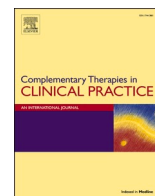




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Efficacy and safety of yinqiao powder combined with western medicine in the treatment of pneumonia: A systematic review and meta-analysis

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ABSTRACT

Objective: This review aimed at systematically evaluating the efficacy and safety of Yinqiao powder combined with western medicine in the treatment of pneumonia.

Methods: A systematic search for randomized controlled trials (RCTs) focusing on pneumonia treatment using a combination of Yinqiao powder and western medicine was performed in PubMed, the Cochrane Library, EMBASE, Web of Science, CNKI, Wanfang, Weipu (VIP) and CBM. The retrieval time limit was from the establishment of the database to June 2020. Two researchers independently screened the literature, extracted the data and evaluated the bias risk of the included studies. A meta-analysis was performed using RevMan5.3 software. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Result: Fifteen RCTs involving 1705 patients were included in the analysis. The meta-analysis results revealed the total effective rate of the treatment group [RR = 1.21, 95% CI (1.15, 1.27), $P < 0.00001$], bacterial clearance rate [RR = 1.13, 95% CI (1.05, 1.22), $P = 0.001$], adverse reactions [RR = 0.54, 95% CI (0.38, 0.76), $P = 0.0005$]. There were statistically significant differences in the cooling time, T cell number, procalcitonin (PCT) and C-reactive protein (CRP) value decline rate ($P < 0.05$). There was no statistically significant difference in the decline rate of neutrophils and leukocytes ($P > 0.05$).

Conclusion: The current evidence indicated that the Yinqiao powder combined with western medicine can improve total efficiency in the treatment of pneumonia patients. The combination therapy performed better when compared to western medicine alone in the cooling time, bacterial clearance rate, T cell count, decline rates of CRP and PCT as well as in the incidences of adverse reactions. However, there was no significant difference in the decline rates of neutrophils and leukocytes between the two groups. The funnel plot, Egger's test and Begg's test indicated publication bias, which may be associated with unpublished negative study results. Due to the limitation of the quality and quantity of the included studies, more high-quality studies should be performed to verify our conclusions.

1. Introduction

Pneumonia refers to the infection of the lung or lung parenchyma. It is an acute inflammation of the lower respiratory tract that is clinically characterized by fever, cough, shortness of breath and malaise [1]. Globally, pneumonia has a high incidence and mortality rates and is the leading cause of death due to infections [1,2]. A study report in the

United States showed that the incidence rates of pneumonia are highest at the extremes of age and common among the elderly and children [3]. Bacterial and viral infections are the main causes of pneumonia [4]. *Streptococcus pneumoniae* is the most common cause of pneumonia infections [5].

The current conventional treatment scheme involves selecting sensitive antibiotics-targeted anti-infection therapy after determining the

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pathogens. Due to the extensive use of antibiotics, the resistance of pathogenic bacteria to antibiotics is gradually increasing, compromising clinical treatment. However, even with effective antibiotics, most resistance may be due to host immune responses that either overreact and cause cytokine storms or enters a period of quiescence and immunoparalysis, which may be problematic [2].

The curative effect of traditional Chinese medicine (TCM) combined with western medicine on pneumonia has been shown to be remarkable and effectively reduces the mortality rate [6,7]. At the end of 2019, the outbreak of coronavirus disease 2019 (COVID-19) was characterized by acute respiratory symptoms that later became a global pandemic [8,9]. China has adopted the combination therapy of TCM and western medicine as an early joint intervention, which may improve the survival rate of patients and effectively control the spread of the pandemic. Yinqiao powder is an effective prescription for the treatment of all kinds of pneumonia. The clinical efficacy of a combination of Yinqiao powder and antibiotics in the treatment of pneumonia is significant. In a randomized controlled trial (RCT), Wang et al. [14] found that a combination of Yinqiao powder and antibiotics had an improved efficacy on pneumonia with low incidences of adverse reactions. Although there are numerous similar reports, a systematic evaluation of the curative effect is lacking. Therefore, it is difficult to achieve a reliable conclusion. In this meta-analysis, we evaluated the RCTs of a combination of Yinqiao powder and western medicine in the treatment of pneumonia. This may provide a reliable treatment plan and evidence-based guideline for clinical work and scientific research.

2. Methods

2.1. Study registration

The protocol and registration information are available at <https://www.crd.york.ac.uk/prospero/#searchadvanced> (registration number: CRD42020186401). We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] statement (Table S1).

2.2. Eligibility criteria

2.2.1. Type of studies

All RCTs were included. Cohort studies, case-control studies, case series studies, retrospective studies, reviews, qualitative studies and uncontrolled trials were excluded. Studies published as conference abstracts for which details could not be obtained after contacting the author were also excluded.

2.2.2. Types of participants

Patients diagnosed with pneumonia. The diagnostic criteria was according to clinical diagnosis and treatment guidelines issued by "The American Thoracic Society Standard" [11].

2.2.3. Types of interventions

The intervention measures of the treatment group involved the oral administration of a combination of modified Yinqiao powder and western medicine. The intervention measures of the control group involved the administration of western medicine alone.

2.2.4. Types of outcome measures

2.2.4.1. Primary outcome. The primary outcome index was total efficiency. The classifications of curative effect were: remarkably effective, effective and ineffective, if the study was classified as clinical control, cured, improved, ineffective. Clinical control and cured were defined as remarkable effects while 'improved' was defined as a normal effect. Total efficiency = (remarkable number + effective number)/total

number × 100%.

2.2.4.2. Secondary outcomes. Secondary outcome indices included: ① Bacterial clearance rate under sputum culture; ② Decline time of body temperature; ③ Decline rate of inflammatory indices (T-cell count, procalcitonin (PCT), C-reactive protein (CRP), neutrophils, leukocytes); ④ Incidence rate of adverse reactions.

2.3. Exclusion criteria

- (1) As for repetitive published studies, the one with the most comprehensive data were included.
- (2) Published abstracts and conference papers that did not provide original data.
- (3) Studies presenting incomplete data or data with noticeable errors, and the original data could not be obtained after contacting authors.
- (4) Studies with high bias risks as assessed by randomization or allocation concealment [12].
- (5) Studies where the treatment group adopted other traditional Chinese medicine therapies beyond Yinqiao powder.
- (6) Studies without relevant outcome indices.

2.4. Data sources and search strategy

Published studies were retrieved from PubMed, the Cochrane Library, EMBASE, Web of Science, CNKI, Wanfang, Weipu (VIP) and CBM. The retrieval time limit was from the establishment of the database to June 2020. Besides, manual retrieval was performed to search for unpublished grey literature in Baidu and Google Scholar. The retrieval methods adopted the method of the combination of Medical Subject Headings (MeSH) terms and free terms. The English retrieval words included Yinqiao, pneumonia, experimental lung inflammation, etc. The Chinese retrieval words included Yinqiao, pneumonia (fei yan), pulmonary infection (fei bu gan ran), etc. PubMed retrieval strategies are shown in Table S2.

2.5. Study selection and data extraction

Two investigators (Yihua Fan and Renhong Wan) independently selected the studies. Firstly, the EndNote ×9 software was used for deduplication. Secondly, literature titles and abstracts were reviewed during preliminary selection. Thirdly, full texts were reviewed for further screening according to the inclusion and exclusion criteria. Discrepancies were resolved by a third party (Shaopeng Du). Where necessary, essential information was obtained by contacting corresponding authors through email or telephone. Excel 2013 was used to extract the relevant information. The following contents were extracted:

Basic information of included studies including the first author's name, year of publication, number of cases in each group, participants' baseline characteristics and disease diagnostic criteria; ② Intervention measures and treatment course of treatment and control groups; ③ Outcome indices; ④ Each risk bias assessment elements in the RCTs.

2.6. Risk of bias assessment

Two investigators (Yihua Fan and Renhong Wan) independently assessed the risk of bias of the included studies and cross-checked the results. Discrepancies were discussed and solved by a third party (Shaopeng Du). Bias risk assessment adopted the recommended RCT bias risk assessment tool in the Cochrane manual 5.1.0 [13].

2.7. Data analysis and synthesis

The meta-analysis was performed using RevMan5.3 software

provided by the Cochrane Collaboration. Continuous variables were expressed as weighted mean difference (WMD) when the instrument and unit of measurement indices were the same as standardized mean difference (SMD) for inconsistent measuring tools or units of measurement. Dichotomous variables were expressed as relative risk (RR) with 95% confidence intervals (95% CI). Chi-square (χ^2) and I^2 tests were used to analyze the heterogeneity between studies. If $P \geq 0.10$ and $I^2 < 50\%$, then, there was no significant heterogeneity among studies, and a fixed-effect model was used to analyze the data. If $P < 0.10$, $I^2 \geq 50\%$, the heterogeneity among the studies was significant. Subgroup and sensitivity analyses were performed to identify the source of heterogeneity, and a randomized effect model was used to analyze the data after excluding obvious clinical and methodological heterogeneity. Sensitivity analysis was used to evaluate a single study influence on combined effect size and to determine the stability of results. For the major outcome indicators, if the included study was ≥ 10 , the funnel plot was used to qualitatively detect publication bias [14]. Moreover, the Egger's and Begg's tests were used to quantitatively assess potential publication bias.

3. Results

3.1. Description of the included studies

A total of 487 relevant studies were obtained from a preliminary examination. After removing duplicates, 223 studies were obtained. Of these, 185 were excluded after the preliminary screening of the titles and abstracts. Of the remaining 38 publications, 23 were excluded after full-text analysis. Finally, 15 studies were eligible for inclusion [15–29]. The

literature-screening flowchart was as shown in Fig. 1.

The basic characteristics of the included studies are shown in Table 1. The treatment group was orally administered with a combination of Yinqiao powder and western medicine while the control group was administered with western medicine only. The characteristics of interventions were as shown in Table 2 with a treatment cycle of 7–14 days.

3.2. Risk of bias assessment

RCT bias risk assessment tool recommended by Cochrane manual 5.1.0 was used to conduct a quality evaluation of the included 15 studies [15–29]. Two articles [16,27] correctly used the method of generating a random sequence. One publication [21] correctly used double-blind while the other 14 publications [15–20,22–29] did not mention the blinding method. In the aspects of allocation concealment, incomplete outcome indicators, selective reporting and other biases, all included studies [15–29] exhibited low bias risks. The results of bias risk assessment are shown in Fig. 2.

3.3. Outcome measurements

3.3.1. Total efficiency

A total of 14 RCTs involving 1585 patients were included [15–19, 21–29]. Heterogeneity test showed that there was no statistically significant heterogeneity between studies ($P = 0.08$, $I^2 = 37\%$). The fixed-effect model was used to calculate the total score of symptoms and signs in the treatment and control groups. There was a significant difference between the groups [RR = 1.21, 95% CI (1.15, 1.27), $P <$

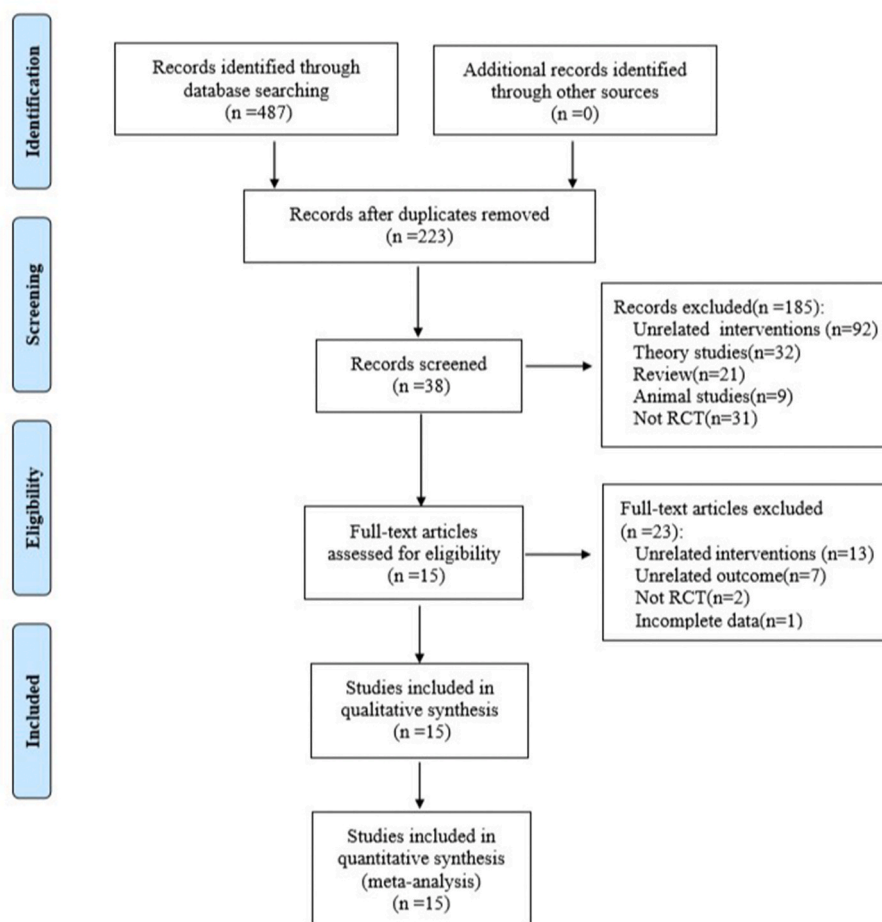


Fig. 1. Flow diagram.

Table 1
Basic characteristics of the included studies.

Study cohort	No (T/C)	Gender		Age		Course (day)	Outcome	Type
		T	C	T	C			
Wang W 2017 [15]	50/50	31/19	29/21	4.18 ± 2.32	4.25 ± 2.25	7	⊗⊗	C
Wang F 2019 [16]	41/41	26/15	23/18	78.12 ± 6.85	78.41 ± 6.93	14		A
Liu T.A 2012 [17]	34/26	17/17	10/16	–	–	5–7		C
Ma L 2014 [18]	40/40	20/20	20/20	–	–	7		C
Liu S.X 2017 [19]	41/41	20/21	23/18	4.74 ± 2.53	4.84 ± 2.45	14		C
Cui J.X 2015 [20]	60/60	38/22	40/20	53.85 ± 10.25	53.29 ± 10.57	14	⊗	A
Huang W.C 2015 [21]	45/45	28/17	29/16	78.9 ± 6.3	79.6 ± 7.1	7	⊗	A
Peng H.X 2013 [22]	116/119	–	–	–	–	14	⊗⊗	A
Bi R.P 2014 [23]	39/39	–	–	–	–	14	⊗	A
Lv F.W 2014 [24]	50/50	–	–	68.1 ± 3.8	67.9 ± 3.6	7		A
Song D.M 2015 [25]	110/111	–	–	–	–	14	⊗	A
Chen X.J 2017 [26]	40/40	–	–	–	–	14		A
Hao Y.L 2015 [27]	80/80	44/36	46/34	4.56 ± 1.2	4.67 ± 1.12	7		C
Chen G.L 2018 [28]	26/26	11/15	12/14	66.3 ± 2.4	65.8 ± 2.7	10	⊗	A
Li C.B 2010 [29]	85/80	46/39	46/34	–	–	7		C

Note: A: Community acquired pneumonia in adults C: Community acquired pneumonia in children.

Outcome: ⊗ Efficiency; ⊗ Antipyretic time; ⊗ Adverse reaction rate; ⊗ bacterial clearance.

–: unclear.

0.00001, Fig. 3]. The 14 RCTs were divided into two subgroups depending on the treatment course: ≤7 days and >7 days. The results showed that whether the treatment time was less than or equal to 7 days or more than 7 days, the efficiency rate of the treatment group was significantly higher compared to that of the control group [RR = 0.120, 95% CI (1.14, 1.27), $P < 0.00001$] and [RR = 0.130, 95% CI (1.20, 1.39), $P < 0.00001$], respectively (Fig. 4). Moreover, the 14 RCTs were divided into two subgroups according to the type of pneumonia: community-acquired pneumonia (CAP) in children and CAP in adults. The CAP in children was included in 6 studies. There was no statistical heterogeneity among the studies ($P = 0.05$, $I^2 = 0\%$). The results indicated that the efficiency rate of the treatment group was higher compared to that of the control group [RR = 1.20, 95% CI (1.14, 1.27), $P < 0.00001$]. The CAP in adults was included in 8 studies. The results showed a statistically significant heterogeneity among the groups ($P = 0.01$, $I^2 = 60\%$) (Fig. 5). A sequential elimination method was employed. When a study by Huang 2015 [21] was eliminated, heterogeneity disappeared ($P = 0.68$, $I^2 = 0\%$). The total efficiency rate differed significantly between the treatment group and the control group [RR = 1.33, 95% CI (1.24, 1.44), $P < 0.00001$].

3.3.2. Bacterial clearance rate

Three RCTs [22,23,25] involving 290 patients reported on the bacterial clearance rate. Heterogeneity test showed that there was no statistically significant heterogeneity between studies ($P = 0.74$, $I^2 = 0\%$). The fixed-effects model was used to calculate the total score of symptoms and signs in the treatment and the control groups. There was a statistically significant difference between the groups [RR = 1.13, 95% CI (1.05, 1.22), $P = 0.001$, Fig. 6].

3.3.3. Cooling time

One RCT [15] involving 100 patients reported on the cooling time. The cooling time of the body temperature of the treatment group was significantly less compared to the control group.

3.3.4. Decline rate of inflammatory index

3.3.4.1. Neutrophils and leukocytes. One RCT [25] showed a significantly decreased number of neutrophils and leukocytes before and after treatment in the treatment group compared to the control group. However, when P -value was >0.05 , there was no statistical difference between the groups.

3.3.4.2. T cell count, PCT and CRP decline rate. One RCT [16] reported

on the decline rate of T cell counts, PCT and CRP. The decline rates of T cell counts, PCT and CRP were significantly higher in the treatment group compared to the control group.

3.4. Safety assessment

Seven RCTs [15,20–23,25,28] involving 909 patients reported on the adverse reaction rate. Heterogeneity test showed that there was no statistically significant heterogeneity between studies ($P = 0.43$, $I^2 = 0\%$). The fixed-effects model was used to calculate the adverse reaction rate and total score of symptoms and signs in the treatment and control groups. The results indicated a statistically significant difference between the groups [RR = 0.54, 95% CI (0.38, 0.76), $P = 0.0005$, Fig. 7].

3.5. Sensitivity analysis

A consecutive one by one elimination method was applied in the sensitivity analysis of the above indices. The effect size and P -value changes were evaluated after consecutive one by one exclusion of the included studies. The results showed that the removal of any publication had no significant change in effect size of the outcomes of the indices, indicating that the meta-analysis was reliable and stable. We used Stata 12.0 to analyze the sensitivity of the outcome indicators. The data analysis results were found to be robust. The sensitivity analysis results are shown in Figs. 8–10.

3.6. Publication bias

Since 15 studies were included in the meta-analysis, we used the funnel pattern to detect publication bias of the main outcomes of the indices. As shown in Fig. 11, the funnel pattern was asymmetric, indicating that there might have been publication bias. This was further confirmed by the Egger's and Begg's tests (Egger's test $P = 0.0029 < 0.05$, Begg's test $P = 0.0118 < 0.05$).

3.7. Evaluation of quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of evidence [30]. The evidence level of total effective rate was found to be LOW, bacterial clearance rate and the evidence level of adverse reaction was VERY LOW. Total efficiency met the two criteria for downgrade. Risk of bias; Two studies used the method of generating random sequences, one study used the double-blind method, while the other 14 studies did not

Table 2
Characteristics of intervention measures.

Study	Interventions of treatment group		Interventions of control group	Course (day)
	Western medicine therapy	Traditional Chinese medicine	Western medicine therapy	
Wang W 2017 [15]	Cefotaxime 100 mg/(kg-d) bid ivgtt OR Aloxycillin sodium 75 mg/(kg-d) bid ivgtt; ambroxol	yinqiao powder	Cefotaxime 100 mg/(kg-d) bid ivgtt OR Aloxycillin sodium 75 mg/(kg-d) bid ivgtt; ambroxol	7
Wang F 2019 [16]	Conventional western medicine treatment	yinqiao powder	Conventional western medicine treatment	14
Liu T.A 2012 [17]	Cefotaxime sodium 100mg/(kg-d) bid ivgtt OR Aloxycillin sodium 75 mg/(kg-d) bid ivgtt; ambroxol	yinqiao powder	Cefotaxime sodium 100 mg/(kg-d) bid ivgtt OR Aloxycillin sodium 75 mg/(kg-d) bid ivgtt; ambroxol	5-7
Ma L 2014 [18]	Ceftazidime sodium 80 mg (kg-d) bid ivgtt OR Azithromycin 100 mg/(kg-d) qd iv.gtt; ambroxol	yinqiao powder	Ceftazidime sodium 80 mg (kg-d) bid ivgtt OR Azithromycin 100 mg/(kg-d) qd ivgtt; ambroxol	7
Liu S.X 2017 [19]	Ceftazidime sodium 80 mg/(kg-d) bid iv.gtt OR Azithromycin 100 mg/(kg-d) qd ivgtt; ambroxol	yinqiao powder	Ceftazidime sodium 80 mg/(kg-d) bid ivgtt OR Azithromycin 100 mg/(kg-d) qd ivgtt; ambroxol	14
Cui J.X 2015 [20]	Cefoperazone/sulbactam 2 g bid ivgtt	yinqiao powder	Cefoperazone/sulbactam 2 g bid ivgtt	14
Huang W.C 2015 [21]	Levofloxacin 200 mg bid ivgtt	yinqiao powder	Gatifloxacin 0.4 g qd ivgtt	7
Peng H.X 2013 [22]	Levofloxacin 200 mg bid ivgtt	yinqiao powder	Levofloxacin 200 mg bid ivgtt	14
Bi R.P 2014 [23]	Levofloxacin 200 mg bid ivgtt	yinqiao powder	Levofloxacin 200 mg bid ivgtt	14
Lv F.W 2014 [24]	Conventional western medicine treatment	yinqiao powder	Conventional western medicine treatment	7
Song D.M 2015 [25]	Levofloxacin 200 mg bid ivgtt	yinqiao powder	Levofloxacin 200 mg bid ivgtt	14
Chen X.J 2017 [26]	Conventional western medicine treatment	yinqiao powder	Conventional western medicine treatment	14
Hao Y.L 2015 [27]	Ceftazidime sodium 80 mg/(kg-d) bid ivgtt OR Azithromycin 100 mg/(kg-d) qd ivgtt	yinqiao powder	Ceftazidime sodium 80 mg/(kg-d) bid ivgtt OR Azithromycin 100 mg/(kg-d) qd ivgtt	7
Chen G.L 2018 [28]	Levofloxacin 100 ml ivgtt	yinqiao powder	Levofloxacin 100 ml ivgtt	10
Li C.B 2010 [29]	Cefuroxime 100 mg/(kg-d), ribavirin 100 mg/(kg-d) ivgtt	yinqiao powder	Cefuroxime 100 mg/(kg-d) ribavirin 100 mg/(kg-d) ivgtt	7

Note: ivgtt, Intravenous drip.

mention the blinding method, and all the studies had no hidden description of assignment, so it was downgraded because it was an objective index. ② Reporting bias: There was publication bias as determined by funnel plots, Egger's and Begg's tests. The bacterial clearance rate and adverse reactions met three downgrade criteria. Risk of bias: the description of random methods was not clear, and the blinding method and allocation concealment were not described; ② Imprecision: the sample size included in the study was small, and the confidence interval was wide; ③ Reporting bias: publication bias was determined by funnel chart and Egger's and Begg's tests (Table 3).

4. Discussion

Pneumonia belongs to a range of lung heat disease (Feire Bing) and wind-warmth disease (Fengwen Bing) in traditional medicine. Over 2000 years ago, the "Su Wen" had the records of the lung heat disease, and the main clinical manifestations were fever, aversion to cold and asthma. The "Wen Re Jing Wei" indicated that the wind-warm disease was common in spring and winter and was manifested by fever, cough and thirst. Modern doctors combine the "lung heat disease" and "wind-warmth disease" into wind-warmth pulmonary fever (Fengwen Feire Bing) depending on the clinical features [31,32]. Yinqiao powder emanated from "Analysis of Heat Diseases" (Wenbing Tiaobian) and is used to treat the wei phase syndrome of the onset of febrile disease and wind-heat disease syndrome. This powder has been used in China for 200 years. Yinqiao powder is composed of *Flos lonicerae* (Jinyinhua), *Fructus forsythiae* (Lianqiao), *Radix platycodonis* (Jiegeng), *Herba menthae* (Bohe), *Fructus arctii* (Niubangzi), *Semen sojae Praeparatum* (Dandouchi), *Herba lophatheri* (Zhuye), *Herba schizonepetae* (Jingjie), *Radix glycyrrhizae* (Shenggancao), with dosage ratios of 10:10:6:6:5:4:4:5 [33]. It functions to resolve superficies syndrome with pungent and cool natured drugs and clears away heat and toxic material [34], which correspond to the etiology and pathogenesis of pneumonia. The Chinese Society of TCM recommends the use of Yinqiao powder in the treatment of CAP [35].

The present meta-analysis evaluated 15 RCTs that assessed the effect of a combination of Yinqiao powder and western medicine on the treatment of pneumonia. A total of 1705 patients were enrolled in the RCTs and results were evaluated between the treatment and control groups. The total efficiency results showed that the curative effect of the combination of Yinqiao powder and western medicine was better when compared to the use of western medicine only. Findings from subgroup analysis also showed a better curative effect in the treatment group compared to the control group, regardless of the treatment course (≤ 7 days or >7 days). Besides, prolonged treatment courses tended to improve the curative effect. Similarly, the curative effect was better in the treatment group compared to the control group, regardless of the type of pneumonia (adult pneumonia or child pneumonia). In addition, the treatment group was advantageous than the control group in the cooling time, bacterial clearance rate and incidence of adverse reactions. Likewise, the treatment group was better compared to the control group in the decline rate of T cell counts, PCT and CRP. However, there was no significant difference in the decline rates of neutrophils and leucocytes between the two groups. In one of the seven RCTs that reported adverse reactions, all patients (50 cases) in the treatment group showed no adverse reactions [15]. In the other 6 studies, adverse reactions included mild diarrhea [20-23,25,28], skin itch [20,22,23,25], mild liver injury [20,21] and mild renal injury [20]. The liver and kidney did not exhibit severe damage and recovered after treatment. These results imply that a combination of Yinqiao powder and western medicine in the treatment of pneumonia has mild adverse reactions and high safety.

Pharmacological studies have documented that this combination has antiviral, antibacterial, anti-inflammatory, antipyretic and immune enhancing effects [36]. *Flos lonicerae* (Jinyinhua) has antipyretic and anti-inflammatory effects. The antipyretic effect acts on the warm-sensitive neuron in the hypothalamus to restrict the produced

Study	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 (attrition bias)	Selective reporting (reporting bias)	Other bias
Bi R.P 2014	?	?	?	?	?	?	?
Chen G.L 2018	?	?	?	?	?	?	?
Chen X.J 2017	?	?	?	?	?	?	?
Cui J.X 2015	?	?	?	?	?	?	?
Hao Y.L 2015	?	?	?	?	?	?	?
Huang W.C 2015	?	?	?	?	?	?	?
Li C.B 2010	?	?	?	?	?	?	?
Liu S.X 2017	?	?	?	?	?	?	?
Liu T.A 2012	?	?	?	?	?	?	?
Lv F.W 2014	?	?	?	?	?	?	?
Ma L 2014	?	?	?	?	?	?	?
Peng H.X 2013	?	?	?	?	?	?	?
Song D.M 2015	?	?	?	?	?	?	?
Wang F 2019	?	?	?	?	?	?	?
Wang W 2017	?	?	?	?	?	?	?

Fig. 2. Summary of risk of bias.

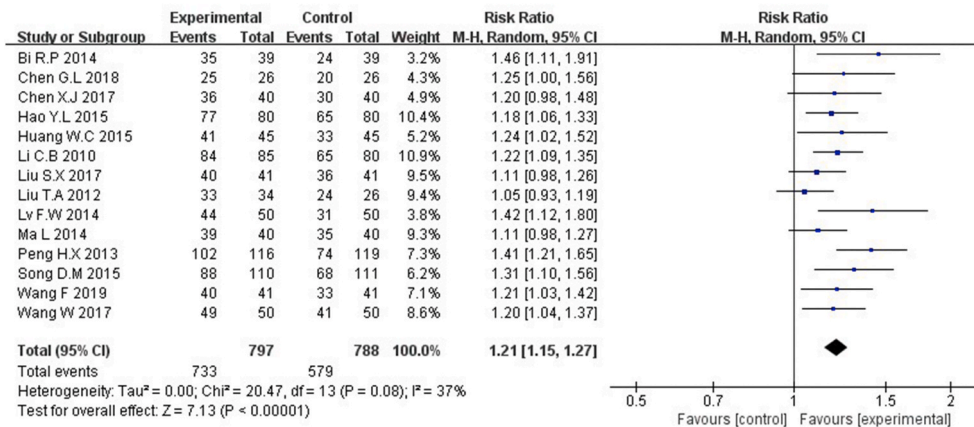


Fig. 3. Comparisons of total efficiency between the treatment group and the control group.

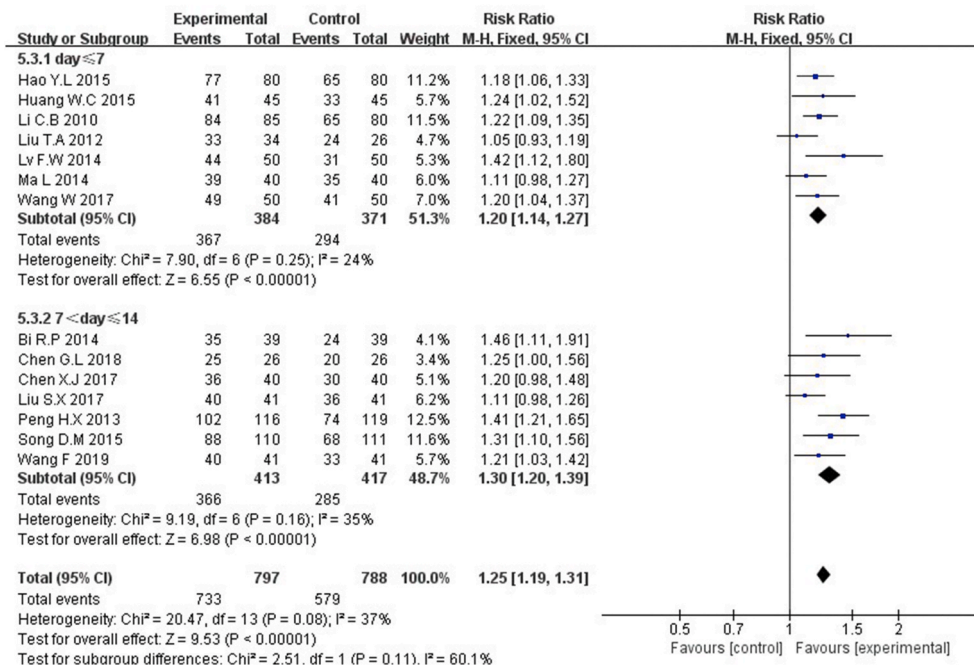


Fig. 4. Efficiency rate according to the treatment course between the treatment group and the control group.

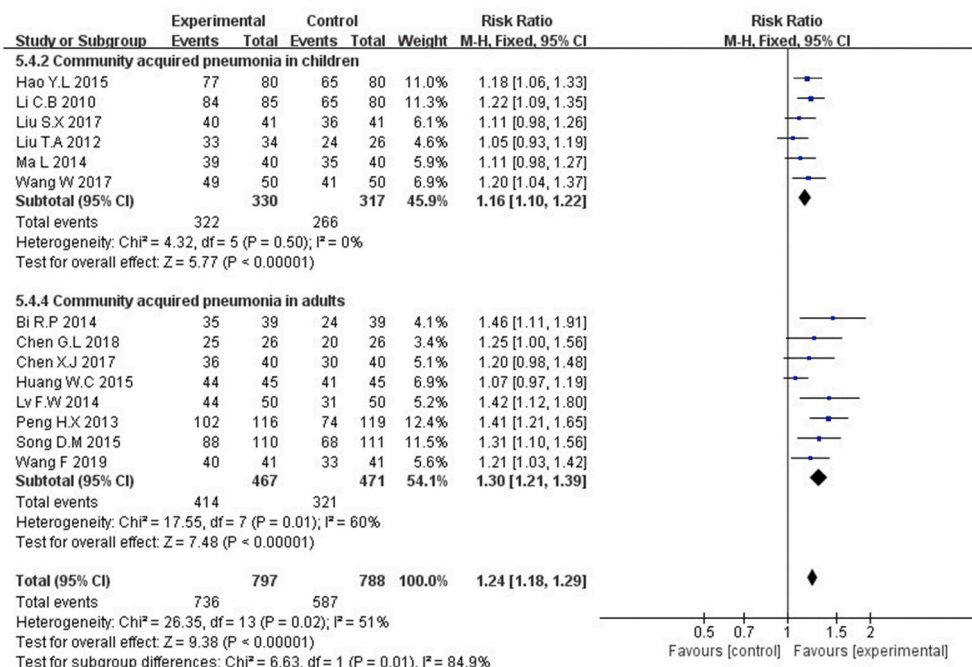


Fig. 5. Efficiency rate according to the type of pneumonia between the treatment group and the control group.

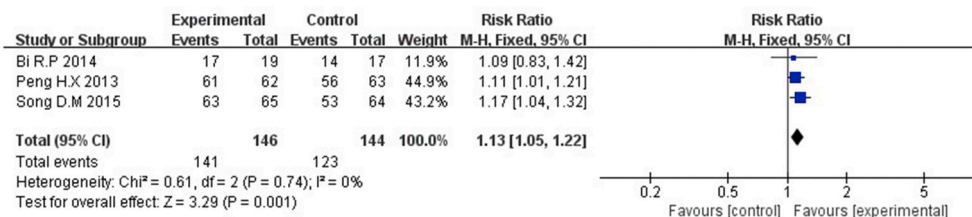


Fig. 6. Comparisons of bacterial clearance rate between the treatment group and the control group.

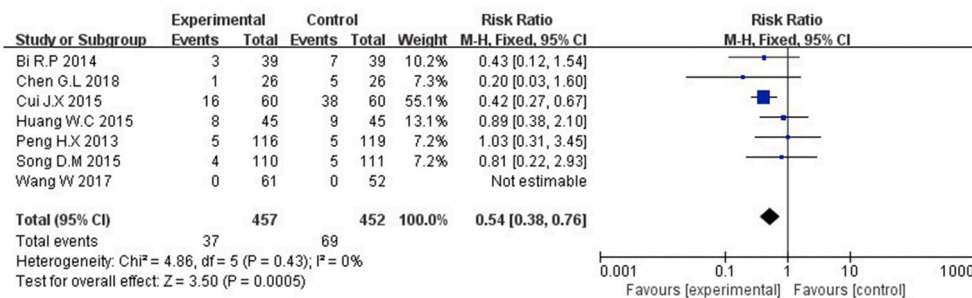


Fig. 7. Comparison of the adverse reaction rate between the treatment group and the control group.

heat while inhibiting the cold-sensitive neurons [37]. An excellent antipyretic effect has been clinically confirmed [38]. *Flos loniceerae* extract exhibited antibacterial and bactericidal effects on *Staphylococcus aureus*, beta *Streptococcus*, *Escherichia coli*, *Pseudomonas Aeruginosa*, *Candida Albicans* and *Klebsiella pneumonia* [39]. *Fructus forsythiae* (Lianqiao) exhibited a significant anti-inflammatory effect and reduced exudation and edema caused by capillary permeability (hyperpermeability). Its contents, forsythiol, forsythiol A and essential oil, have a significant broad-spectrum antibacterial effect. The essential oil had a significant inhibitory effect on influenza virus [37,40]. Through molecular docking and network pharmacological analysis, it was found that saponins from *Radix platycodonis* (Jiegeng) and ester glycosides from *Fructus forsythiae* (Lianqiao) and angiotensin-converting enzyme 2

(ACE2), targets of the novel coronavirus, have a strong binding force, which may have a certain inhibitory effect on the coronavirus [41]. Evidence has shown that the saponins from *Radix platycodonis* and ester glycosides from *Fructus forsythiae* have a good anti-respiratory tract virus effect [42,43].

In traditional medicine, COVID-19 belongs to the “Yi Bing” and “Shi Yi” categories [44]. With fever, dry cough, fatigue, sore throat, as the mild and ordinary clinical manifestations of COVID-19, early treatment should resolve superficialities syndrome with pungent and cool natured drugs and clear away heat and toxic material, which is consistent with the therapeutic principle of the Yinqiao powder [45,46]. Due to the COVID-19 pandemic, Yinqiao powder has been recommended as the classic prescription for patients with mild or normal symptoms in

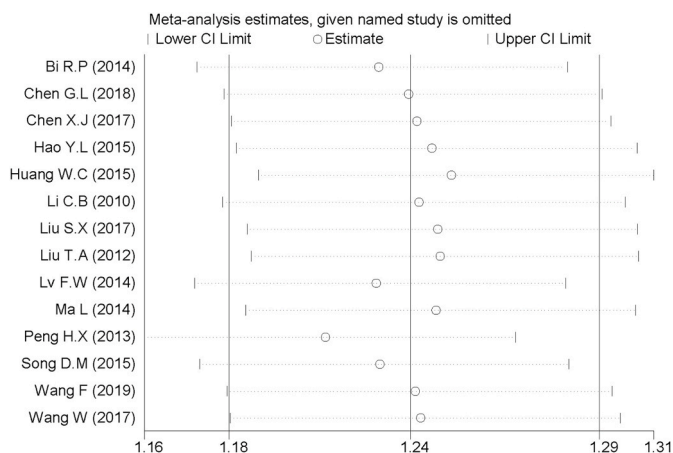


Fig. 8. Total effective rate.

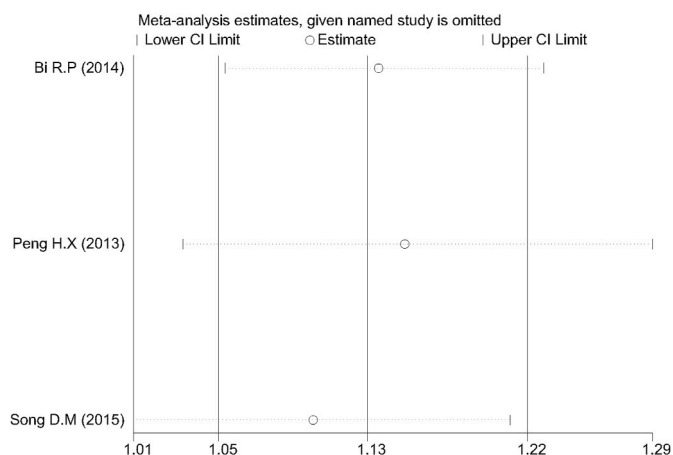


Fig. 9. Bacterial clearance rate.

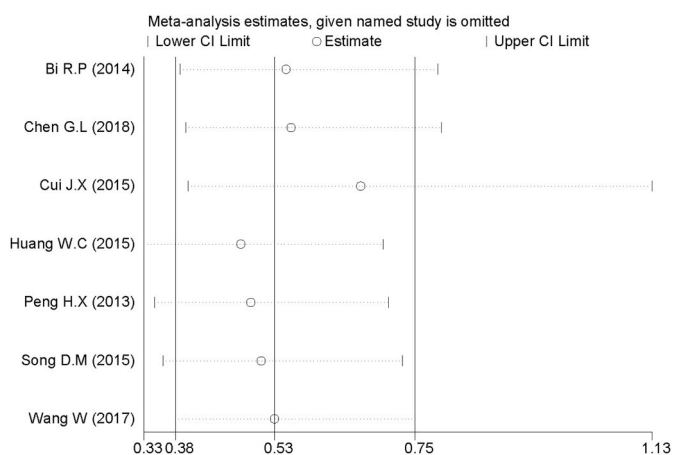


Fig. 10. Incidence of adverse reactions.

various regions in China [45]. Yinqiao powder may play an important role in the treatment of influenza virus [47]. Currently, COVID-19 is spreading all over the world, and traditional Chinese medicine has its unique advantages [48]. Through network pharmacology and molecular docking technology, studies have established that *Fructus forsythiae* powder contains multi-components, multi-targets and multi-pathways which can improve COVID-19 symptoms. This powder binds angiotensinII and serine proteases on PTGS2, HSP90AA1, AR, PCP4, F7 and

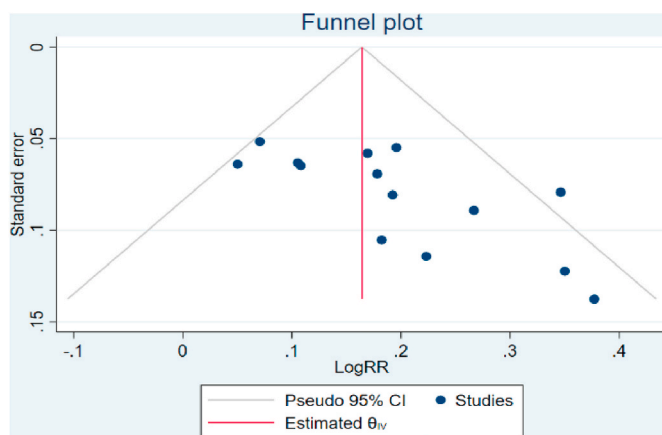


Fig. 11. Funnel plot of publication bias.

other targets to regulate PI3K-Akt signal pathway, MAPK signal pathway, apoptosis pathway, cell senescence pathway, non-small cell lung cancer pathway. Through this mechanism, it exerts therapeutic value in COVID-19 [49]. The results of this study may provide some therapeutic avenues for the clinical therapy of COVID-19-induced pneumonia.

This study has some limitations. First, due to the limited quality and quantity of the included studies, more high-quality studies should be performed to confirm our conclusions. Second, since some of the included studies were of low quality with less of them describing the operation of specific allocation concealment and blinding method, there might have been selection bias, implementation bias and measurement bias, etc. Third, all the included studies were from China, with regional restrictions and poor universality. Finally, due to the particularity of the traditional Chinese medicine decoction, the composition and dosage of prescriptions used in each study varied, perhaps influencing the outcomes.

5. Conclusions

It was found that the combination of Yinqiao powder and western medicine improved total efficiency in the treatment of pneumonia patients. The combination therapy performed better when compared to western medicine alone in the cooling time, bacterial clearance rate, T cell count, decline rates of CRP and PCT as well as in the incidences of adverse reactions. However, there was no significant difference in the decline rates of neutrophils and leucocytes between the two groups. The funnel plot, Egger's test and Begg's test indicated publication bias, which may be associated with unpublished negative study results. Owing to the limitation of the quality and quantity of the included studies, more high-quality studies should be performed to verify our conclusions.

Ethical considerations

Aggregate data were extracted from published studies; no patients were involved in this study; thus, ethical approval and informed consent were not required.

Authors' contributions

This study was conceived by Yihua Fan, Wei Liu and Renhong Wan. Renhong Wan and Yihua Fan drafted the manuscript. Renhong Wan, Shaopeng Du, Yihua Fan and Aihua Wang participated in the design of the data synthesis analysis scheme. Yihua Fan, Wei Liu, Qing Xie and Rumeng Yang reviewed and revised the manuscript.

Yihua Fan, Wei Liu contributed equally to this work and should be

Table 3
GRADE quality grading evaluation.

No of studies	Design	Summary of findings						Quality			
		Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients				
								Effect	Absolute		
								control	Relative (95% CI)		
Effective rate											
14	Randomized trials	serious ^a	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ^b	733/797 (92%)	579/788 (73.5%) 78.7%	RR 1.21 (1.15–1.27)	154 more per 1000 (from 110 more to 198 more) 165 more per 1000 (from 118 more to 212 more)	⊕⊕○○ LOW
3	Bacterial clearance randomized trials	serious ^c	no serious inconsistency	no serious indirectness	Serious ^d	reporting bias ^e	141/146 (96.6%)	123/144 (85.4%) 82.8%	RR 1.13 (1.05–1.22)	111 more per 1000 (from 43 more to 188 more) 108 more per 1000 (from 41 more to 182 more)	⊕○○○ VERY LOW
7	adverse reaction rate randomized trials	serious ^c	no serious inconsistency	no serious indirectness	serious ^d	reporting bias ^e	37/457 (8.1%)	69/452 (15.3%)	RR 0.54 (0.38–0.76)	70 fewer per 1000 (from 37 fewer to 95 fewer)	⊕○○○ VERY LOW

Note.
^a Risk of bias: Two studies correctly used the method of generating random sequences. One study used the double-blind method, while the other 14 studies did not mention the blinding method. All the studies had no hidden description of assignment, therefore, it was downgraded because it was an objective index.
^b Reporting bias: There was publication bias as determined by funnel plots, Egger's and Begg's tests. The bacterial clearance rate and adverse reactions meet three downgrade criteria.
^c Risk of bias: the description of random methods is not clear, and the blinding method as well as allocation concealment were not described.
^d Imprecision: the sample size included in the study was small, and the confidence interval was wide.
^e Reporting bias: publication bias was indicated by funnel chart and Egger's and Begg's tests.

considered co-first authors. All authors have read and approved the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctcp.2020.101297>.

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