A meta-analysis for Lianhua Qingwen on the treatment of Coronavirus disease 2019 (COVID-19)

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ABSTRACT

Background: Traditional Chinese medicine (TCM) has been proven to played a great important role on the treatment of COVID-19. As one of the drugs recommended in Chinese guidelines, Lianhua Qingwen Granules or Capsules (LQ) are widely used.This systematic review and meta-analysis amis to evaluate the clinical efficacy of LQ on the treatment of COVID-19.
Methods: Seven databases (PubMed, EMBASE, CENTRAL, CNKI, VIP, CBM and Wanfang) were searched to include all appropriate clinical trials that explore the efficacy of LQ on the treatment of COVID-19.
Result: A total of 3 trials including 245 COVID-19 patients were eventually enrolled.Compared with the control group,the LQ group showed great significant difference on reducing the rate of clinical change to severe or critical condition[$RR = 0.38$, 95 %CI (0.17,0.85), $P < 0.05$]and the fever time ($SMD =$-0.57,95 %CI (-0.96,-0.17), $P < 0.05$),as well as the significant improvement on the disappearance rate of the clinical symptoms: fever [$RR = 1.36$,95 %CI (1.14,1.61), $P < 0.05$],cough[$RR = 1.99$,95 %CI (1.39,2.86), $P < 0.05$],fatigue[$RR = 1.52$,95 %CI (1.15,2.01), $P < 0.05$] and anhelation [$RR = 4.18$,95 %CI (1.99,8.81), $P < 0.05$], but no significance on expectoration[$RR = 2.46$,95 %CI (0.81,7.51), $P < 0.05$].
Conclusion: The clinical application of LQ on the treatment of COVID-19 has significant efficacy in improving clinical symptoms and reducing the rate of clinical change to severe or critical condition. Nevertheless, due to the limited quantity and quality of the included studies, more and higher quality trials with more observational indicators are expected to be published.

1. Introduction

Since being defined as a "Public Health Emergency of International Concern" by WHO,the epidemic of COVID -19 is still increasingly getting worse at home and abroad.[1] Until now, hundreds of thousands of cases have been confirmed in almost every countries and regions of the globe, among them the death toll is still rising.[2]Undoubtedly,the situation shows that it has formed the trend of global pandemic, causing enormous impact and challenges in the global economy, the medical industry, sports, transportation and many other fields. However, it is also a great pity that there is no confirmed effective antiviral therapy for COVID -19,symptomatic and supportive treatment are still the main approaches.[3] Early detection, early diagnosis, early isolation and adherence to the integrated treatment of traditional Chinese medicine (TCM) and western medicine are the most important therapeutic measures for the China's successful fight against the epidemic[4] Especially for

the mild and moderate patients who account for the majority of COVID -19,TCM can relieve clinical symptoms and prevent the transition to severe disease, reduce the medical pressure and psychological burden of patients,which is of great significance for the prevention and treatment. Thanks to the previous successful experience in the prevention and treatment of SevereAcuteRespiratorySyndrom(SARS) and influenza A (H1N1), a large number of experimental and clinical meaningful studies on the efficacy of TCM therapy for viral infections have been carried out in China.[5]

LQ is a kind of compound Chinese patent medicine developed based on the theory of "plague" in TCM, which has been highly recommended and widely used in clinical work for many years.[6] It is made from two very classic and effective formulae,Yinqiao Powder and Ma Xing Shi Gan Tang.[7] It's main ingredients are the following 13 traditional Chinese medicines: Fructus Forsythiae (Lianqiao),Flos Lonicerae Japonicae (Jinyinhua), Herba Ephedrae (Mahuang),Semen Armeniacae Amarum (Kuxingren), Gypsum Fibrosum (Shigao), Radix Isatidis (Banlangen), Rhizoma Dryopteridis Crassirhizomatis (Mianmaguanzhong), Herba Houttuyniae(Yuxingcao), Herba Pogostemonis (Guanghuoxiang), Radix et Rhizoma Rhodiolae Crenulatae (Hongjingtian), Radix et Rhizoma Rhei (Dahuang) and Radix et Rhizoma Glycyrrhizae (Gancao),menthol (Bohe).Thanks to years of researches and development,LQ has been proved that has the curative effect of broad spectrum antivirus, anti-bacterial, antipyretic and anti-inflammatory,reducing cough and expectoration, immune regulation on the respiratory system and so on.[8] And because of that,LQ has been recommended over 20 times by the National Health Commission and the State Administration of TCM for the prevention and treatment of respiratory infectious diseases. Now being a representative Chinese patent medicine in response to respiratory public health events, LQ has been listed as recommended drug for many times by the diagnosis and treatment program of COVID -19 (Trial version 5),[9] and even been delivered to some countries such as Italy as priority aid drugs.In the past, there are several Meta-analysis studies have shown that LQ are more effective than oseltamivir on improving symptoms and reducing fever in people with influenza.[10-12] Since the outbreak of COVID -19, LQ combined with conventional treatment has also received a great deal of satisfactory clinical efficacy feedback from the battle front. Thus, this Meta-analysis focused on the effectiveness of LQ on the treatment of COVID-19 and summarized all the results of included trials, so as to provide further evidence for subsequent clinical treatment.

2. Methods

This study complied with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement[13]

2.1. Study selection

2.1.1. Types of studies

All trials that reported the clinical application of LQ on the treatment of COVID-19 were included.There were no statistical differences in basic data such as age, sex ratio, previous medical history and body temperature between the groups compared in the trials.Studies those meet the following conditions will be excluded: (1)There were no comparisons between the control group and the LQ group; (2)Duplicate studies; (3) There are other TCM drugs in the study except LQ; (4)There are obvious errors in data incomplete or unable to extract; (5)The outcomes do not match.

2.1.2. Types of participants

All enrolled patients must meet the diagnostic criteria of confirmed COVID-19 or suspected,including symptoms and signs, past history, laboratory examination, positive nucleic acid test or pulmonary CT imaging examination, [9]. Patients with the following conditions were excluded : (1)Severe or critical patients;(2)Acute respiratory diseases

that did not caused by 2019 novel coronavirus (2019-nCoV);(3)Any other chronic respiratory diseases or bacterial infections of the respiratory system such as suppurative tonsillitis, acute tracheal-bronchitis, sinusitis, otitis media and other respiratory diseases that affect the evaluation of clinical trials; (4)Asthma patients who need long-term treatment, chest X-ray or CT confirm the existence of serious lung interstitial lesions, bronchiectasis and other basic lung diseases;(5)Patients with severe primary immunodeficiency disease, acquired immunodeficiency syndrome, congenital respiratory tract abnormalities, congenital heart disease, abnormal lung development and other basic diseases.

2.1.3. Types of interventions

Follow the diagnosis and treatment guidelines,[9]all enrolled patients in the control group were given symptomatic treatment, nutritional support treatment, antiviral and antibacterial drugs and other routine treatment;while patients in the LQ group were treated with LQ(6 g/ bag, Sig.6 g,Tid,PO) on the basis of treatment in the control group. The observation time was 7 days.

2.1.4. Types of outcome measures

Primary outcome was the rate of clinical change to severe or critical condition.Secondary outcomes include

the fever time, the disappearance rate of the major symptoms (fever, fatigue, cough) and secondary symptoms (expectoration,anhelation).

2.1.5. Search strategies

For more comprehensive inclusion, the electronic databases from November 2019 up to March 2020 we searched are listed below:CENTRAL (2019–2020), EMBASE (2019–2020), PubMed (2019–2020),the Chinese National Knowledge Infrastructure (CNKI, 2019–2020), the Chinese Scientific Journal Database (VIP, 2019–2020), the Chinese Biomedical Literature Database(CBM, 2019–2020) and the Wanfang Database (2019–2020).By the means of using different relevant major medical subject heading and without the limitations of country,region and language,all relevant studies were retrieved. For avoiding some omissions, bibliography of all potential articles were also retrieved in detail.The key terms for literature searching were:('corona virus disease 2019'OR'COVID-19'OR'2019 novel coronavirus' OR'2019-nCoV' OR'novel coronavirus') AND ('Lianhua Qingwen Granules' OR'Lianhuaqingwen Granules' OR'Lianhua Qingwen Capsules' OR'Lianhuaqingwen Capsules'OR'Lianhua Qingwen'OR'Lianhuaqingwen'OR'Traditional Chinese medicine' OR'combine traditional Chinese and western medicine').

2.1.6. Data extraction and analysis

Two independent researchers (Master.Dai Xingzhen, Master.Wu Qihua) reviewe and evaluate all retrieved literatures,and then determine the final studies that met the inclusion criteria. Afterwards,they will extract some basic data from the included studies, including the first author's name, publication date, sample size, intervention and observation time of LQ group and control group, and outcome indicators.If any disagreement happens,a third researcher (Dr. Hairong Cai) will participate in the discussion and resolve it together.

All outcomes were Meta analyzed by The RevMan 5.3 software. Measurement data (continuous variables) were represented by standard mean variance (*SMD*) and 95 % confidence interval (95 % *CI*), while enumeration (binary variables) data were represented by relative risk (*RR*) and 95 % *CI*.I^2 test was used for heterogeneity test. If $P > 0.1$ and $I^2 < 50$ %, Fixed Effect model was used for analysis,while $P \leq 0.1$ and $I^2 \geq 50$ %, heterogeneity between the included studies was indicated, and Random Effect model was used for analysis.

2.1.7. Risk of bias assessment

Another two reviewers (Master.Zhang Weizhang,Dr. Huang Xiaoyan) independently evaluated the risk of bias of each study by using the assessment tool from the Cochrane Handbook. The criteria consisted

of the following seven items: ① Allocation concealment (selection bias);② Randonm sequence generation (selection bias); ③ Blinding of participants and personnel (performance bias); ④ Blinding of outcome assessments (detection bias); ⑤ Incomplete outcome data (attrition bias); ⑥ Selective reporting (reporting bias); ⑦ Other sources of bias. And egger analysis and funnel plot were used by the RevMan 5.3 software to analyze the potential publication bias of the article.

3. Results

3.1. Study identification

The process of study selection and identification was shown in Fig. 1. A total of 30 possibly relevant articles were selected by our study retrieval strategy,and all of them were first published online by Chinese in various magazines without printed version.No duplicate studies were found, so 30 articles were preliminarily screened. After reviewing titles and abstracts, 27 articles were excluded because they were theoretical studies,pharmacology research,review or different intervention. Then the remaining 3 articles were evaluated for full text. Ultimately,3 studies were assessed to be eligible in our review. among them 1 article [14] was randomized controlled trial (RCT) and 2 articles [15,16] were retrospective case-control study.

3.2. Study characteristics

The basic characteristics of the included trials are summarised in Table 1. A total of 245 COVID-19 patients were enrolled,and 135 in the LQ group and 110 in the control group. The sample sizes for 3 studies ranged from 42 to 102 and all participants were from China.Two diagnostic criteria source for COVID-19 were reported: Trial version 4 [17] and Trial version 5 [9] of the Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus Infection,which we found the diagnostic criteria were basically the same.Other details of interventions, course time and outcomes are listed in the table.

3.3. Risk of bias within studies

The methodological quality of the involved trials is shown in Figs. 2 and 3.

3.4. Outcome measures

3.4.1. Primary outcomes: the rate of clinical change to severe or critical condition

2 studies[14,15] reported the rate of clinical change to severe or critical condition in the course of treatment.The Meta-analysis result showed significant difference between two groups in the rate [$RR = 0.38$, 95 %CI (0.17,0.85), $P < 0.05$; Fig. 4]with no significant heterogeneity ($p = 0.90$, $I^2 = 0\%$),which means that patients in the LQ group are less likely to change to severe or critical condition.

3.4.2. Secondary outcomes

3.4.2.1. The fever time. 2studies[14,16] assessed the effect of LG on reducing the fever time compared with the control group.The combined effects of the independent trial results suggested that there was significant difference between two groups in the fever time[$SMD = -0.57$,95 % CI (-0.96,-0.17), $P < 0.05$,Fig. 5], with no significant heterogeneity ($P = 0.68$,$I^2 = 0\%$).

3.4.2.2. The disappearance rate of the major symptoms (fever, cough, fatigue). 3 studies [14–16] reported the difference in the disappearance rate of the major symptoms (fever, fatigue, cough) between the LQ group and the control group.And the meta-analysis results showed that LQ can significantly increase the disappearance rate of the major symptoms (fever [$RR = 1.36$,95 %CI (1.14,1.61), $P < 0.05$, Fig. 6]; cough [$RR = 1.99$,95 %CI (1.39,2.86), $P < 0.05$,Fig. 7]; fatigue[$RR = 1.52$,95 %CI (1.15,2.01), $P < 0.05$, Fig. 8]) with no significant heterogeneity (fever[$P = 0.80$,$I^2 = 0\%$]; cough [$P = 0.29$,$I^2 = 18$ %]; fatigue [$P = 0.77$,$I^2 = 0\%$]).
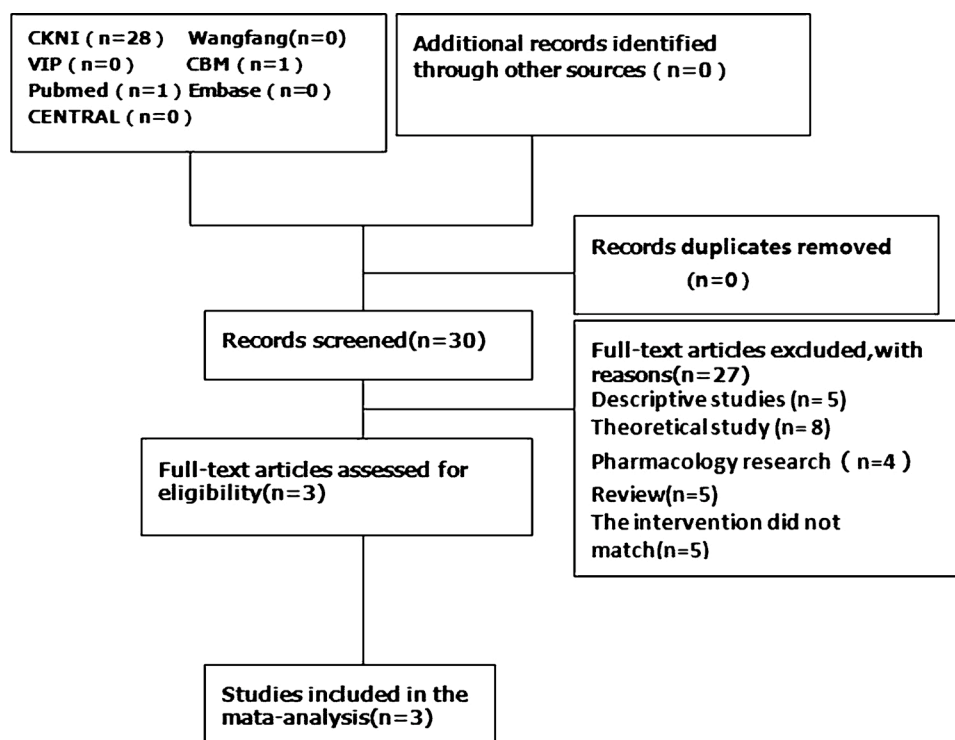

Fig. 1. The process of studies selection and identification.

Table 1

Basic characteristics of included Studies.

Studies	Diagnosis standard	n(T/C)	LQ group	Control group	Course(d)	Outcomes
Cheng Dz 2020[14]	FI	51/51	LQ + CT	CT	7	①②③④⑤⑥⑦
Lv Rb 2020[15]	FO	63/38	LQ + CT	CT	7	①③④⑤⑥⑦
Yao Kt 2020[16]	FO	21/21	LQ + CT	CT	N	②③④⑤⑥⑦

T：The Treatment Group;**C**：The Control Group;**FO**：Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus Infection (Trial version 4)；**FI:** Diagnosis and Treatment of Pneumonia caused by Novel Coronavirus Infection (Trial version 5); **LQ：** Lianhua Qingwen Granules;**CT:**Conventional Treatment;**N:**Not clear；① ：The rate of clinical change to severe or critical condition ；② ：The fever time ；③ ：The disappearance rate of fever ；④ ：The disappearance rate of fatigue ；⑤ ：The disappearance rate of cough ；⑥ ：The disappearance rate of expectoration ；⑦The disappearance rate of anhelation.

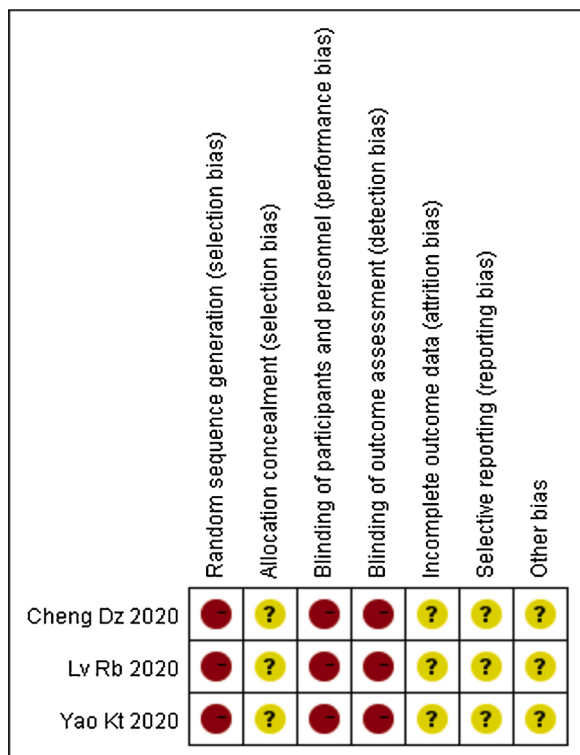**Fig. 2.** Risk of bias summary.

3.4.2.3. The disappearance rate of the secondary symptoms (expectoration, anhelation). 3 trials[14–16] recorded the comparison of the disappearance rate of the secondary symptoms (expectoration, anhelation) among two groups. Compared with the control group, LQ group can significantly improve the disappearance rate of the secondary symptoms (anhelation [$RR = 4.18,95\ \%CI$ (1.99,8.81)，$P < 0.05$, Fig. 9] with no significant heterogeneity ($P = 0.78, I^2 = 0\%$),but no significant difference on expectoration[$RR = 2.46,95\ \%CI$ (0.81,7.51)，$P > 0.05$, Fig. 10] with significant heterogeneity ($P = 0.04, I^2 = 69\ \%$)and Fixed Effect model was used for analysis.Meanwhile,sensitivity analysis was conducted by removing these studies one by one since the heterogeneity was substantial with $I^2 = 69\ \%$, resulting in significant changes when it's turn to one trial.[16]So heterogeneity may result from different research types was considered.

3.4.2.4. Evaluation of publication bias. Because of the limited number of included studies,there is no point in making funnel plot analysis to show the risk of publication bias.

4. Discussion

COVID-19 is caused by the 2019-nCoV, which has now becoming a global pandemic since it was first detected in Wuhan, China. 2019-nCoV has a variety of transmission routes (droplets, contact, aerosol, fecal mouth, etc.) and the characteristics of high infectivity in the general population,[9]that resulting in a large number of global human infections with some major symptoms such as fever, cough, shortness of breath,[18] and even dyspnea, acute respiratory failure, renal failure or death in some severe cases.[19] In the pathologic anatomy of COVID19 patients, medical experts found the presence of diffuse alveolar injury with cellular fiber mucous exudation, pulmonary interstitial lymphocyte infiltration, and decreased lymphocytes in blood, indicating the appearance of immune disorders.[20] Additionally,there was a large amount of white colloidal mucus in the trachea cavity and alveoli.[21]As a result,many serious clinical consequences such as acute respiratory distress syndrome, hypoxemia and metabolic acidosis will gradually
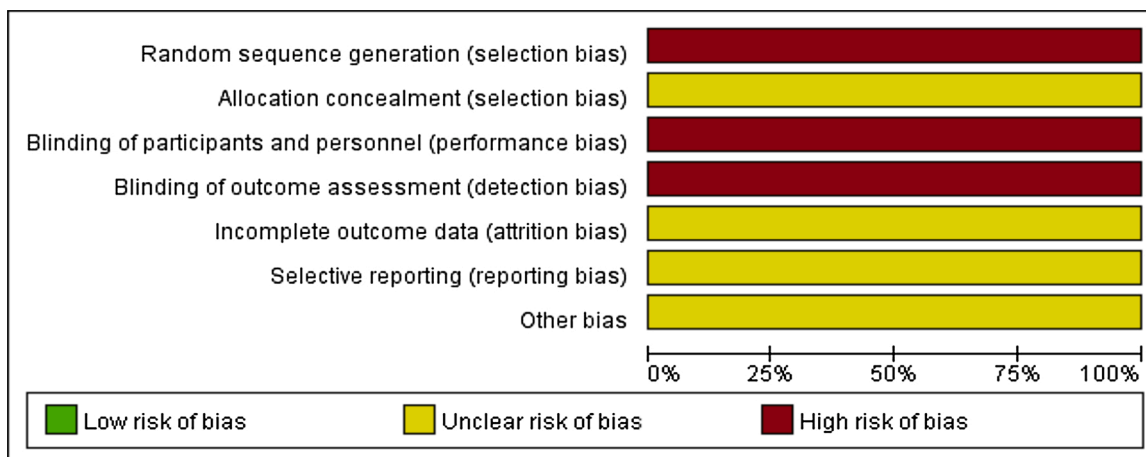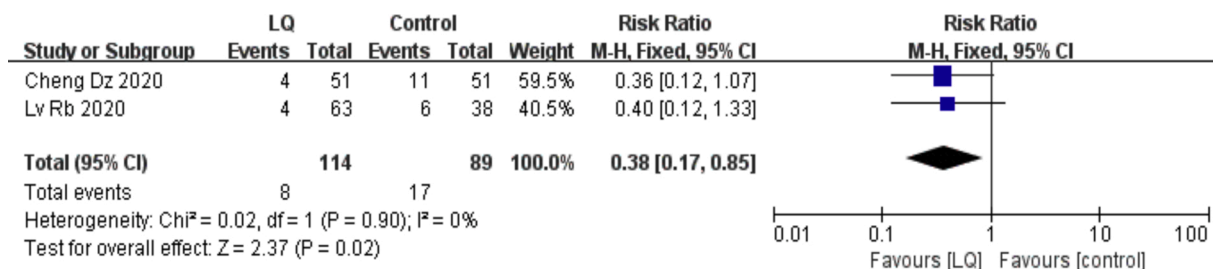

Fig. 3. Risk of bias graph.

Fig. 4. The rate of clinical change to severe or critical condition.
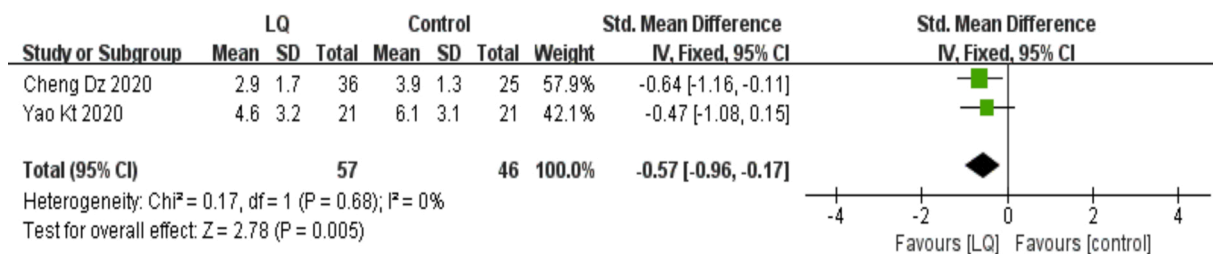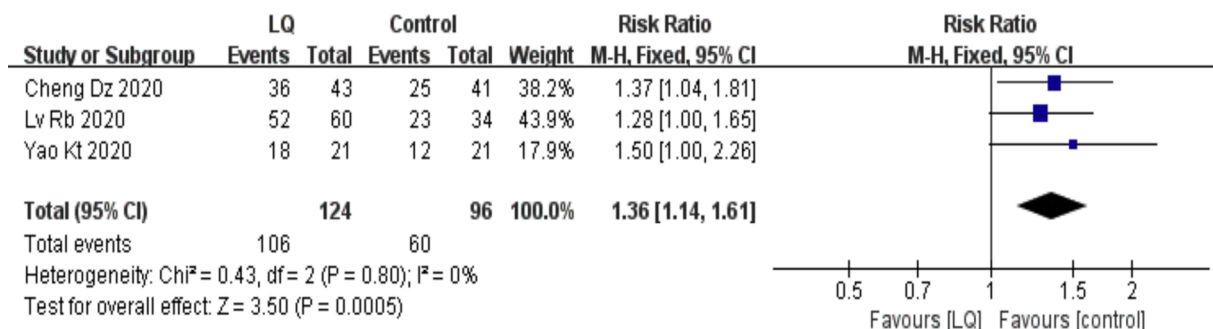

Fig. 5. The fever time.

Fig. 6. The disappearance rate of fever.

come to the fore.Therefore, the rapid elimination of inflammatory response transmitters, blocking the diffuse lung injury caused by inflammatory storms, and the regulation of immune disorders are of great significance for the control of patients' conditions and the prevention of the development of severe or critical illness[22]

In the absence of specific drugs and vaccines in China,the major clinical treatment is the integration of TCM and western medicine.[23]As a proprietary Chinese medicine strongly recommended by the guidelines in China, LQ playing an important role in this outbreak.A study on the network pharmacology and preliminary evidence of LQ on the treatment of COVID-19 speculates that many active ingredients of LQ have the holistic therapeutic effect on broad-spectrum antiviral, antibiosis, reducing cough and phlegm, immune regulation through multi-targets and multi-signal pathways. [24] In the past, some studies have proved that LQ can inhibit the SARS-CoV[25] and MERS-CoV activities in vitro. [26] Recently,a study have shown that the components of LQ, honeysuckle and forsythia may alleviate the damage of the virus to host cells by blocking many binding sites of human angiotensin-converting enzyme to SARS-CoV-2.[27]Another recent study researched by the Key Laboratory of Respiratory Diseases in China found that LQ could inhibit the activity of 2019-nCoV,reduce the number of viruses in the cell membrane and

cytoplasm, and inhibit the overactivation of cytokines.[28]Generally speaking,a large number of previou and recent researches results have provided the experimental and clinical basis for the treatment of COVID-19 with LQ. Fortunately, this Meta analysis results also shows that LQ plus routine therapy appears to improve the symptoms of fever, fatigue, cough and anhelation in COVID-19 patients,as well as to reduce the rate of clinical change to severe or critical condition.

However, from the perspective of research methodology, the limitations of this Meta-analysis mainly include:(1)All included studies were only first published online without the print version;(2)Limited quantity, low quality and small sample of the included studies may lead to the selectivity bias;(3) All included studies were published by Chinese, so there may be some regional differences and publication bias;(4)The included literatures include not only RCTs but also retrospective studies, which may result in some heterogeneity and reduce the persuasiveness of the results.In view of the current special epidemic period, many reasons like the short time since the epidemic outbreak, the high pressure of clinical work and the complexity and variability of treatment option may lead to the emergence of these limitations.We are looking forward to more multicenter, large-sample and high-quality research reports are published in the future.
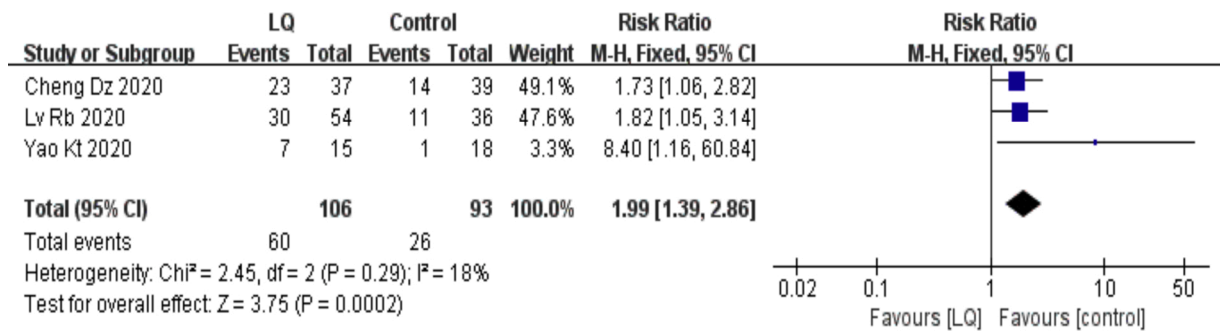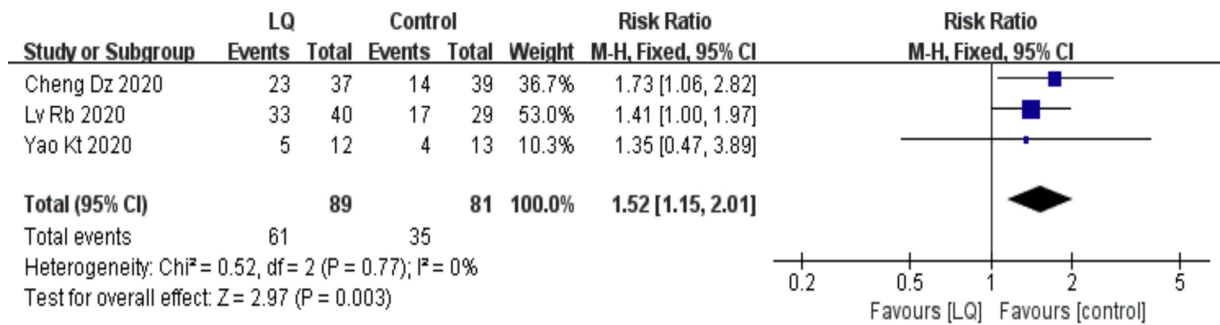
Fig. 7. The disappearance rate of cough.

Fig. 8. The disappearance rate of fatigue.
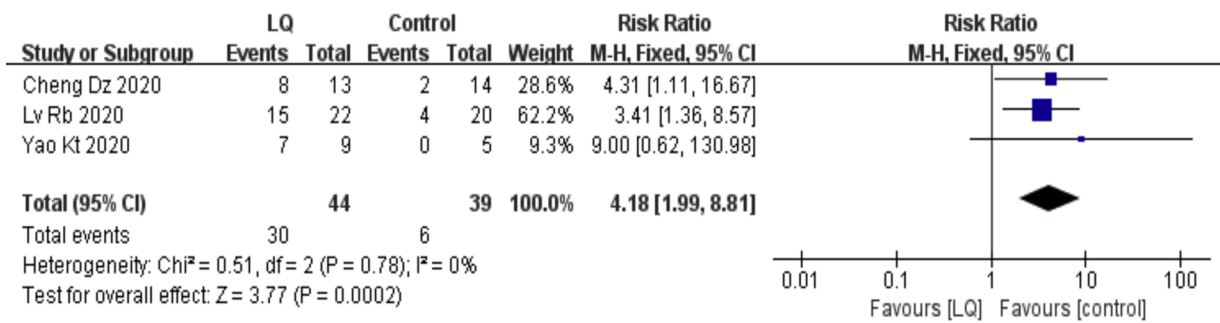

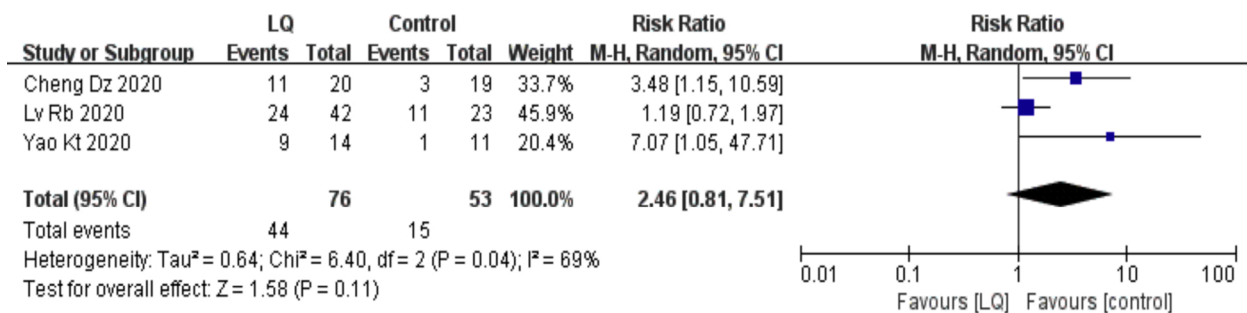**Fig. 9.** The disappearance rate of expectoration.

Fig. 10. The disappearance rate of anhelation.

5. Conclusions

To sum up, the results of this systematic review and Meta analysis support the clinical use of LQ on the treatment of COVID-19,which has significant efficacy in improving clinical symptoms and reducing the rate of clinical change to severe or critical condition. However, due to the insufficient quantity and quality of the included studies, more and higher quality studies with more observational indicators such as inflammatory factors, immune function and long-term follow-up of patients' prognosis are expected to be published.

PROSPERO registration

CRD42020182257

Author's contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZJ conceived and drafted the study. DX and WQ were responsible for literature retrieval, data collection and analysis. ZW and HX contributed to the revision of the manuscript. All authors contributed to the interpretation of the data and made critical comments on the manuscript to be published.

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Ethics and dissemination

Ethics approval is not required.

Research involving human participants and/or animals

Not applicable.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2021.102754.

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