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The clinical efficacy and safety research of Lianhuaqingwen (LHQW) in treatment of COVID-19: A systematic review and meta-analysis

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ABSTRACT

Background: Although vaccines have been launched, COVID-19 has not been effectively curbed, and the number of infections is increasing. Compared with western medicine, Traditional Chinese Medicine has made some achievements in the treatment of COVID-19, which should be paid attention to and play a greater role. As a classical Chinese medicine prescription for treating pestilence, Lianhuaqingwen (LHQW) has gone to many countries with the Chinese medical team to participate in the local fight against the epidemic, which has been widely recognized.

Methods: We searched MEDLINE, EMBASE, AMED, Chchane Central Register of Controlled Trials (CENTRAL), PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), VIP Information Database (VIP), Chinese Biomedical Literature Database (CBM), and Wanfang Database from inception up to November 24, 2021, which formed the basis for evidence used to formulate recommendations. Sixteen randomized controlled trials (RCTs) involving 1896 patients were enrolled. LHQW is a traditional Chinese medicine compound preparation, which contains 13 traditional Chinese medicine (TCM) components. Two dosage formulations of LHQW were included: granule and capsule. The most commonly used dosage formulation was granule (15/17, 88.24%), followed by capsule (2/17, 11.76%).

Conclusion: This systematic review and Meta analysis suggested that, in the treatment of COVID-19, LHQW Capsule (Granule) could not only significantly improve the fever symptoms, shorten the fever time, but also reduce the cough and fatigue symptoms, improve the clinical efficiency, improve the lung CT, significantly reduce the number of patients with mild to severe diseases, and have certain anti-inflammatory effect. And there is no server adverse events which support the safety of LHQW Capsule (Granule) for the treatment of COVID-19. As a classic formula of TCM, LHQW Capsule (Granule) could be used as potential candidates for COVID-19 in this battle.

1. Introduction

Currently, the cumulative number of confirmed cases on COVID-19 globally has been more than 250 million, and the cumulative number of deaths has reached 5.1 million. As a global pandemic, the epidemic continues to rage and shows no sign of stopping. Although vaccines have been launched, COVID-19 has not been effectively curbed, and the number of infections is increasing.

As a responsible pow, China has taken strict epidemic prevention measures from the beginning, actively responded to the epidemic situation and achieved good results, in which Traditional Chinese Medicine (TCM) has also played an important role. Many scholars have studied the treatment of COVID-19 with TCM, with certain experimental data records and comparative analysis [1–4]. For example, Yu et al. summed up a number of TCM clinical experts' prevention and treatment pro-

grams for providing advice, and found that the location of COVID-19 was mainly in the lung, and the etiology and pathogenesis were mostly the Qi of pestilence, mainly "dampness" [5]. The pharmacological research on the intervention of relevant Chinese herbal medicine, traditional Chinese medicine prescription and traditional Chinese medicine preparation on covid-19 inflammatory storm was summarized [6]. Compared with western medicine, Traditional Chinese Medicine has made some achievements in the treatment of COVID-19, which should be paid attention to and play a greater role.

As a classical Chinese medicine prescription for treating pestilence, LHQW has gone to many countries with the Chinese medical team to participate in the local fight against the epidemic, which has been widely recognized. Although many articles have studied meta-analysis of LHQW in treatment of COVID-19, there are two obvious limitations. Firstly, the experimental results referred to in some articles were not

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comprehensive, which may be because the epidemic was still spreading in China at that time, and some new experimental results came out after the publication of the articles. Secondly, the analysis indicators in published results [7–12] were not comprehensive. After the epidemic subsided in China, it is necessary to conduct a comprehensive combing and analysis. Literature [7] did not use randomized controlled experiments to study the effect of LHQW on COVID-19. Literature [8] focused on children, which should also be excluded. The control group studied in literature [9] was LHQW, and the experimental group was western medicine combined with LHQW. Literature [10–12] have a few experiments and a few indicators for comparison.

Therefore, in this study, a systematic review of RCTs was performed to evaluate the current clinical efficacy and safety of LHQW in the treatment of COVID-19. At a time when the epidemic is still spreading around the world, such research is of great significance. It is not only an exchange of experience in treatment methods, but also an opportunity for the world to understand traditional Chinese medicine.

2. Methods

The study was conducted in accordance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13] and registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021292658).

2.1. Selection criteria

2.1.1. Types of studies

All RCTs trials that reported the clinical application of LHQW in the treatment of COVID-19 were included. There were no statistical differences in basic data such as size, age, sex ratio between the groups compared in the trials. Studies meeting the following conditions were excluded: (1) No distinction was made between the experimental group and the control group, or the experimental group did not include LHQW; (2) Duplicate studies reporting the same results; (3) The data was incomplete or cannot be extracted due to obvious errors; (4) No indicators of concern in the outcomes.

2.1.2. Types of participants

All Patients with COVID-19 could be enrolled in this review. There were no restrictions on gender, age and nationality, to ensure the inclusion of all relevant studies.

2.1.3. Types of interventions

The dosage forms of LHQW prescription contain granule and capsule [14,15]. Patients in the treatment group should be treated by LHQW Capsule or LHQW Granule and Conventional Western Medicine (CMW). Patients in the control group should be treated by CWM. CWM included symptomatic treatment, nutritional support treatment, antiviral and antibacterial drugs and other routine treatment. The name, dosage and dose of CWM in the treatment group and the control group must be the same. There are no restrictions on the dosage form, type, quantity or course of treatment of LHQW. The observation time ranged from 7 days to 14 days.

2.1.4. Types of outcome measures

The primary outcome measure was defined as lung CT, clinical cure rate, ranging from mild to critical cases, death, cough, fever, fatigue, length of hospital stay, time for nucleic acid conversion, total score of clinical symptoms; The second type was other clinical symptoms, including sore throat, chest tightness, anhelation, expectoration, muscle pain, sickness, headache, anorexia, diachoea; The third type was biological inflammation, including blood cell (WBC), Procalcitonin (PCT), lymphocyte (LYM), and C-reactive protein (CRP).

2.2. Search strategies

We searched MEDLINE, EMBASE, AMED, Chchrene Central Register of Controlled Trials (CENTRAL), PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), VIP Information Database (VIP), Chinese Biomedical Literature Database (CBM), and Wanfang Database from inception up to November 24, 2021, which formed the basis for evidence used to formulate recommendations. Relevant studies were retrieved by using different relevant main medical subject headings, regardless of national, regional and language restrictions. In order to avoid some omissions, the bibliography of potential articles were also searched manually as possible as we can. The key terms of literature search were: ('corona virus disease 2019' OR 'COVID-19' OR '2019 novel coronavirus' OR 'SARS-Cov-2' OR 'novel coronavirus pneumonia') AND ('Lianhua Qingwen Granule' OR 'Lianhuaqingwen Granule' OR 'Lianhua Qingwen Capsule' OR 'lian hua qing wen') AND ('clinical trial' OR 'clinical study' OR 'Lianhua Qingwen' OR 'randomized controlled trial' OR 'RCT').

2.3. Inclusion criteria and study selection

The inclusion criteria comprised research papers related to case reports and case data, which reported the COVID-19 treatment with LHQW granules. Single arm research results were excluded because only some effects were verified without comparison, so its authority is unknown. In order to avoid repetition and wrong weight of research papers cited or discussed more frequently, review papers, meta-analysis, editorial letters and expert opinions are not included. The meeting minutes were also excluded because their complete research report could not be evaluated and their scientific rigor had not been peer reviewed. Considering that the research content belongs to the category of traditional Chinese medicine, studies published in Chinese language were included.

All articles identified by searching seven databases are imported into Endnote for filtering. Screening included two rounds of studies. In the first round, two researchers (Fang L and Sheng HF) independently evaluated all retrieved studies separately by reviewing titles, abstracts and key terms. In the second round of screening, full texts of the articles determined during the initial screening was retrieved and read in detail to assess their eligibility. Possible inconsistencies in the study selection process were discussed with a third reviewer (Zhan Y) to reach a consensus.

2.4. Data extraction

Two independent researchers (Fang L and Sheng HF) collected information on study characteristics, treatment details, patient characteristics, and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Basic data from the included studies, including the name of the first author, publication date, sample size, intervention and observation time of experimental group and control group, and outcome indicators. If any disagreement happens, a third researcher (Qu LP) will participate in the discussion and resolve it together.

2.5. Assessment of methodological quality

The methodological quality of the included trials was also independently assessed by two reviewers (Fang L and Zhan Y). According to the tools of Cochrane Collaboration, six fields of risk of bias (ROB) were evaluated as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (analysis bias), selective reporting (reporting bias), other bias. Each field was evaluated as "Yes"(low ROB), "No" (high rob), or "Unclear" (unclear ROB), and was given the same weight, and the overall bias of the trails was obtained.

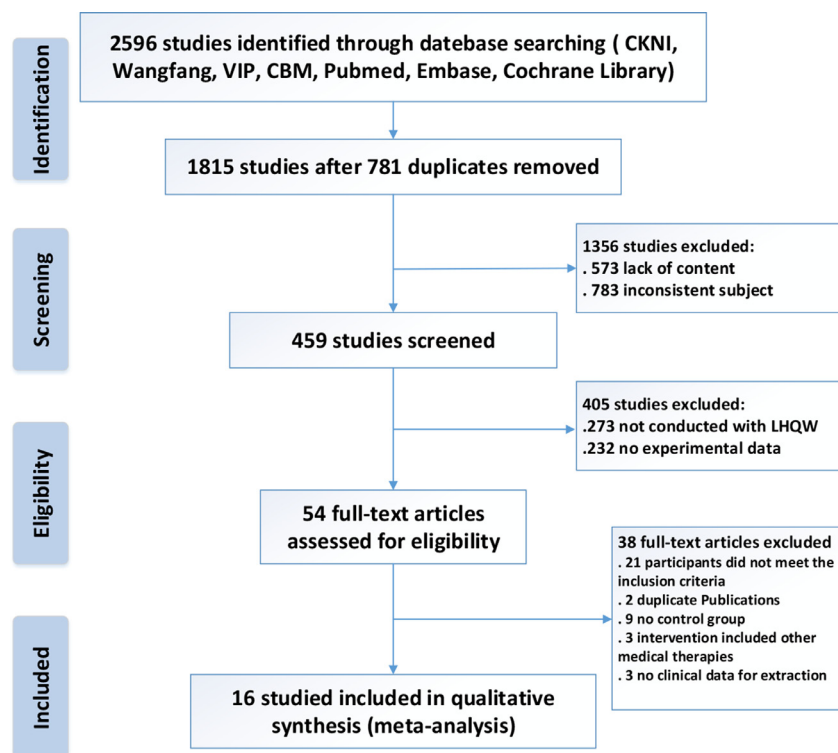


Fig. 1. Flow diagram for study inclusion and exclusion process.

2.6. Data analysis

We utilized Revman 5.3 software to conduct the meta-analysis of dichotomous and continuous outcome measures extracted from original studies. Measurement data (continuous variables) were represented by standard mean variance (SMD) and 95% confidence interval (95% CI), while enumeration data (binary variables) 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 selected, while $P \leq 0.1$ and $I^2 \geq 50\%$, heterogeneity between included studies was identified, Random Effect model was applied. Funnel plot was also used to assess publication bias. It was considered as marked difference when $P < 0.05$.

3. Results

3.1. Study identification

The initial search retrieved 2596 results from the above 7 electronic databases. All articles identified were imported into Endnote for screening. After removing duplicates, 1815 papers were remained. In the screening by reviewing titles, abstracts, and key terms related to LHQW and COVID-19, 1356 publications were excluded for less relevant, most of them were reviews, commentaries, editorials, case reports, case series, experimental researches, data mining articles. The rest 459 articles were identified to be potentially relevant and then assessed for eligibility. 405 articles were excluded as follows: 273 articles did not conducted with LHQW, and 232 articles had no experimental data. After that, 38 articles were further excluded: participants did not meet the inclusion criteria ($n = 21$); duplicate publications ($n = 2$); no control group ($n = 9$); intervention included other medical therapies ($n = 3$); no clinical data for extraction ($n = 3$). Ultimately, 16 articles met all the inclusion criteria and were included in this review (Fig. 1).

3.2. Study characteristics

Basic features of the included studies and subjects were presented in Table 1. Among the 16 included trials, 6 were multi-centered tri-

als [16–18,22,24,29] and the rest 10 were single-centered trials. All of the 16 studies were conducted in mainland China since 2020. 4 articles were online published in advance with English language [16,22,24,28], and the rest were in Chinese. There were altogether 1896 patients enrolled in this review, with the sample size ranged from 18 to 158. All the included trials evaluated the effects of LHQW combined with CWM treatment compared to CWM treatment alone. The name, usage, dosage of western medicine used in trial group should be the same as used in control group. There is no trial utilized LHQW placebo. Treatment duration varied from 6 to 15 days. All clinical outcomes were analyzed in detail in the following chapters.

3.3. Assessment of methodological quality

As shown in Table 2, the methodological quality of the enrolled studies was evaluated based on the criteria in Cochrane handbook. Detailed information on sequence generation of randomization was reported in 6 trials (6/16, 37.5%) [16,20,23–25,29]. Specific method of allocation concealment was not described in this review. 2 trials reported no application of blinding [24,29]. 3 trials [16,24,29] were reported blinding of participants and personnel, and 2 trials [24,29] were reported blinding of outcome assessment. We gave the same weight to the evaluation indicators and got an overall evaluation: 3 trials were medium risk and the other 13 were low risk.

3.4. Description of LHQW

LHQW is a traditional Chinese medicine compound preparation, which contains 13 traditional Chinese medicine (TCM) components: Forsythia Fruit (Lianqiao, Fructus Forsythiae Suspensae), Honeysuckle bud and flower (Jinyinhua, Flos Lonicerae), Ephedra (Mahuang, Herba Ephedrae), Bitter Apricot Seed (Kuxingren, Semen Armeniacae Amarum), Gypsum (Shigao, Gypsum Fibrosum), Indigowoad Root (Banlangen, Radix Isatidis), Male fern rhizome (Mianma Guanzhong, Rhizoma Dryopteris Crassirhizomae), Heartleaf houttuynia herb (Yuxingcao, Herba Houttuyniae), Cablin patchouli herb (Huoxiang, Herba

Table 1
Basic characteristics of selected trials and subjects.

No.	References	Trial groups				Control groups				Treatment duration	Outcome measures
		Size	Age (yrs)	T/C (M/F)	Intervention	Size	Age (yrs)	T/C (M/F)	Intervention		
1	Hu et al. [16]	142	50.4 ± 15.2	79/63	LHQW capsule (1.4 g/time, 3 times / day) + CWM	142	51.8 ± 14.8	71/71	CWM treatment (supportive therapy, oxygen therapy, antiviral therapy, symptomatic treatment)	14	A1,A2,A3,A5,A6,A9,B2,C5
2	Cheng et al. [17]	51	55.5 ± 12.3	26/25	LHQW granule (6 g / time, 3 times / day) + CWM	51	55.8 ± 11.6	27/24	CWM treatment (supportive therapy, antiviral therapy, antibiotics, symptomatic treatment)	7	A1,A2,A3,A5,A6,A7,B2,B3,B4,B5,B6,B8
3	Yao et al. [18]	21	57.1 ± 14.0	16/5	LHQW granule (6 g / time, 3 times / day) + CWM	21	62.4 ± 12.3	12/9	CWM treatment	7	A3,A5,A6,A7,B1,B2,B3,B4,B5,B6,B7,B8,B9
4	Lv et al. [19]	63	59.12±16.56	28/35	LHQW granule (6 g / time, 3 times / day) + CWM	38	60.20±17.01	18/20	CWM treatment (nutritional support treatment, symptomatic treatment, antiviral and antibiotic)	10	A3,A5,A6,A7,B1,B2,B3,B4,B5,B6,B7,B8,B9,C5
5	Yu et al. [20]	147	48.27±9.56	82/65	LHQW granule (6 g / time, 3 times / day) + CWM	148	47.25±8.67	89/59	Abidol (0.2 g/time, 3 times / day), moxifloxacin hydrochloride tablets (0.4 g/time, 1 time / day), ambroxol hydrochloride tablets (30 mg / time, 3 times / day)	7	A1,A2,A3,A4,A6,A7,A10,B1, B2,C1,C2,C3,C4,C5
6	Tian et al. [21]	24	46.6 ± 14.0	15/9	LHQW granules (4 capsules / time, 3 times / day) + CWM	23	41.2 ± 14.8	11/12	CWM treatment	7	A1,A4,A5,A6,A7,A8,A10,B4,C5
7	Shen et al. [22]	158	59.08±15.55	82/76	LHQW granule (6 g / time, 3 times / day) + CWM	90	58.73±15.60	49/41	CWM treatment	7	C1,C2,C4
8	Chen et al. [23]	30	50.16±5.11	17/13	LHQW granules (4 capsules / time, 3 times / day) + CWM	30	49.52±5.06	18/12	CWM treatment (Antiviral therapy)	7	A5,A5,A6,A7,A8,C2,C4,C5
9	Xiao et al. [24]	94	54.58±13.76	58/36	LHQW granules(1bag/time,3 times / day) + CWM	94	54.06±13.90	16/26	CWM treatment (Antiviral therapy with oral oseltamivir, Antimicro therapy)	7	A3,A5,A6,A7,A9,B2,B6,B8,B9

(continued on next page)

Table 1 (continued)

No.	References	Trial groups				Control groups				Treatment duration	Outcome measures
		Size	Age (yrs)	T/C (M/F)	Intervention	Size	Age (yrs)	T/C (M/F)	Intervention		
10	Chen et al. [25]	35	44.75±4.92	18/17	LHQW capsule (1.4 g / time, 2 times / day), atomized interferon α -2b + CWM	35	45.21±4.68	20/15	CWM treatment	15	A1,A2,A5,A6,A7,A10,B1,B2
11	Yu et al. [26]	85	50.0 ± 5	43/42	LHQW capsule (4 capsules / time, 3 times / day)	38	51.5 ± 5	19/19	Abidol (0.2 g / time, 3 times / day)	8	A2,A3,A8
12	Xu et al. [27]	26	56.62±11.58	11/15	LHQW granule (6 g / time, 3 times / day) + CWM	26	52.04±13.41	11/15	CWM treatment (antiviral, anti infection, hormone and auxiliary supporting drugs, nutritional support treatment)	10	A1,A2,A6,A8,A9,C1,C2,C3,C4
13	Liu et al. [28]	68	59.5 ± 15.6	32/36	Arbidol(200 mg,3 times a day), LHQW(1400 mg, 3times a day)	40	54.8 ± 19.1	15/25	Arbidol(200 mg,3 times a day)	14	A1,A2,C1,C3,C4,C5
14	Sun et al. [29]	32	45.4 ± 14.10	17/15	LHQW granule (6 g / time, 3 times / day) + CWM	25	42.0 ± 11.70	11/14	CWM treatment (antiviral drugs α -Interferon, supportive therapy)	14	A1,A3,A5,A6,A7,B1,B4
15	Xia et al. [30]	34	54.18±13.08	17/17	LHQW granule (6 g / time, 3 times / day) + CWM	18	53.67±12.70	6/12	CWM treatment (antiviral drugs, anti infective drugs, auxiliary supportive drugs)	7	A1,A2,A3,A4,A6,A8,A9, A10,C5
16	Shi et al. [31]	49	47.94±14.46	26/23	Chinese patent medicine (LHQW, etc.) + CWM	18	46.72±17.40	10/8	CWM treatment (oxygen therapy, antiviral and symptomatic support treatment)	6	A1,A2,A3,A4,A6,A8,A9,A10

Abbreviation: C: control; F: female; M: male; NR: Not reported; A1: lung CT, A2: clinical cure rate, A3: ranging from mild to critical cases, A4: death, A5: cough, A6: fever, A7: fatigue, A8: length of hospital stay, A9: time for nucleic acid conversion, A10: total score of clinical symptoms; B1: sore throat, B2: chest tightness, B3: anhelation, B4: expectoration, B5: muscle pain, B6: sickness, B7: headache, B8: anorexia, B9: diarrhoea; C1:WBC, C2: PCT, C3: LYM, C4: CRP, C5: adverse effects.

Table 2
Risk of bias summary according to Cochrane handbook.

References	A	B	C	D	E	F	G	Over all
Hu et al. [16]	+	?	-	+	+	?	?	medium
Cheng et al. [17]	?	?	?	?	+	?	?	low
Yao et al. [18]	?	?	?	?	+	?	?	low
Lv et al. [19]	?	?	?	?	+	?	?	low
Yu et al. [20]	+	?	?	?	+	?	?	low
Tian et al. [21]	?	?	?	?	+	?	?	low
Shen et al. [22]	?	?	?	?	+	?	?	low
Chen et al. [23]	+	?	?	?	+	?	?	low
Xiao et al. [24]	+	?	-	-	+	?	?	medium
Chen et al. [25]	+	?	?	?	+	?	?	low
Yu et al. [26]	?	?	?	?	+	?	?	low
Xu et al. [27]	?	?	?	?	+	?	?	low
Liu et al. [28]	?	?	?	?	+	?	?	low
Sun et al. [29]	+	?	-	-	+	?	?	medium
Xia et al. [30]	?	?	?	?	+	?	?	low
Shi et al. [31]	?	?	?	?	+	?	?	low

Abbreviation: A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); F: Selective reporting (reporting bias); G: Other bias; +: Low risk; -: High risk;?: Unclear.

Pogostemonis), Rhubarb Root and Rhizome (Dahuang, Radix Et Rhizoma Rhei), Rose-boot (Hongjingtian, Herba Rhodiolae), menthol, and Liquoric Root (Gancao, Radix Glycyrrhizae).

In the prescription, Forsythia Fruit clear away heat and detoxification, eliminate swelling and disperse knot; Honeysuckle bud and flower, Male fern rhizome clear away heat and detoxification; Ephedra perspires to dissipate cold, relieve lung and asthma; Bitter Apricot Seed relieve cough and asthma, moisten intestines and defecate; Indigowoad Root not only clear away heat and detoxification, but also make blood cool and benefit the throat; Rose-boot relieve asthma and cough. All the drugs play the effects of clearing away plague and detoxification, dispersing lung and relieving heat. Pharmacological studies show that Honeysuckle and Indigowoad Root have many functions, such as antiviral, bacteriostasis, anti-inflammatory, antipyretic, and enhancing immunity. This is consistent with the pathogenesis of infectious diseases and the pathological characteristics of Western medicine.

Two dosage formulations of LHQW were included: granule and capsule. The most commonly used dosage formulation was granule (15/17, 88.24%), followed by capsule (2/17, 11.76%).

3.5. Main outcomes assessment

3.5.1. Lung CT

Ten trials assessed the efficacy of LHQW on lung CT [16,17,20,21,25,27-31]. There were 608 patients in experimental

group and 526 in control group. A significant improvement in lung CT was identified by LHQW in this meta-analysis (10 trials, $n = 1134$; $RR = 1.23$; 95% CI: 1.14-1.34; $I^2 = 49\%$, $P < 0.00001$; Fig. 2a).

3.5.2. Clinical cure rate

Clinical cure rate was defined as the following 4 discharge criterion in guideline for the diagnosis and treatment of COVID-19 infected pneumonia: a) body temperature returned to normal for more than 3 days, b) respiratory symptoms improved significantly, c) pulmonary imaging showed obvious absorption of inflammation, and d) two consecutive times of novel coronavirus nucleic acid test negative in respiratory tract (the sampling interval shall be at least 1 day) [7].

Nine trials evaluated the effects of LHQW on clinical cure rate [16,17,20,26-28,30,31]. There were 637 patients in experimental group and 516 in control group. LHQW exhibited a significant improvement on clinical cure rate (9 trials, $n = 1153$; $RR = 1.24$; 95% CI: 1.08-1.42; $I^2 = 76\%$, $P = 0.003$; Fig. 2b).

3.5.3. Range from mild to server or critical condition

In this study effects of LHQW on ranging from mild to critical cases were evaluated in 10 trials [16-20,24,26,29-31]. There were 693 patients in experimental group and 566 in control group. A significant improvement on ranging from mild to critical cases was observed by CHM (10 trials, $n = 1259$; $RR = 0.48$; 95% CI: 0.35 to 0.65; $I^2 = 0\%$, $P < 0.00001$; Fig. 2c).

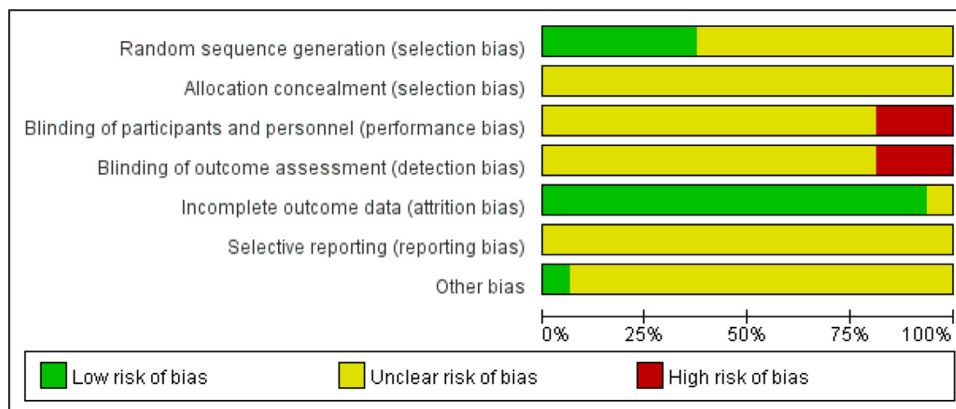
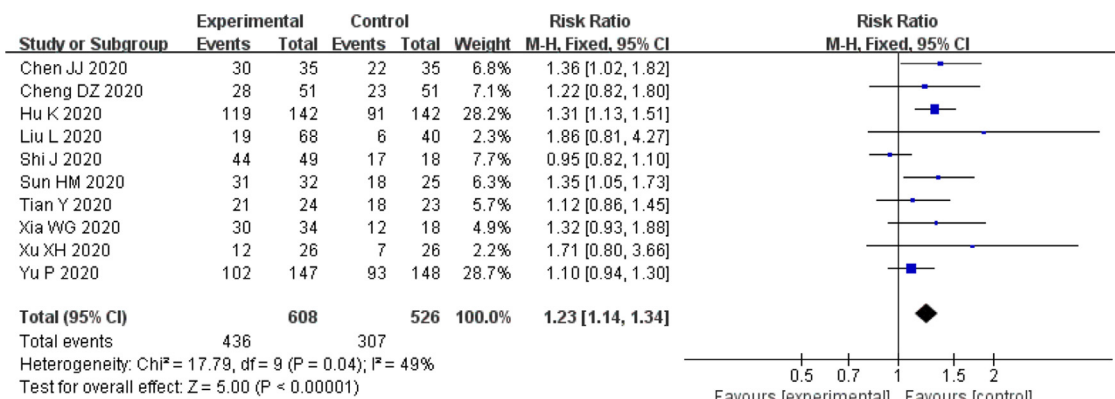
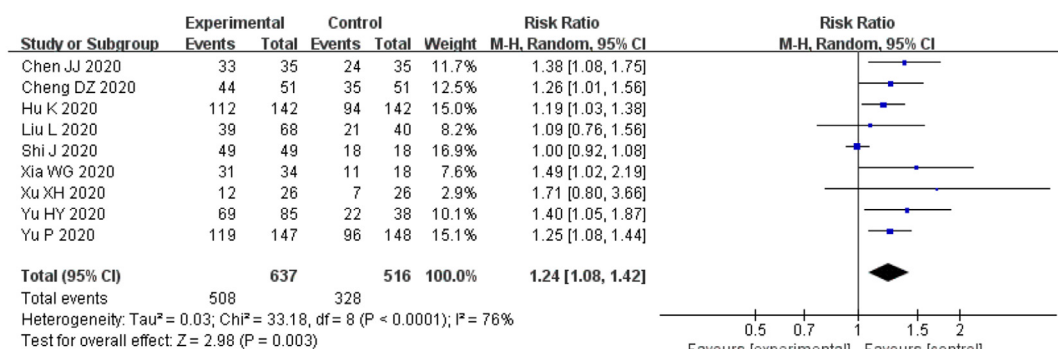


Fig. 2. Risk of bias graph.

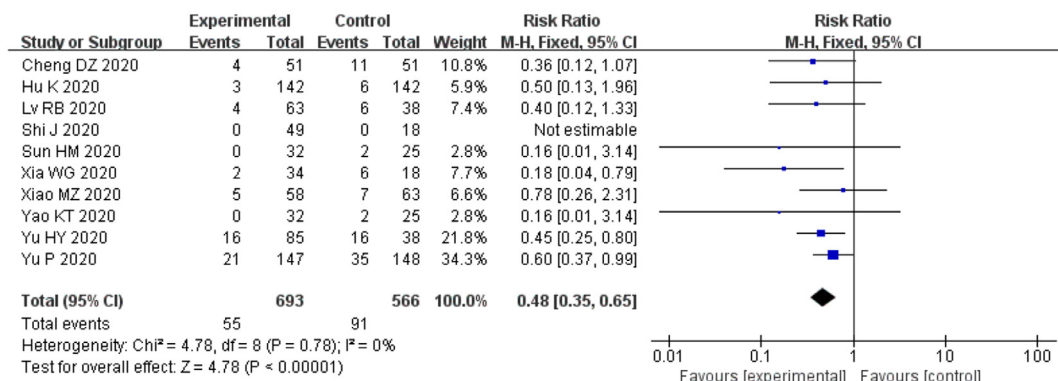
Forest plot of the effects of LHQW for outcomes of (a) Lung CT, (b) Clinical cure rate, (c) Clinical change from mild to server or critical condition, (d) Death.



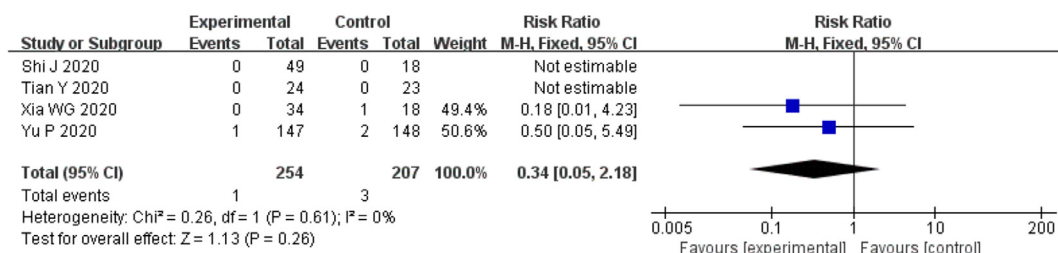
(a) Lung CT



(b) Clinical cure rate



(c) Range from mild to server or critical condition



(d) Death

Fig. 2. Continued

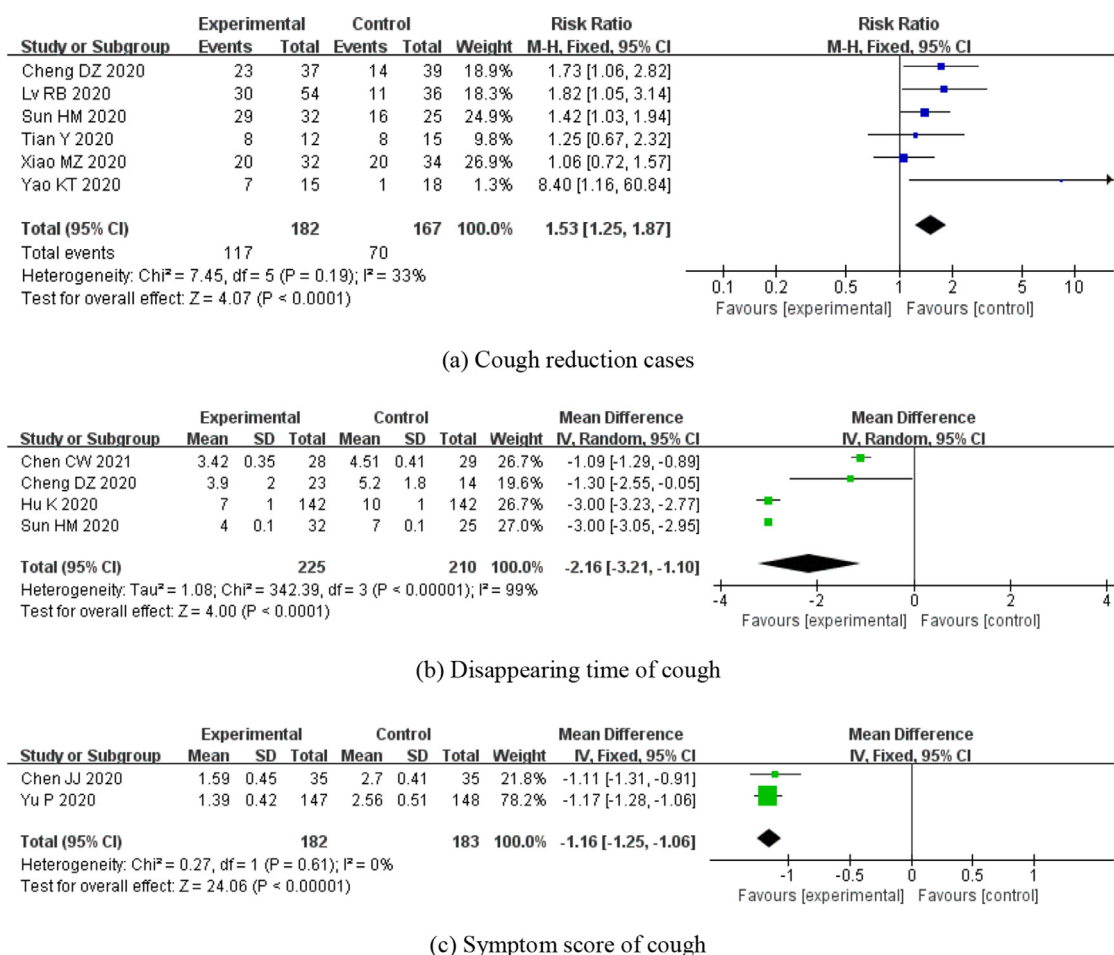


Fig. 3. Forest plot of the effects of LHQW for outcomes of (a) Cough reduction cases, (b) Disappearing time of cough, (c) Symptom score of cough.

3.5.4. Death

The effect of LHQW on death was reported in 4 trials [20,21,30,31]. There were 254 patients in experimental group and 207 in control group. Meta analysis showed no significant difference on death between LHQW and CWM (4 trials, $n = 461$; RR = 0.34; 95% CI: 0.05–2.18; $I^2 = 0\%$, $P = 0.26$; Fig. 2d).

3.5.5. Cough

The symptom of cough was reported in all the trials, and only 9 were enrolled in this review [16–19,21,23–25,29]. Among them, 6 studies reported number of cough reduction cases [17–19,21,24,29], 4 studies reported disappearing time of cough [16,17,23,29], and 2 studies reported disappearing time of cough [20,25].

In the field of number of cough reduction cases, there were 182 patients in experimental group and 167 in control group. A significant improvement on number of cough reduction cases was observed by LHQW in this study (6 trials, $n = 349$; RR = 1.53; 95% CI: 1.25–1.87; $I^2 = 33\%$, $P < 0.0001$; Fig. 3a).

In the field of disappearing time of cough, there were 225 patients in experimental group and 210 in control group. Meta-analysis showed a significant improvement on disappearing time of cough by LHQW (4 trials, $n = 435$; WMD: -2.16 ; 95% CI: -3.21 to -1.10 ; $I^2 = 99\%$, $P < 0.0001$; Fig. 3b).

For symptom score of cough, there were 182 patients in experimental group and 183 in control group. Compared to CWM, a significant improvement on symptom score of cough was observed by LHQW (2 trials, $n = 365$; WMD: -1.16 ; 95% CI: -1.25 to -1.06 ; $I^2 = 0\%$, $P < 0.00001$; Fig. 3c).

3.5.6. Fever

The symptom of fever was reported in 13 trials [16–21,23–25,27,29–31]. Among them, 6 studies reported number of fever reduction cases [17–19,21,24,29], 9 reported fever reduction time [16–19,21,23,27,30,31], and 2 reported disappearing time of fever [20,25].

In the field of number of fever reduction cases, there were 174 patients in experimental group and 149 in control group. Meta analysis showed no significant difference on number of fever reduction cases between LHQW and CWM (6 trials, $n = 323$; RR = 1.25; 95% CI: 0.96–1.64; $I^2 = 0\%$, $P = 0.10$; Fig. 4a).

In the field of disappearing time of fever, there were 409 patients in experimental group and 310 in control group. The aggregated results suggested that disappearing time of fever was significantly improved by LHQW (9 trials, $n = 719$; WMD: -1.05 ; 95% CI: -1.35 to 0.74 ; $I^2 = 88\%$, $P < 0.00001$; Fig. 4b).

For symptom score of fever, there were 182 patients in experimental group and 183 in control group. Compared to CWM, a significant improvement on symptom score of fever was observed by LHQW (2 trials, $n = 365$; WMD: -0.56 ; 95% CI: -0.61 to -0.50 ; $I^2 = 0\%$, $P < 0.00001$; Fig. 4c).

3.5.7. Fatigue

The effect of CHM on fatigue was evaluated in 9 studies [17–21,23–25,29]. Among them, 6 studies reported number of fatigue reduction cases [17–19,21,24,29], 3 reported individual symptom score [16,17,23], and 2 reported disappearing time of fatigue [20,25].

For number of fatigue reduction cases, there were 149 patients in experimental group and 140 in control group. A significant improvement on number of fatigue reduction cases by LHQW was identified in

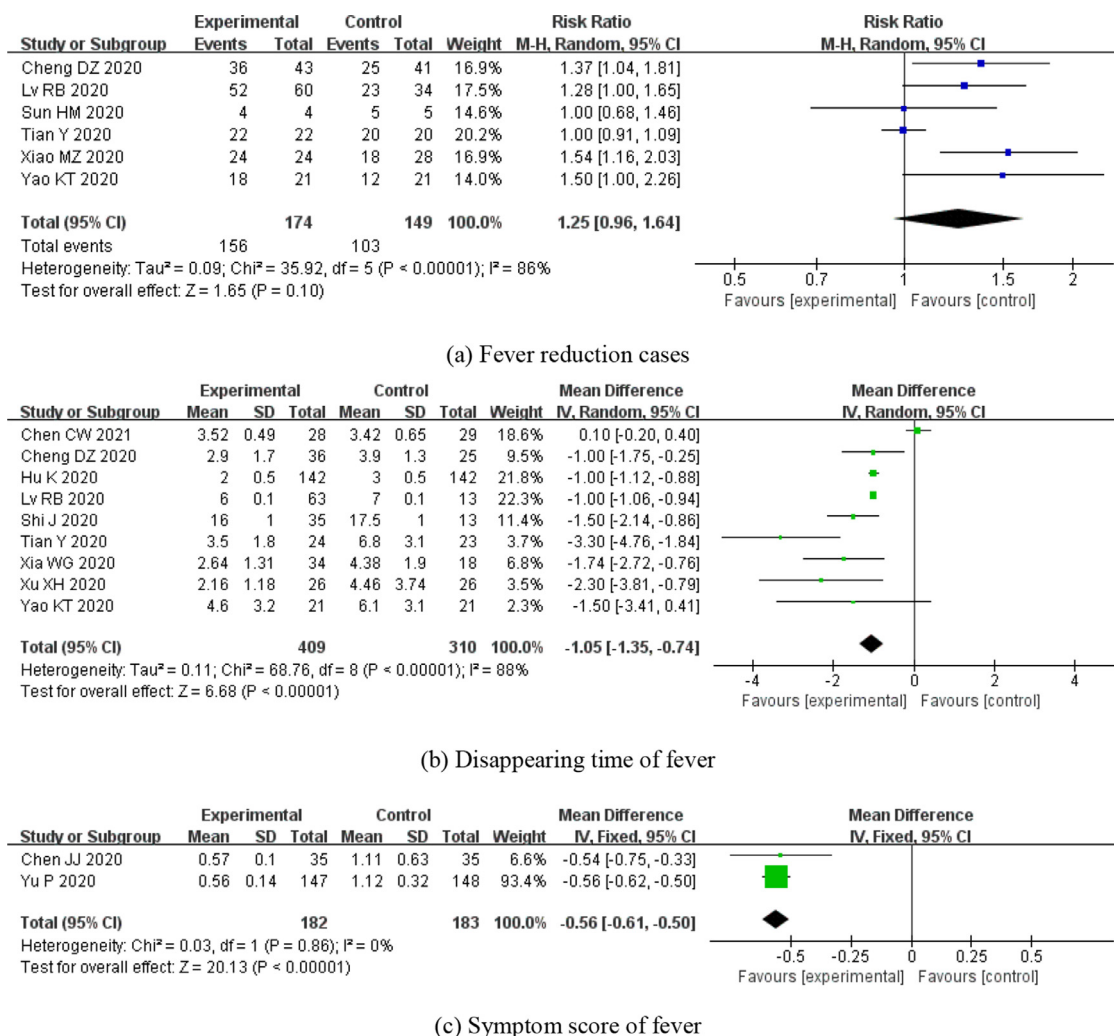


Fig. 4. Forest plot of the effects of LHQW for outcomes of (a) Fever reduction cases, (b) Disappearing time of fever, (c) Symptom score of fever.

this meta analysis (6 trials, $n = 289$; RR = 1.41; 95% CI: 1.19–1.68; $I^2 = 45%$, $P = 0.0001$; Fig. 5a).

For disappearing time of fatigue, there were 189 patients in experimental group and 183 in CWM group. Improvement on disappearing time of fatigue was also identified in LHQW group compared to CWM group (3 trials, $n = 372$; WMD: -2.25 ; 95% CI: -3.13 to -1.36 ; $I^2 = 85%$, $P < 0.00001$; Fig. 5b).

For symptom score of fatigue, there were 182 patients in experimental group and 183 in control group. Compared to CWM, no significant improvement on symptom score of fatigue was observed by CHM (2 trials, $n = 365$; WMD: 0.12 ; 95% CI: -0.82 to 1.06 ; $I^2 = 96%$, $P = 0.80$; Fig. 5c).

3.5.8. Length of hospital stay

Six trials evaluating length of hospital stay were included for further analysis in this study [21,23,26,27,30,31]. There were 246 patients in experimental group and 152 in control group. Meta-analysis showed a significant reduction on length of hospital stay by LHQW (6 trials, $n = 398$; WMD: -0.80 ; 95% CI: -1.37 to -0.23 ; $I^2 = 49%$, $P = 0.006$; Fig. 6a).

3.5.9. Time for nucleic acid conversion

The effect of LHQW on time for nucleic acid conversion was reported in 6 trials [16,23,24,27,30,31]. There were 337 patients in experimental group and 296 in control group. Compared with CWM, a significant improvement on time for nucleic acid conversion was identified by

LHQW (6 trials, $n = 633$; RR = -1.98 ; 95% CI: -3.11 – -0.85 ; $I^2 = 88%$, $P = 0.0006$; Fig. 6b).

3.5.10. Total score of clinical symptoms

Clinical symptoms including fever, dry cough, expectoration, fatigue, sore throat, itchy throat, chest tightness, asthma, shortness of breath, poor appetite, diarrhea, nausea, vomiting, abdominal distention, and abdominal pain were reported in all the included studies [16–31]. As fever, dry cough, and fatigue were main clinical symptoms of COVID-19, individual symptom score, disappearing time, number of improved cases, and total score of clinical symptom were summarized.

Total score of clinical symptom was evaluated in 5 studies [20,21,25,30,31]. There were 290 patients in experimental group and 241 in control group. Meta analysis revealed a significant improvement on total score of clinical symptom (5 trials, $n = 531$; WMD: -2.67 ; 95% CI: -3.54 to -1.79 ; $I^2 = 65%$, $P < 0.00001$; Fig. 6c).

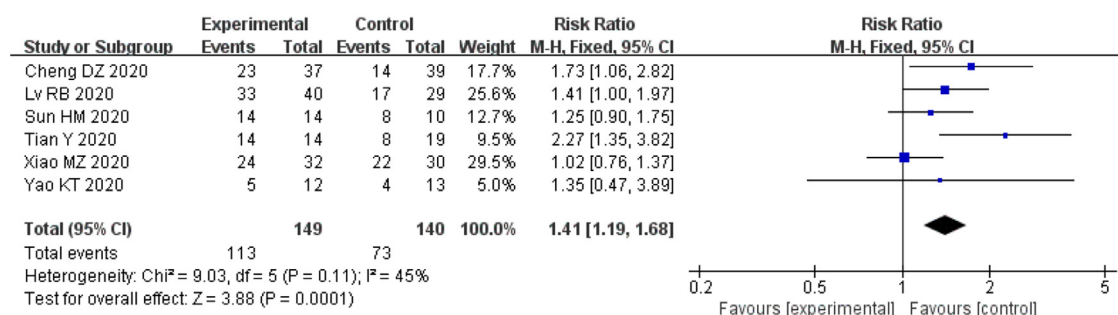
3.6. Other clinical symptoms assessment

3.6.1. Sore throat

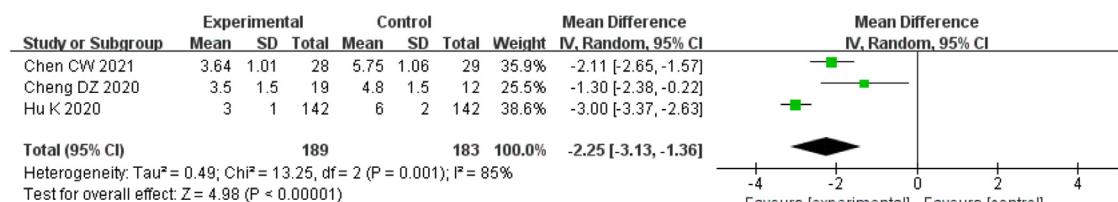
The effect of LHQW on sore throat was evaluated in 5 studies [18–20,25,29]. Among them, 3 studies reported number of sore throat reduction cases [18,19,29], and 2 reported individual symptom score [20,25].

For number of sore throat reduction cases, there were 10 patients in experimental group and 9 in control group. Meta analysis showed no significant difference on number of sore throat reduction cases between

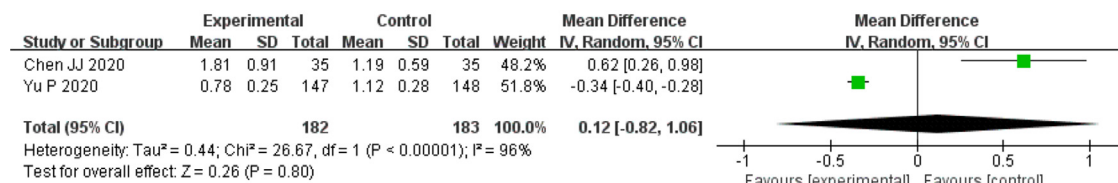
identified in this meta analysis (6 trials, $n = 289$; $RR = 1.41$; 95 % CI: 1.19–1.68; $I^2 = 45\%$, $P = 0.0001$; Fig. 5a).



(a) Fatigue reduction cases



(b) Disappearing time of fatigue



(c) Symptom score of fatigue

Fig. 5. Forest plot of the effects of LHQW for outcomes of (a) Fatigue reduction cases, (b) Disappearing time of fatigue, (c) Symptom score of fatigue.

LHQW and CWM (3 trials, $n = 19$; $RR = 2.00$; 95% CI: 0.19–20.61; $I^2 = 0\%$, $P = 0.56$; Fig. 7a).

For symptom score of sore throat, there were 182 patients in experimental group and 183 in control group. Compared to CWM, a significant improvement on symptom score of sore throat was observed by LHQW (2 trials, $n = 365$; $WMD: -0.98$; 95% CI: -1.69 to -0.28 ; $I^2 = 98\%$, $P < 0.006$; Fig. 7b).

3.6.2. Chest tightness

The effect of LHQW on chest tightness was evaluated in 6 studies [17–20,24,25]. Among them, 4 studies reported number of chest tightness reduction cases [17–19,24], and 2 reported individual symptom score [20,25].

For number of chest tightness reduction cases, there were 79 patients in experimental group and 70 in control group. Meta analysis showed a significant improvement on number of chest tightness reduction cases by LHQW (4 trials, $n = 149$; $RR = 1.36$; 95% CI: 1.02–1.83; $I^2 = 25\%$, $P = 0.04$; Fig. 7c).

For symptom score of chest tightness, there were 182 patients in experimental group and 183 in control group. Compared to CWM, a significant improvement on symptom score of chest tightness was observed by LHQW (2 trials, $n = 365$; $WMD: -0.47$; 95% CI: -0.57 to -0.36 ; $I^2 = 0\%$, $P < 0.00001$; Fig. 7d).

3.6.3. Anhelation

Three trials evaluating anhelation reduction cases were included for further analysis [17–19]. There were 39 patients in experimental group

and 38 in control group. Compared to CWM, a significant improvement on number of anhelation reduction cases was observed by LHQW (3 trials, $n = 77$; $RR = 3.43$; 95% CI: 1.68–7.02; $I^2 = 0\%$, $P = 0.0007$; Fig. 8a).

3.6.4. Expectoration

In this study five trials evaluating expectoration reduction cases were included for further analysis [17–19,21,29]. There were 104 patients in experimental group and 79 in control group. No significant difference on number of expectoration reduction cases between LHQW and CWM was identified in this meta analysis (5 trials, $n = 183$; $RR = 1.53$; 95% CI: 0.85–2.75; $I^2 = 62\%$, $P = 0.16$; Fig. 8b).

3.6.5. Muscle pain

Three trials evaluating muscle pain reduction cases were included for further analysis [17–19]. There were 24 patients in experimental group and 25 in control group. A significant improvement on number of muscle pain reduction cases by LHQW was identified in this meta analysis (3 trials, $n = 49$; $RR = 2.09$; 95% CI: 1.15–3.80; $I^2 = 2\%$, $P = 0.02$; Fig. 8c).

3.6.6. Sickness

Four trials evaluating sickness reduction cases were included for further analysis [17–19,24]. There were 37 patients in experimental group and 20 in control group. No significant difference on number of sickness reduction cases between LHQW and CWM was identified in this meta analysis (4 trials, $n = 57$; $RR = 1.12$; 95% CI: 0.79–1.61; $I^2 = 37\%$, $P = 0.52$; Fig. 8d).

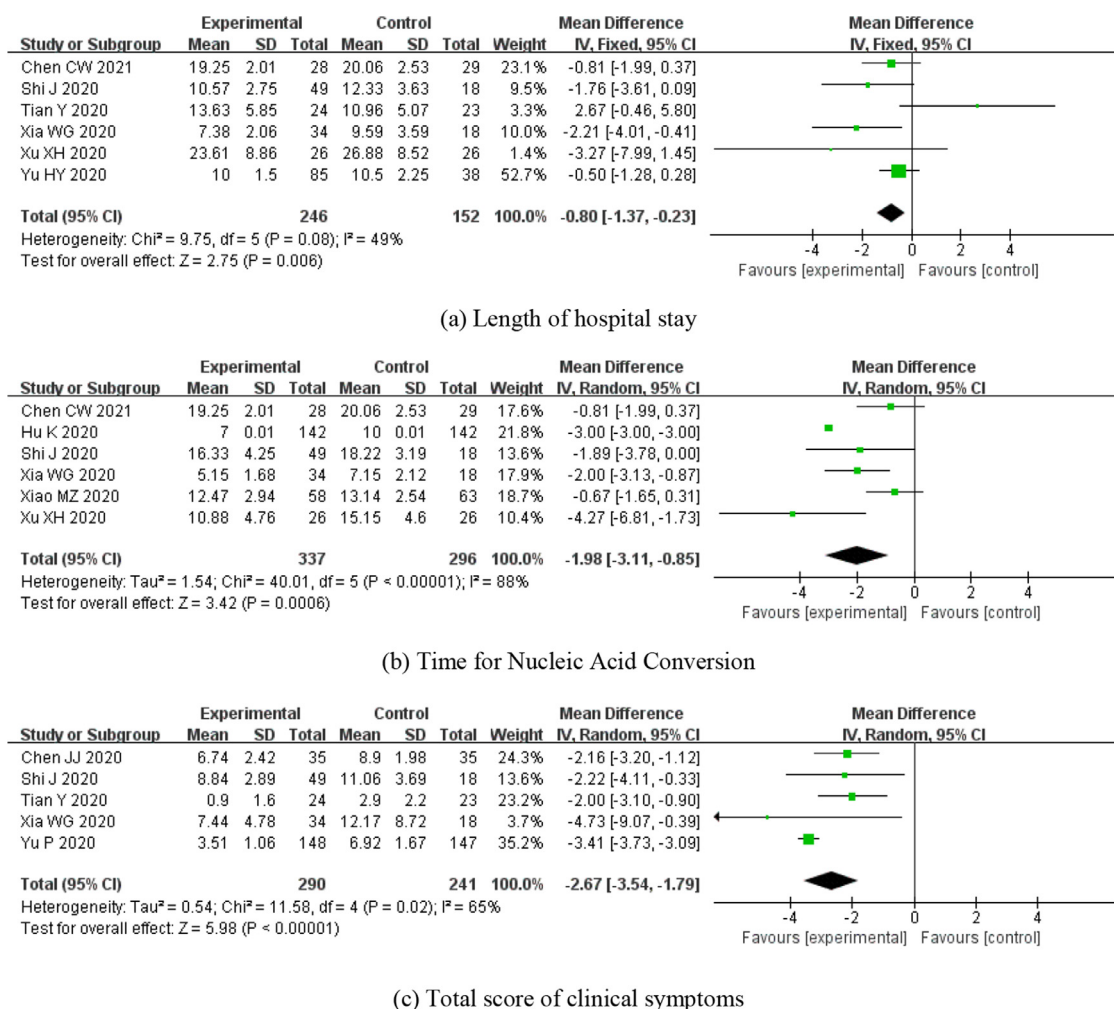


Fig. 6. Forest plot of the effects of LHQW for outcomes of (a) Length of hospital stay, (b) Time for Nucleic Acid Conversion, (c) Total score of clinical symptoms.

3.6.7. Headache

Two trials evaluating headache reduction cases were included for further analysis [18,19]. There were 10 patients in experimental group and 7 in control group. No significant difference on number of headache reduction cases between LHQW and CWM was identified (2 trials, $n = 17$; $\text{RR} = 1.36$; 95% CI: 0.67–2.80; $I^2 = 0\%$, $P = 0.40$; Fig. 9a).

3.6.8. Anorexia

Four trials evaluating anorexia reduction cases were included for further analysis [17–19,24]. There were 88 patients in experimental group and 85 in control group. No significant difference on number of anorexia reduction cases between LHQW and CWM was identified (4 trials, $n = 173$; $\text{RR} = 1.72$; 95% CI: 0.83–3.58; $I^2 = 86\%$, $P = 0.14$; Fig. 9b).

3.6.9. Diachocia

Three trials evaluating diachocia reduction cases were included for further analysis [18,19,24]. There were 21 patients in experimental group and 11 in control group. No significant difference on number of diachocia reduction cases between LHQW and CWM was identified (3 trials, $n = 32$; $\text{RR} = 1.09$; 95% CI: 0.69–1.72; $I^2 = 0\%$, $P = 0.72$; Fig. 9c).

3.7. Inflammatory biomarkers

3.7.1. WBC

Four trials evaluated the efficacy of LHQW on number of WBC [20,22,27,28]. There were 331 patients in experimental group and 372

in control group. Meta-analysis showed no significant difference between LHQW and CWM on the number of WBC in patients with COVID-19 (4 trials, $n = 703$; $\text{WMD} = 0.17$; 95% CI: -0.46 to 0.80 ; $I^2 = 73\%$, $P = 0.60$; Fig. 10c).

3.7.2. PCT

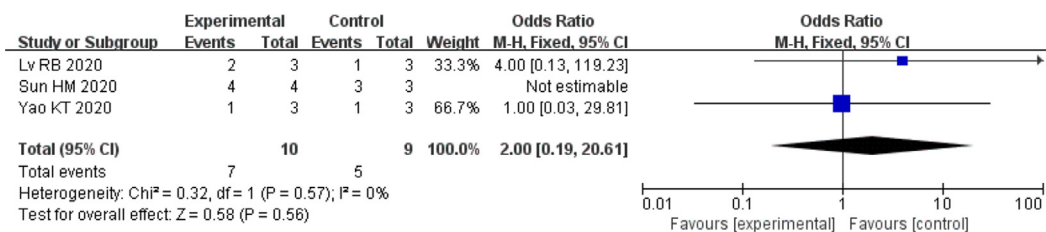
Four trials evaluated the efficacy of LHQW on number of PCT [20,22,23,27]. There were 288 patients in experimental group and 354 in control group. Meta-analysis showed a significant improvement between LHQW and CWM on the number of PCT in patients with COVID-19 (4 trials, $n = 642$; $\text{WMD} = -0.18$; 95% CI: -0.25 to -0.11 ; $I^2 = 99\%$, $P < 0.00001$; Fig. 10b).

3.7.3. LYM

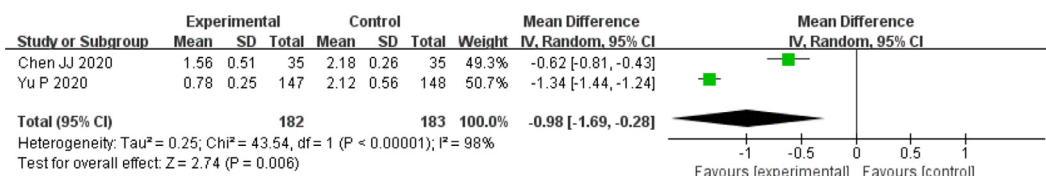
Effects of LHQW on the level of LYM were assessed in 3 trials [20,27,28]. There were 241 patients in experimental group and 214 in control group. Meta-analysis showed no significant difference between LHQW and CWM on the level of LYM (3 trials, $n = 455$; $\text{WMD} = 0.11$; 95% CI: -0.02 to 0.24 ; $I^2 = 72\%$, $P = 0.09$; Fig. 10c).

3.7.4. CRP

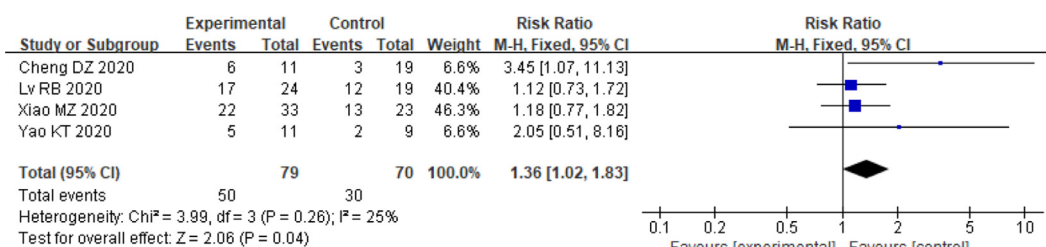
Effects of LHQW on the level of CRP were assessed in 5 trials [20,22,23,27,28]. There were 358 patients in experimental group and 399 in control group. Meta-analysis showed no significant difference between LHQW and CWM on the level of CRP (5 trials,



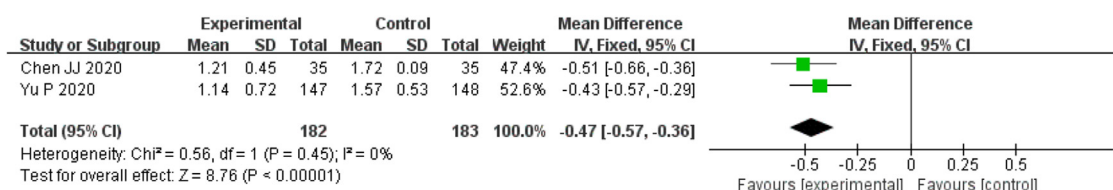
(a) sore throat reduction cases



(b) Symptom score of sore throat



(c) chest tightness reduction cases



(d) Symptom score of chest tightness

Fig. 7. Forest plot of the effects of LHQW for outcomes of (a) Sore throat reduction cases, (b) Symptom score of sore throat, (c) chest tightness reduction cases, (d) Symptom score of chest tightness.

n = 757; WMD: -2.61; 95% CI: -6.17 to 0.96; I² = 98%, P = 0.15; Fig. 10d).

3.7.5. Adverse effects

In this review, 7 trials reported adverse effects (7/16, 43.75%) [16,19–21,23,28,30]. Among them, no adverse effect was identified in both LHQW and CWM groups [20,21,28,30]. Adverse effects in the rest 2 trials included gastrointestinal reactions (abdominal distention, diarrhea, abdominal pain, nausea, vomiting, belching, acid reflux, poor appetite), headache, dizziness, drowsiness, abnormal liver function, renal dysfunction, and drug allergy [16,19]. All of the reported adverse effects were released spontaneously in both LHQW and CWM groups. Meta-analysis identified that no significant difference between CHM and CWM was identified (7 trials, n = 946; RR = 0.73; 95% CI: 0.38–1.40; I² = 60%, P = 0.34; Fig. 10e).

3.7.6. Publication bias

Publication bias was detected by the funnel plot of indicators studied. The asymmetry showed a mild publication bias, and the results were reliable in the study (Fig. 11).

4. Discussion

4.1. Summary of evidence

Traditional Chinese medicine classifies COVID-19 into the category of epidemic febrile disease, because it is highly infectious and belongs to epidemic febrile disease. The clinical manifestations of this disease are diverse, mostly respiratory symptoms [32]. In China's COVID-19 outbreak, Traditional Chinese Medicine (TCM) participated deeply in the whole process and participated in the eight versions of the Chinese medicine treatment plan, and successfully launched a number of effective Chinese medicines, such as three drugs and three parties. The efficacy of TCM has been tested in practice. The COVID-19 prevention and treatment programs issued by National Health Commission recommended LHQW Capsule (Granule). Therefore, quantitative study of the effect and safety of LHQW Capsule (Granule) in the prevention and treatment of COVID-19 has a important practical significance. There have been some previous studies on the role of TCM on COVID-19 treatment, based on which we further focused on the utility of LHQW Capsule (Granule) on COVID-19. To our knowledge, this is the first rigorously designed systematic review and meta-analysis of all published RCTs to

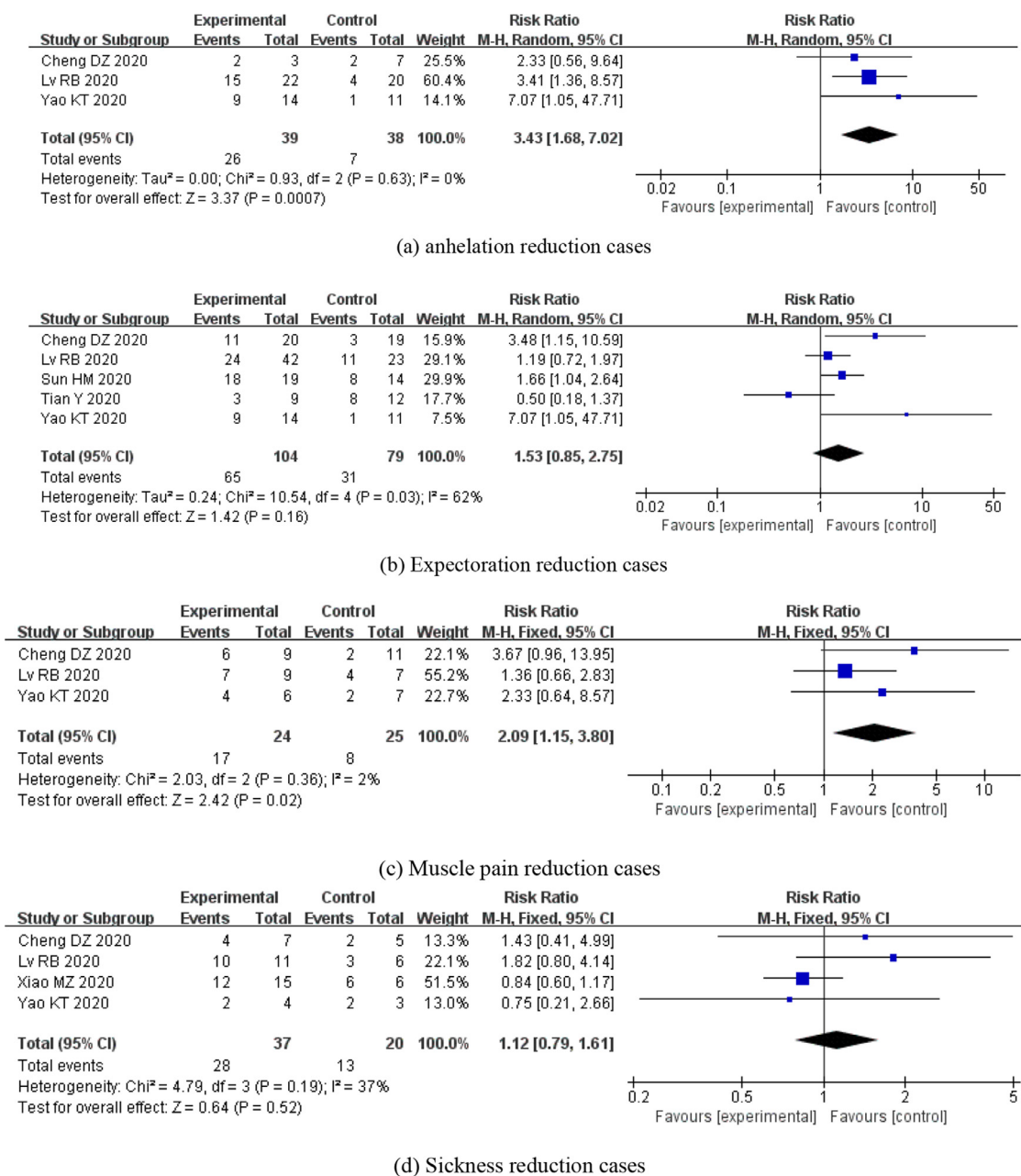


Fig. 8. Forest plot of the effects of LHQW for outcomes of (a) Anhelation reduction cases, (b) Expectoration reduction cases, (c) Muscle pain reduction cases, (d) Sickness reduction cases.

evaluate the effectiveness and safety of LHQW Capsule (Granule) on COVID-19 in English.

There are two points to focus on in this study. Firstly, when the data quoted in different references are different, we insisted on starting from the original text and carefully verified it. Secondly, in order to make full use of the data, we carefully and reasonably processed the data: adding individual data to increase the effectiveness of a group of data; selecting data scientifically. For example, when selecting the index of fever disappearance rate, we selected the total number of fever, not the number of the whole group. Thirdly, extensive literature search was conducted on relevant clinical trials published in Chinese and English databases. The number of RCTs included in the published research results was no more than 5. In our study, up to 16 trials were included, and the conclusions are more convincing and feasible. In the absence of specific drugs and high mortality of COVID-19, these data and research results are very valuable and timely.

Secondly, large number of objective and subjective outcome measures were utilized to assess the efficacy of LHQW comprehensively, which were divided into three types. The first type was the main clinical symptoms, including lung CT, clinical cure rate, ranging from mild to critical cases, death, cough, fever, fatigue, length of hospital stay, time for nucleic acid conversion, total score of clinical symptoms; The second type was other clinical symptoms, including sore throat, chest tightness, anhelation, expectoration, muscle pain, sickness, headache, anorexia, diarrhoea; The third type was biological inflammation, including WBC, PCT, LYM, CRP, adverse effects, and publication bias.

The whole research findings from 16 trials involving 1896 patients showed that lung CT, clinical cure rate, ranging from mild to critical cases, number of cough reduction cases, disappearing time of cough, symptom score of cough, disappearing time of fever, symptom score of fever, number of fatigue reduction cases, disappearing time of fatigue, length of hospital stay, time for nucleic acid conversion, total score of

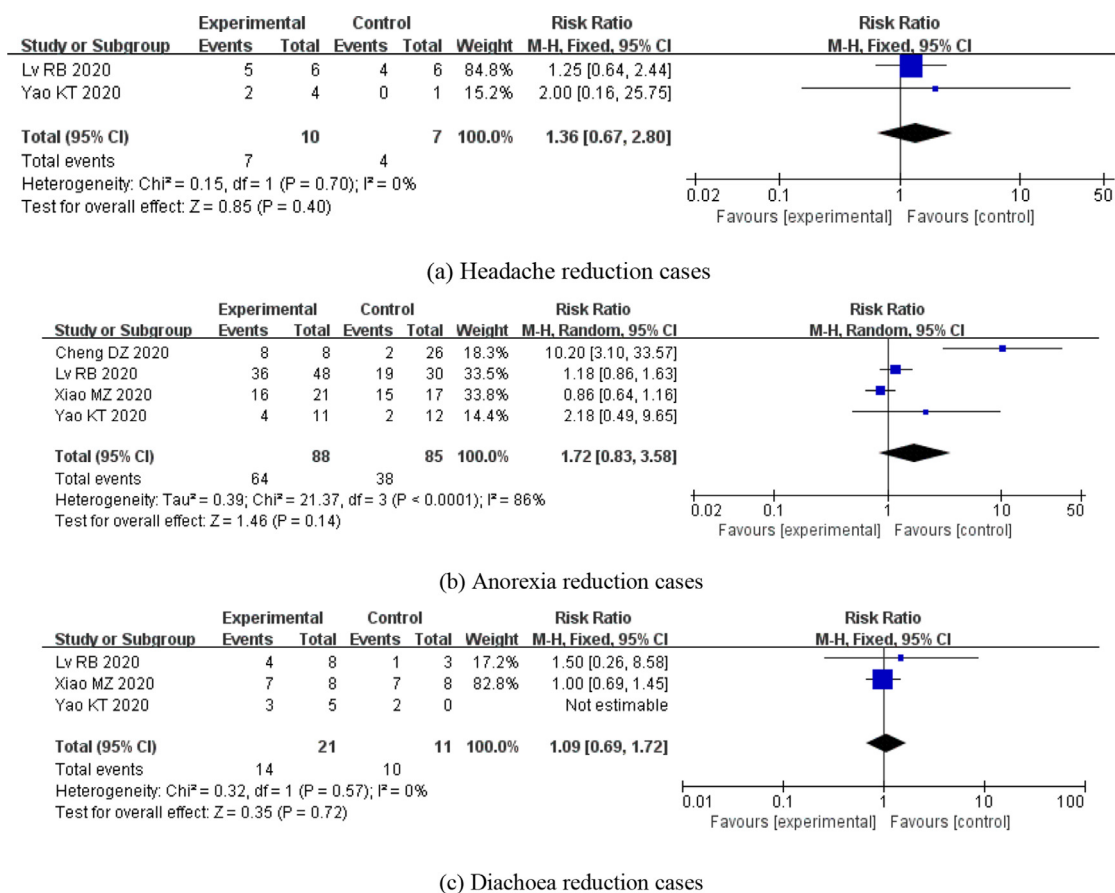


Fig. 9. Forest plot of the effects of LHQW for outcomes of (a) Fatigue reduction cases, (b) Disappearing time of fatigue, (c) Diarrhoea reduction cases.

clinical symptoms, symptom score of sore throat, number of chest tightness reduction cases, symptom cases of chest tightness, anhelation, muscle pain, inflammatory biomarkers (PCT) were significantly improved by LHQW Capsule (Granule). The evaluation results show that on the basis of conventional western medicine standard treatment, the combination of LHQW Capsule (Granule) could not only significantly improve the fever symptoms, shorten the fever time, but also reduce the cough and fatigue symptoms, improve the clinical efficiency, improve the lung CT, significantly reduce the number of patients with mild to severe diseases, and have certain anti-inflammatory effect. Although other studies [33–35] have reached similar conclusions, the analysis of this paper is richer, more comprehensive and more persuasive.

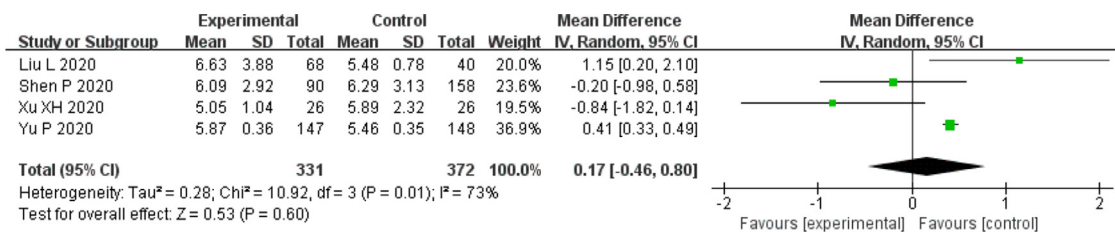
Thirdly, in terms of safety evaluation, adverse events were reported in seven studies. Five of the studies indicate no adverse effects, and two other studies provide detailed descriptions and data statistics of adverse events, which may be associated with factors such as disease progression. Therefore, there is a proper reason to believe the safety of LHQW Capsule (Granule) for the treatment of COVID-19.

Fourthly, the medical composition of LHQW Capsule (Granule) was also analysed in this study. Based on the classic TCM prescription "Ma Xing Shi Gan Tang" [23], LHQW is made from Forsythia suspensa, honeysuckle, roasted ephedra, fried bitter almond, gypsum, isatis root, Mianma Guanzhong, Houptuynia cordata, patchouli, rhubarb, Rhodiola, menthol, licorice and other traditional Chinese medicines through modern extraction technology [16]. Forsythia suspensa and honeysuckle are king drugs to clear away heat, detoxify, eliminate plague and eliminate evil, which could block the binding of SARS-CoV-2 with the angiotensin converting enzyme [36]; Roasted ephedra and fried bitter almonds are minister drugs to relieve lung heat, relieve asthma and cough; Rhubarb has the effect of clearing heat and cooling blood, purging fire

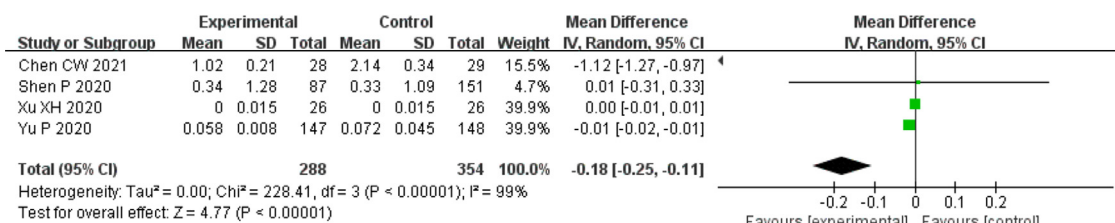
and detoxifying, which could effectively resist the binding of spinous process protein and angiotensin converting enzyme [40], and inhibit the excessive release of inflammatory mediators, and improve lung injury [41]; Banlangen, Mianma Guanzhong, patchouli, Houptuynia cordata, menthol, clear heat and detoxification, dispel wind and promoting pharynx, which has been shown to improve diarrhea and host defense of gastrointestinal tract [37]; Gypsum can clear away heat and cool blood, reduce fire and eliminate annoyance; Rhodiola can invigorate Qi and blood circulation, relieve cough and asthma, which could ameliorate lung injury via the suppression of oxidative stress and apoptosis [38] and abrogation of pulmonary inflammation [39]. Licorice blend, applied in all drugs, has the effects of warming the lung, strengthening the spleen and removing dampness [23]. These observations provide evidence for the antiviral effect of LHQW.

4.2. Limitations

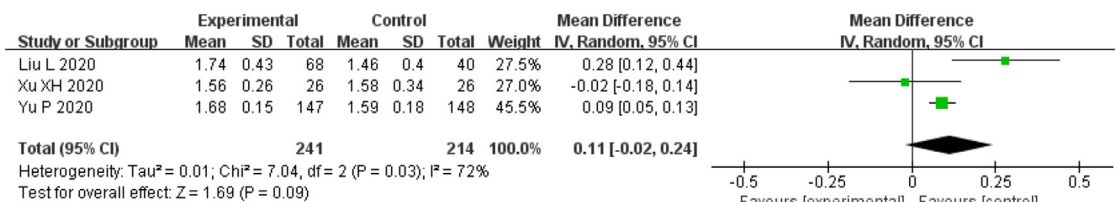
Limitations in this review should also be mentioned. Firstly, Although the 16 trials collected in the study are far more than similar studies, the sample is still relatively small, and almost all comes from China, which has a certain impact on the methodological quality of literatures, and leads to language bias. Secondly, some studies adopted open distribution and lacked blind methods for participants, which led to high-risk bias. Thirdly, there is statistical heterogeneity in the research results of some indicators, such as clinical cure rate, disappearing time of cough. Therefore, random effect model was adopted. Due to the small sample size, subgroup analysis, multilevel meta-analysis, perceptual analysis and other methods in line with clinical characteristics were hardly carried out. Fourthly, the significant effect of LHQW in the treatment of COVID-19 was analyzed merely from the aspect of pharmaceutical components, which needs further research and confirmation.



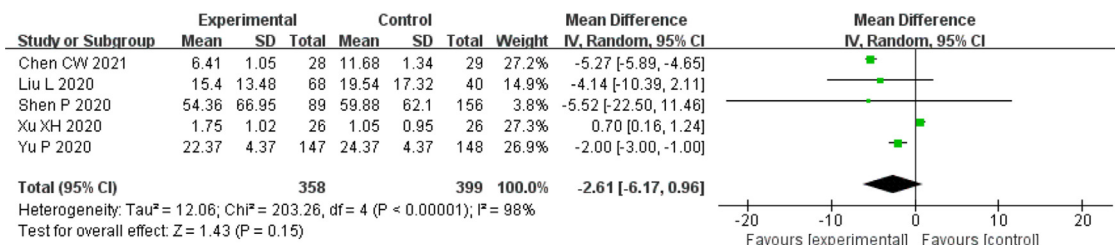
(a) WBC



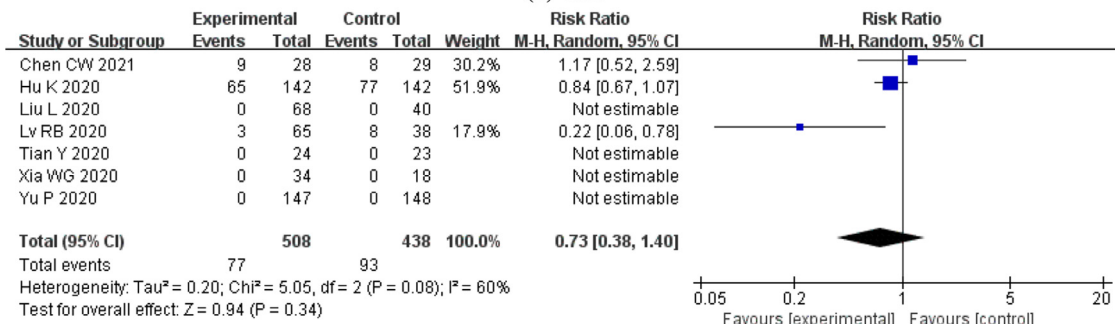
(b) PCT



(c) LYM



(d) CRP



(e) Adverse effects

Fig. 10. Forest plot of the effects of LHQW for outcomes of (a) WBC, (b) PCT, (c) LYM, (d) CRP, (e) Adverse effects.

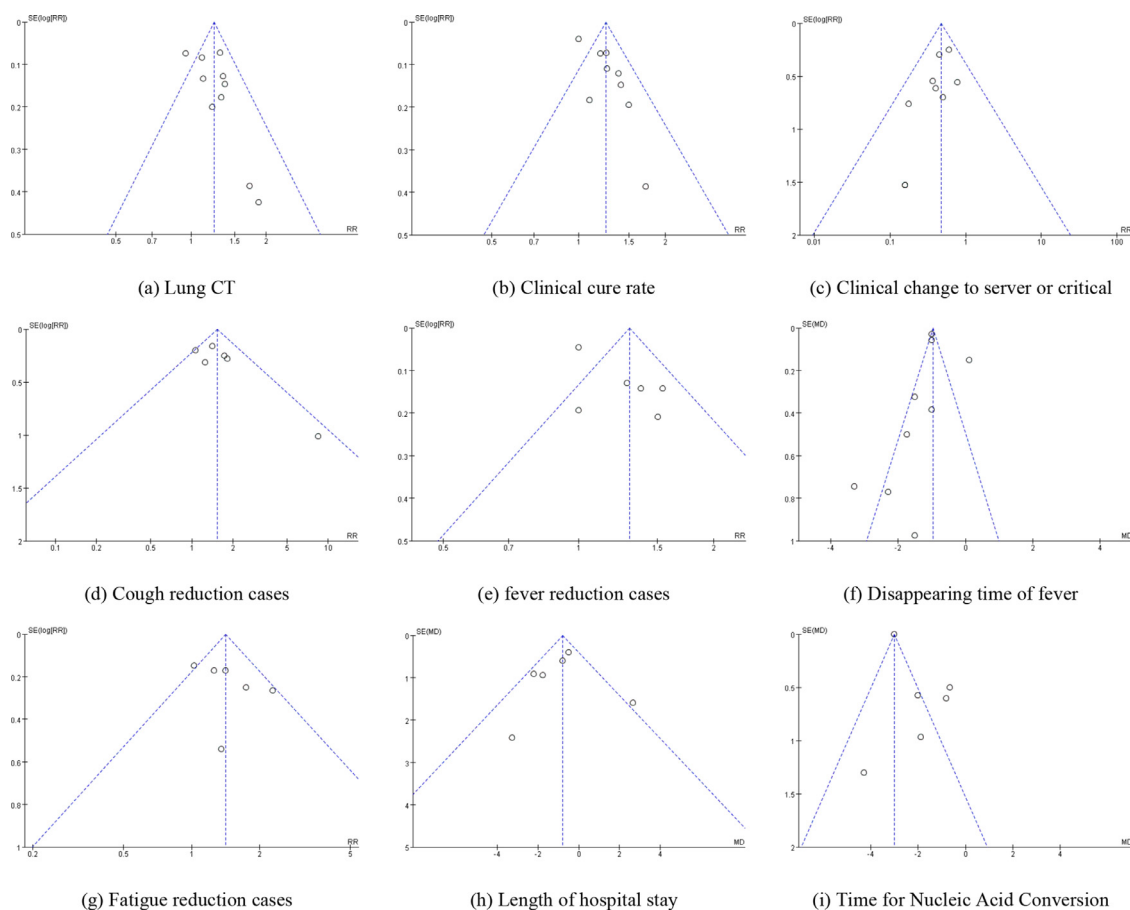


Fig. 11. Funnel plot of outcome of (a) Lung CT, (b) Clinical cure rate, (c) Clinical change to server or critical, (d) Cough reduction cases, (e) fever reduction cases, (f) Disappearing time of fever, (g) Fatigue reduction cases, (h) Length of hospital stay, (i) Time for Nucleic Acid Conversion.

5. Conclusions

To sum up, The evaluation results of this systematic review and Meta analysis suggested that, in the treatment of COVID-19, LHQW Capsule (Granule) could not only significantly improve the fever symptoms, shorten the fever time, but also reduce the cough and fatigue symptoms, improve the clinical efficiency, improve the lung CT, significantly reduce the number of patients with mild to severe diseases, and have certain anti-inflammatory effect. And there is no server adverse events which support the safety of LHQW Capsule (Granule) for the treatment of COVID-19. As a classic formula of TCM, LHQW Capsule (Granule) could be used as potential candidates for COVID-19 in this battle.

Author contributions

L.F. was involved in all parts of the study: design, acquisition of data, analysis, interpretation, drafting of paper, and final approval. L.P.Q., Y.Z. and H.F.S. participated in study select, data extraction, and assessment of the methodological quality. H.F.S. helped to revise the manuscript. L.F. and H.F.S. contributed to the interpretation of the data and made critical comments on the manuscript to be published.

Declaration of Competing Interest

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.prmcm.2022.100092](#).

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