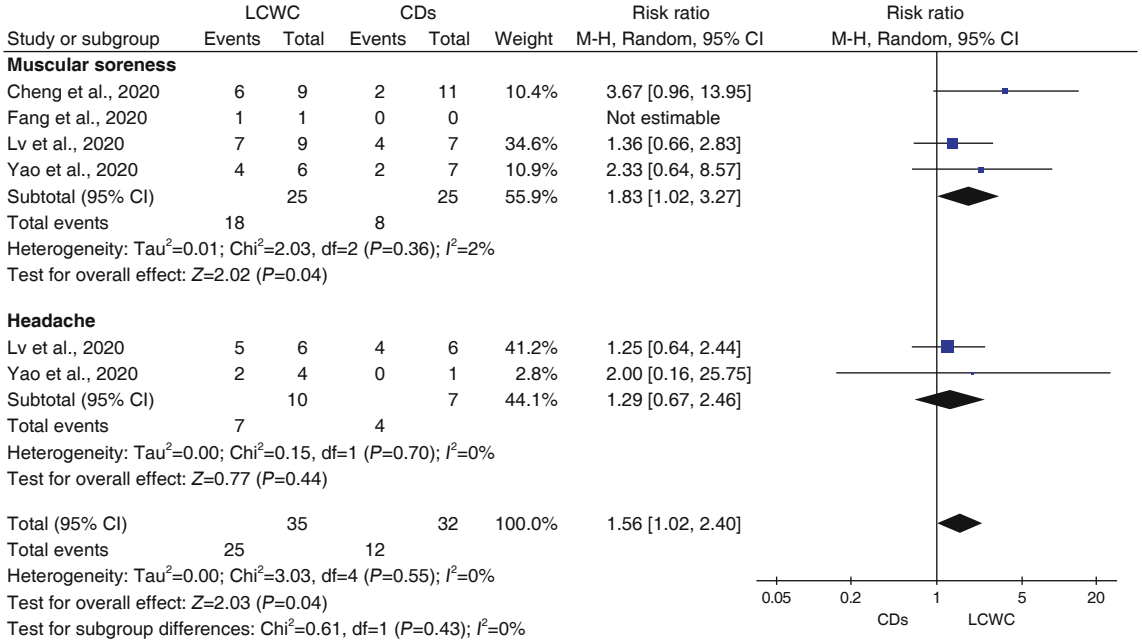

Figure 6. Forest Plot of the Trials Showing Disappearance Rate of Other Symptoms in LCWC *vs*. CDs

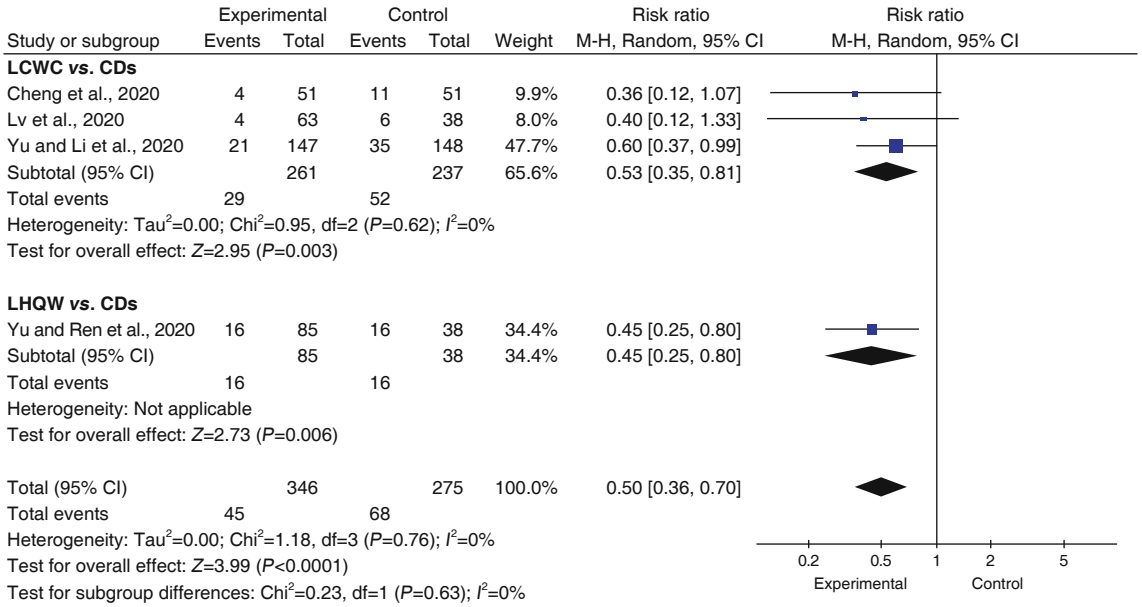

Figure 7. Forest Plot of the Trials Showing Exacerbation Rate in Different Interventions

COVID-19 in a strict sense, thus the research results were more reliable.

LHQW plays an important role in the prevention and treatment of viral public health events and has clinical application value. It has been proved to have some effect against COVID-19 in *in-vitro* experiments and clinical trials.[28] Experimental study has shown that LHQW has a broad-spectrum effect on a series of influenza viruses by inhibiting virus proliferation and regulating immune function.[29] And some clinical studies have shown that LHQW can not only enhance the body's immunity and inhibit respiratory inflammation,[30] but also affect the relevant cytokines and ameliorate lung injury associated with inflammatory cell infiltration.[31] Therefore, LHQW might treat COVID-19 through multi-target comprehensive intervention. Further studies are needed to demonstrate the potential therapeutic effect of LHQW in COVID-19 patients.

There were some important advantages in this study. Methodologically, our study benefited from the rigorous methods, the breadth of search, and the comprehensiveness of analytical indicators. In addition, as many indicators as possible were selected to reflect the advantages of LHQW in treating COVID-19, and multi-system symptoms of COVID-19 patients were analyzed and summarized in this study, which comprehensively reviewed the efficacy and safety of LHQW, and provided help for its clinical treatment.

The following limitations should be considered in this study. Because most of the current clinical trials on LHQW in the treatment of COVID-19 were retrospective studies and only a few were RCTs with insufficient sample size and short duration of the treatment, the methodological quality was subject to certain risk bias, so there were considerable clinical and methodological heterogeneities in the included trials. Therefore, in order to make the results more reliable, we still used the random effect model when I^2<50% to reduce the possible impact of these heterogeneities on the results. In addition, as the application of CM in other countries is limited, LHQW is mainly used in China. Therefore, although LHQW is widely used, the data is limited, which may affect the results.

In summary, multiple outcomes were used to systematically evaluate the efficacy and safety of LHQW for COVID-19 in this study. LHQW could treat COVID-19 through a comprehensive action of many herbs, which could not only improve some clinical symptoms, but also inhibit the progression of the disease, with no obvious adverse reactions. According to the results, LHQW is more suitable for the treatment of COVID-19 patients with obvious expectoration, shortness of breath and muscle soreness. Of course, more clinical trials in the future are expected to provide stronger evidence for LHQW in the treatment of COVID-19.

Conflict of Interest

The authors have no potential conflicts of interest to declare.

Author Contributions

Sun XH, Zhang Sh and Tang YP were responsible for the conception and design of the study; Sun XH, Zhang Sh, Yang Z, Chen ZL, Yue SJ and Zhang S conducted the statistical analysis, drew the tables and pictures, and drafted the manuscript; Sun XH, Zhang Sh and Chen ZL retrieved the database, screened the trials, extracted the data, evaluated the methodological quality. All authors critically revised the manuscript and approved the final version.

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