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Research article

Efficacy evaluation and potential pharmacological mechanism of tanreqing injection in the treatment of COPD combined with respiratory failure based on meta-analysis and network pharmacology

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ABSTRACT

Background: Tanreqing injection (TRQI) is a Chinese patent medicine. It is commonly used in the treatment of acute exacerbation of COPD in China. It substantially improves the partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide (PaCO2), and lung function in patients with COPD combined with respiratory failure (RF) and improves the total clinical effective rate.

Materials and methods: Relevant randomized controlled trials (RCTs) on the treatment of COPD combined with RF with TRQI were collected through search of PubMed, Web of Science, Embase, Cochrane Library, CBM, VIP, Wanfang, and CNKI up to October 2, 022. Two investigators in this study independently evaluated the quality of the literature and utilized RevMan 5.4 software for analysis. In network pharmacology, TCMSP database, PubChem database, DisGeNet, Genecards, and other databases were searched to screen the chemical components and targets of TRQI and mapped with COPD-RF targets to obtain potential action targets, which were then analyzed using bioinformatics techniques to initially explore their effects.

Result: A total of 18 RCTs containing 1485 patients, showed that TRQI combined with conventional treatment improved the total clinical efficiency of patients with COPD combined with RF compared with that of the conventional treatment group ([$RR = 1.33$, 95% CI (1.25, 1.41), $P < 0.01$]), PaCO2 [$SMD = -1.29$, *95% CI* (−1.41, −1.17), $P < 0.00001$], PaO2 [$SMD = 1.19$, *95% CI* (1.06, 1.31), $P < 0.00001$], pulmonary function [$SMD = 1.00$, *95% CI* (0.79, 1.21), $P < 0.00001$]. Through network pharmacology analysis, 284 potential TRQI and 19 common targets were identified. TNF, TP53, SIRT1, SRC, CCND1, IL-10, NF-κB, MAPK14, STAT3, SMAD3 are core targets proteins. In addition, 56 related pathways of TRQI were identified, such as the TNF, MAPK, IL-17, NF-κB signaling pathways.

Conclusion: In conclusion, the efficacy of TRQI combined with conventional treatment for COPD combined with RF was higher than that of conventional treatment alone. These findings suggest

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that TRQI acts on COPD-RF through a multi-target, multi-component, and multi-pathway mechanism. Future studies may explore the active components of TRQI.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a devastating lung disease characterized by incomplete reversibility of airflow limitation, progressive development, and is associated with an abnormal inflammatory response to harmful gases or particles [27,50]. COPD has become a serious public health problem in China [65]. Approximately 600 million COPD patients will be diagnosed with COPD worldwide in 2020, and this number will continue to increase as the population ages [23]. Respiratory failure (RF) often occurs during acute exacerbations of COPD and is a common complication of COPD. Its symptoms are devastating, and it is prone to hypoxemia and hypercapnia, which can have clinical manifestations of hypoxia and carbon dioxide retention.

The current treatment for COPD with RF is mainly supportive therapy, which is based on keeping the airway open, correcting hypoxia, active anti-infection, and symptomatic support therapy, and it is incurable [18]. Many studies have recently shown that Chinese medicine can reduce acute exacerbations, shorten the duration of acute exacerbations, alleviate symptoms and improve the quality of survival of patients with COPD [39].

TRQI, as a Chinese patent medicine, has the effect of clearing heat and detoxifying, relieving cough, and resolving phlegm [33]. It is clinically used to treat acute, chronic bronchitis, pneumonia, and upper respiratory tract infections caused by bacteria or viruses [43]. A large amount of clinical evidence shows that TRQI has significant advantages over conventional treatment with Western medicine alone in the treatment of COPD combined with RF [28,30]. Meanwhile, several in vivo experimental studies have also confirmed that TRQI can improve the inflammatory response of airway mucosa in rats with COPD induced by smoke and LPS, reduce the expression of IL-8, TNF-α and mucin 5AC (MUC5A) in alveolar lavage fluid [29,32], thereby inhibiting airway mucus hypersecretion and improving the structure of airway cilia in rats, which, to a certain extent, can play a role in delaying the deterioration of lung function [32]. This suggests that the application of TRQI in COPD rats can improve the ultrastructure of lung tissue and inhibit the release of inflammatory factors [4], thus playing a good role in the prevention and treatment of COPD combined with RF.

However, the specific mechanism of action of TRQI for the treatment of COPD combined with RF is still unclear. Therefore, based on meta-analysis bridging network pharmacology, this study is the first to comprehensively evaluate the efficacy of TRQI combined with conventional therapeutic drugs in the treatment of COPD combined with RF, and preliminarily explore its potential mechanism of

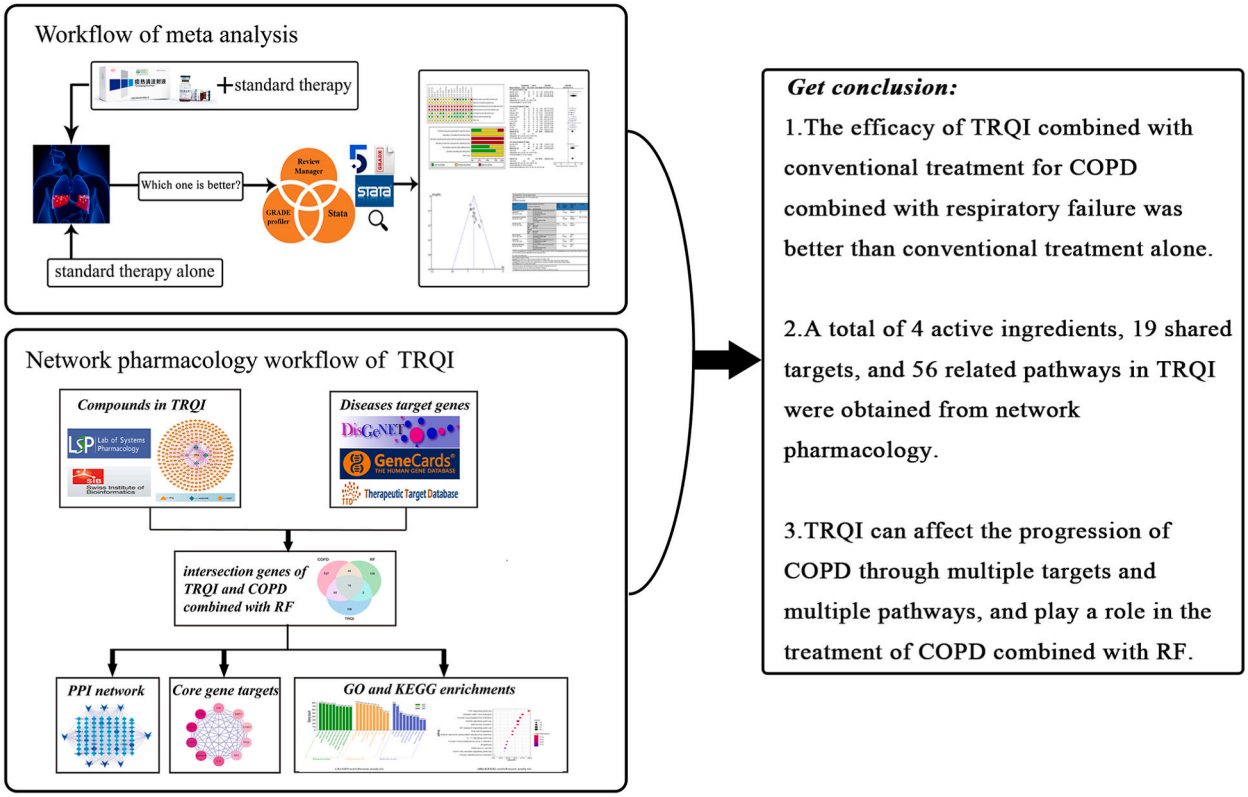


Fig. 1. Meta-analysis and network pharmacology flowchart.

action, to provide evidence-based medical evidence and reference for its clinical application, as well as a basis for follow-up studies (Fig. 1)

2. Methods

2.1. Meta-analysis

2.1.1. Inclusion criteria

(1) **Participants:** Patients diagnosed with COPD combined with RF, regardless of sex, age, and race, with diagnostic criteria by the Treatment Guidelines for COPD (2021 Revision) on the diagnostic conditions of COPD and the blood gas diagnostic criteria related to RF. Clinical (2) **Interventions:** The treatment group was treated with intravenous TRQI, along with conventional medical treatment. (3) **Comparators:** The control group was given conventional medical treatment, including anti-infection, oxygenation, antispasmodic and asthma, etc. (4) **Outcome indexes:** Primary outcome indicators including total clinical efficiency, PaO2, PaCO2, FEV1/FVC. Secondary outcome indicators including adverse reactions and duration of mechanical ventilation. (5) **Study design:** Only clinical randomized controlled Trials (RCTs) were included. (6) **Time periods:** The search period is from the establishment of the database to October 2022, with an unlimited sample size, and articles published in any language.

2.1.2. Exclusion criteria

(1) Non-RCT: including basic research literature and review literature; (2) repeatedly published literature; (3) inconsistent baseline information of included studies; (4) literature of too low quality; and (5) literature with missing data.

2.1.3. Sources and search strategy

The China National Knowledge Infrastructure (CNKI), Wanfang Digital Full-text Journal Database (Wanfang Data), Weipu Chinese Journal Database (VIP), China Biology Medicine Database (CBM), PubMed, Embase, and Cochrane Library databases were searched up to October 2022. We use a combination of theme words and free word as the search mode. Index words included Tanreqing Injection, chronic obstructive pulmonary disease, COPD, respiratory failure, randomized clinical trial, and RCT, together with the corresponding Chinese words. The search terms were limited to "Tanreqing Injection [Mesh] AND {((Chronic Obstructive Pulmonary Diseases [Mesh] OR COPD [Text Word]) AND respiratory failure [Mesh]) OR (Pulmonary Diseases, Chronic Obstructive [Mesh] AND respiratory failure [Mesh] OR Chronic respiratory failure [Text Word])}" (Table S1).

2.1.4. Data extraction

Two investigators compiled the literature, independently extracted the data, and cross-checked them. If differences were encountered, a third investigator assisted in resolving them after consultation. The extracted information included: (1) basic information of the included studies: title, authors, date of publication, and literature sources; (2) basic characteristics of the study population: sample size of the control and experimental groups; (3) specific treatment interventions: drugs, dose, duration of treatment, etc; and (4) main outcome indicators and additional outcome indicators.

2.1.5. Quality evaluation

The evaluation criteria in the Cochrane Handbook 5.1 were used, and the indicators included randomization methods, allocation concealment, blinding of investigators and subjects, blinded evaluation of study outcomes, completeness of outcome data, reporting bias.

2.1.6. Statistical analysis of data

Statistical analysis of data for each study was performed using Review Manager 5.4 and Stata/SE 16.0 software, and GRADE profile 3.6.1 software was used to evaluate the quality of the outcome indicators. Dichotomous and continuous variables were expressed using relative risk (*RR*) and mean difference (*MD*) or standardized mean difference (*SMD*), respectively. Relative risk (*RR*) and 95% confidence interval (*95% CI*) were used as effect indicators for each study outcome; and heterogeneity tests were performed using I^2. If the heterogeneity was small ($P \geq 0.1$, $I^2 \leq 50\%$), a fixed-effects model was selected; if the heterogeneity was significant ($P \leq 0.1$, $I^2 \geq 50\%$), a random-effects model was selected. Publication bias of the included studies was analyzed using forest plots and funnel plots.

2.2. Network pharmacology

2.2.1. Acquisition of active ingredients of TRQI

Referring to domestic and foreign literature to identify the active ingredients and the content of the main ingredients of TRQI [13,26,52,63], the four main ingredients, baicalin, ursodeoxycholic acid, chenodeoxycholic acid, and chlorogenic acid were selected [52,63] and the information related to the ingredients was retrieved from the TCMSP (http://tcmspw.com/) database [45] to obtain their unique Mol IDs (Table S2).

2.2.2. Collection of TRQI-related targets and construction of the ingredient-target network

The PubChem (http://pubchem.ncbi.nlm.nih.gov/) database [14] was used to find the Canonical SMILES number and 2D molecular formulas of the active ingredient of TRQI (Table S2), and the Swiss Target Prediction (http://www.swisstargetprediction.cn/) database [15] was used to predict the relevant targets (Table S3). The screened targets were sorted and imported into Cytoscape 3.9.2 to construct a TRQI active ingredient-target network, and network topology analysis was performed using the network analyzer plug-in to obtain the degree value, between centrality and other related parameters, where the degree value reflects its biological importance, and the higher the value, the more important the node is in the network.

2.2.3. Acquisition of COPD and RF related gene targets

Utilizing "Chronic Obstructive Pulmonary Diseases" with "Respiratory Failure" as the search keywords, we searched the DisGeNet (http://www.disgenet.org/home/) database [40], Genecards (http://www.genecards.org/) database [46], and TTD (http://db.idrblab.net/ttd/) database [64] to obtain COPD and RF related gene targets. The targets obtained from these three databases were combined, and the final number of targets was obtained by filtering with the median and eliminating duplicate values.

2.2.4. Construction of protein-protein interaction (PPI) network and core targets network

To illustrate the role of target proteins in the network, TRQI for COPD combined with RF potentially acting targets were imported into the STRING (http://string-db.org) database [48], species defined as homo sapiens, with a combined score >0.4 as the screening criterion, and no more than 10 indirect genes were set in the first layer and no more than 10 in the second layer. The obtained PPI network map was imported into Cytoscape 3.9.2 software for visualization and network topology analysis to access degree values, and the core targets were filtered according to the magnitude of the values. Thus, the node color shade changes with the degree value size.

2.2.5. GO and KEGG enrichment analysis

Potential functional proteins for the treatment of COPD combined with RF by TRQI were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes Genomes (KEGG) analyses using the DAVID 6.8.0 database (http://david.ncifcrf.gov/home) [22]. GO biology analysis resulted in three components shown—biological process(BP), molecular function (MF), and cellular component (CC)—and the top 10 components are shown. For the KEGG enrichment analysis, a p-value<0.05 was an inclusion criterion, and the top 14 were reported.

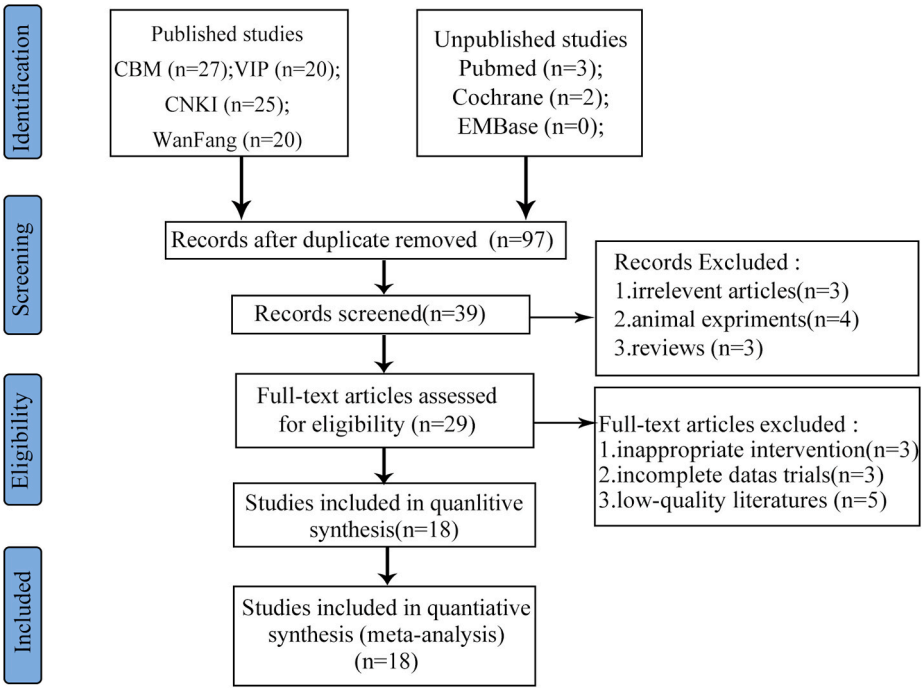


Fig. 2. Literature retrieval and screening process.

3. Results

3.1. Results of meta-analysis

3.1.1. Literature search and screening

A total of 97 articles were screened using database search. Duplicate articles, reading titles, and abstracts were excluded after screening, and non-RCTs, basic research articles, and review articles were also excluded, and 18 RCTs [5,7,8,11,12,16,20,21,28,36–38,42,47,49,53,60,61,66] were finally included, including 1485 patients. The literature retrieval and screening process are illustrated in Fig. 2.

3.1.2. Characteristics of included studies

In the studies included, the control group was treated with Western medicine alone, and the experimental group was treated with TRQI combined with Western medicine. A total of 1485 patients were enrolled, including 741 and 744 in the control and experimental groups. Three studies [5,36,66] did not mention the average age of the patients, and five studies [5,8,11,36,66] did not mention the average course of the disease. A detailed description is shown in Table 1 [7], [20], [47], [12], [53], [16], [11], [42], [21], [66], [36], [5], [60], [49], [38], [8], [28], [61],.

3.1.3. Quality assessment of included studies

All the included studies were conducted in China. Seven studies [7,11,12,16,20,28,53] used the allocation sequence generated from a table of random numbers method and were assessed as a low risk of bias. Five studies [38,42,49,61,66] only mentioned the "randomized" and did not demonstrate the specific randomization method, and were assessed as unclear risk of bias. Three studies [5, 37,47] did not mention the allocation method and were assessed as unclear risk of bias. Three studies [8,21,60] follow the inappropriate principle of random sequence generation, such as the time of admission, were assessed as high risk. None of the included

Table 1
General characteristics of included studies ($\bar{x} \pm s$)

Study	Sample (T/C)	Mean age (T/C)	Mean Course (T/C)	Interventions		Duration (d)	Outcomes
				T	C		
[7]	48/49	71.96 ± 5.17/72.5 ± 4.45	7.04 ± 2.06/6.46 ± 2.03	TRQI 15 ml,5%GS250ml, ivgtt, qd	Standard therapy	14	①④
[20]	25/25	64.49 ± 6.29/64.35 ± 6.21	16.72 ± 7.99/15.26 ± 8.25	TRQI20ml,0.9%NaCl250ml, ivgtt,qd	Standard therapy	14	①②③
[47]	60/60	49.3 ± 2.5/48.1 ± 4.7	6.3 ± 2.2/6.2 ± 1.7	TRQI15ml,0.9%NaCl200ml, ivgtt, qd	Standard therapy	21	①②
[12]	58/58	57.93 ± 4.23/59.3 ± 5.38	8.94 ± 1.73/8.25 ± 2.21	TRQI20ml,0.9%NaCl250ml, ivgtt,qd	Standard therapy	14	①②③
[53]	50/50	68.8 ± 5.3/68.5 ± 5.1	2.05 ± 0.42/1.96 ± 0.37	TRQI 20 ml, 5%GS, ivgtt, qd	Standard therapy	10–14	①②⑥
[16]	87/87	75.32 ± 6.03/74.73 ± 5.37	17.18 ± 9.32/16.48 ± 9.68	TRQI 20 ml,0.9%NaCl 250 ml, ivgtt, qd	Standard therapy	14	①②③
[11]	46/46	66.3 ± 3.4/66.5 ± 3.2	–	TRQI 20 ml,0.9%NaCl250ml, ivgtt, qd	Standard therapy	15	①②
[42]	20/20	58.71 ± 10.95/58.46 ± 11.24	5.38 ± 2.05/5.41 ± 2.12	TRQI 30 ml,5%GS400ml, ivgtt, qd	Standard therapy	7	①②
[21]	50/50	45.0 ± 10/47.0 ± 9	35.0 ± 10/34.0 ± 8	TRQI 21 ml, 5% GS, ivgtt, qd	Standard therapy	12–14	①②④
[66]	40/40	–	–	TRQI 20 ml, 0 .9%NaCl 250 ml, ivgtt,qd	Standard therapy	14	①②④
[36]	35/35	–	–	TRQI 20 ml,0.9%NaCl 250 ml, ivgtt,qd	Standard therapy	14	①②
[5]	38/38	–	–	TRQI 20 ml, 5%GS, ivgtt,qd	Standard therapy	10–14	①②⑤
[60]	30/30	65.4 ± 11.8/64.7 ± 12.3	16.3 ± 11.5/16.2 ± 11.6	TRQI 20 ml, 0.9%NaCl 150 ml, ivgtt,qd	Standard therapy	10	①②
[49]	37/37	62.3 ± 7.4/64.7 ± 8.6	12.5 ± 8.1/12.4 ± 7.3	TRQI 20 ml,0.9%NaCl 250 ml, ivgtt,qd	Standard therapy	10–14	①③
[38]	16/16	37–71/35–70	1.5–10/2–10	TRQI 30 ml, 5%GS 400 ml, ivgtt, qd	Standard therapy	10	①②④
[8]	42/40	65.4 ± 11.2/63.7 ± 12.5	–	TRQI 30 ml, 5%GS 250 ml, ivgtt, qd	Standard therapy	14	①②
[28]	32/30	62.0 ± 11.21/61.12 ± 12.35	10.32 ± 2.43/11.03 ± 2.17	TRQI 20 ml, 5% GS, ivgtt, bid	Standard therapy	14	①②④
[61]	30/30	67 ± 7.65/66 ± 8.51	1.49 ± 0.39/1.51 ± 0.38	TRQI 20 ml, 5% GS 250 ml, ivgtt, qd	Standard therapy	7	①②③④

Note: T: treatment group. C: control group. ①blood gas analysis(BG) (PaO2 and PaCO2). ②total clinical effectiveness. ③FEV1/FVC%. ④adverse reactions. ⑤mechanical ventilation time.

studies mentioned whether allocation concealment and were assessed as unclear risk of bias; None of the included studies used blinding methods and were assessed as "high" risk of bias; None of the studies had the missing data and was assessed as "low" risk of bias; None of the studies determined other sources of bias and were evaluated as unclear". A detailed description of the risk of bias is presented in Fig. 3.

3.1.4. Total clinical effectiveness

Sixteen studies [5,8,11,12,16,20,21,28,36,38,42,47,53,60,61,66] reported the total clinical effective rate between the experimental group and the control group before and after treatment. A total of 1314 patients were enrolled, including 659 and 655 in the experimental and control groups, respectively. The heterogeneity test results showed slight heterogeneity ($P = 0.11$, $I^2 = 31\%$), and the cause of the heterogeneity may be related to the different treatment times of each group. Therefore, to reduce the heterogeneity, subgroup analyses were performed according to the number of days of treatment. The heterogeneity test results suggest no heterogeneity in the studies for 7 days of treatment ($P = 0.57$, $I^2 = 0\%$), and slight heterogeneity between 8 and 14 days of treatments ($P = 0.04$, $I^2 = 45\%$) and 15–21 days of treatments ($P = 0.23$, $I^2 = 30\%$) studies. We used a fixed-effect model to conduct the heterogeneity test, Fig. 4 shows that compared with the control group, the total clinical effective rate of the treatment group is significantly higher than that of the control group ([$RR = 1.33$, *95%CI* (1.25, 1.41), $P < 0.00001$]), and the total clinical effective rate of patients after 7 days of treatment is more obvious and statistically significant, which indicates that the combination of TRQI with conventional treatment can improve the total clinical effective rate of patients with COPD-RF.

3.1.5. PaCO2

Eighteen studies [5,7,8,11,12,16,20,21,28,36,38,42,47,49,53,60,61,66] reported on the arterial blood PaCO2 levels between experimental group and control groups. A total of 1485 patients were included, including 744 and 741 in the experimental and control groups. The heterogeneity test shows that heterogeneity among the studies was relatively high ($P < 0.01$, $I^2 = 94\%$). A sensitivity analysis was performed and it was found that removing any of the documents could not have a significant impact on the heterogeneity

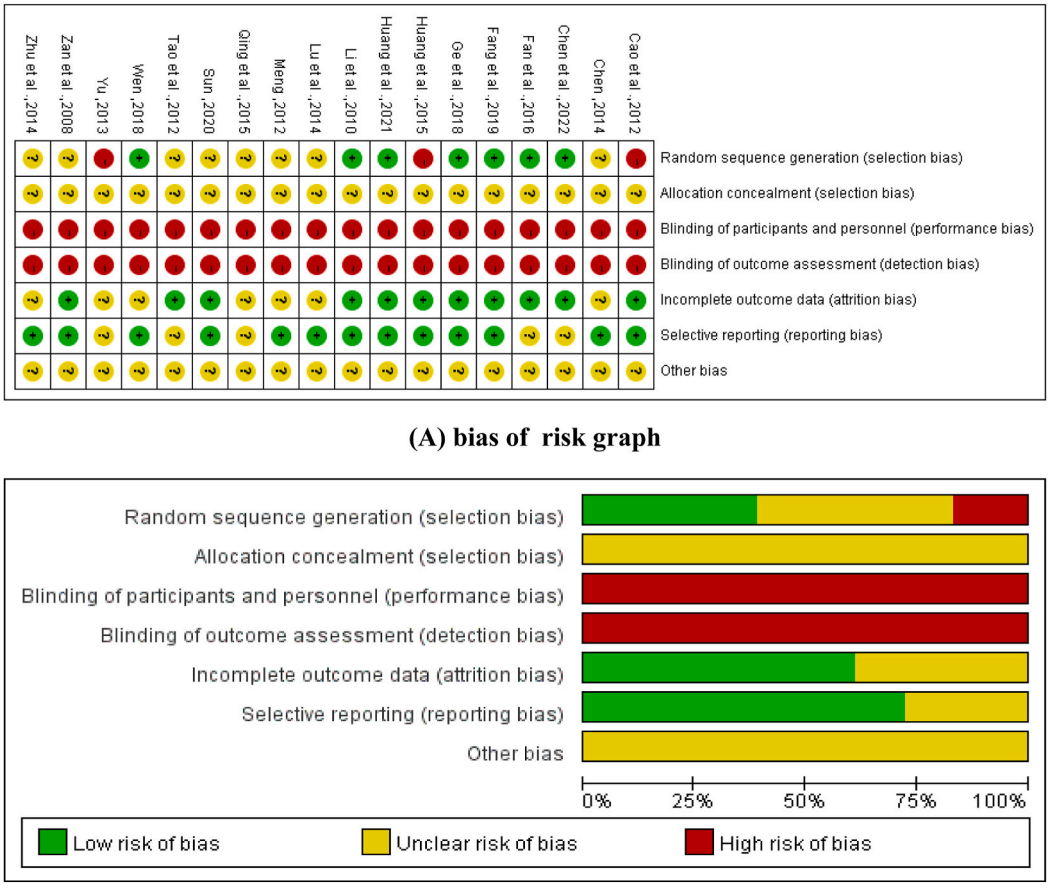


Fig. 3. Quality evaluation of included studies. A: bias of risk graph: risk of bias is shown separately for each included study; B: bias of risk summary: the display of each type of bias by percentage.

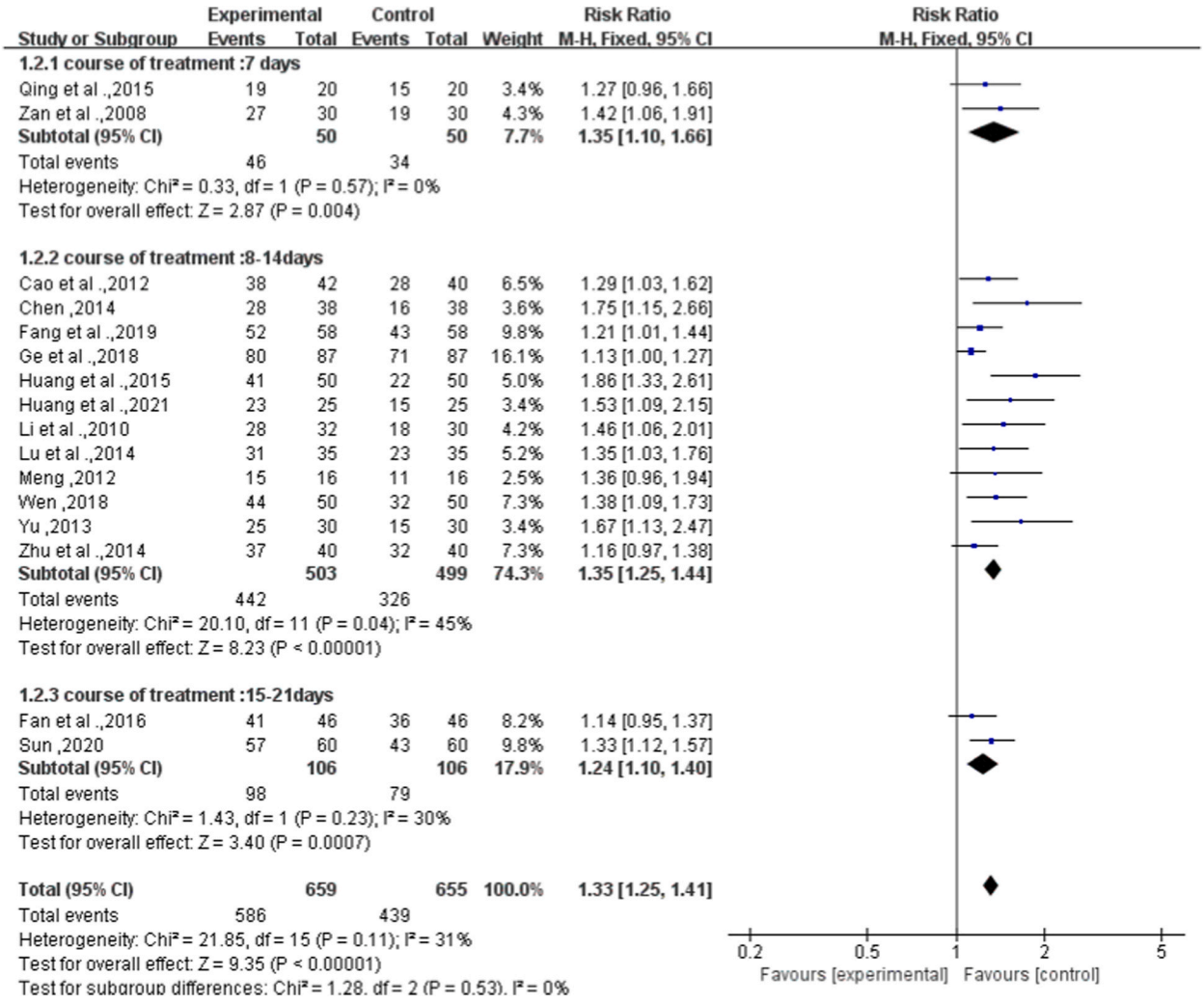


Fig. 4. Meta-analysis of total effective rates in included studies: forest plot of individual and overall effect of the experiment vs the control group on total effective rates outcome.

results, which indicated that the result was stable, therefore, the random-effects model was used. Fig. 5 shows that the results are statistically different [*SMD* = −1.29, *95%CI* (−1.41, −1.17), $P < 0.00001$], indicating that TRQI combined with conventional treatment is superior to conventional treatment alone in reducing PaCO2 in patients with COPD and RF.

3.1.6. PaO2

Seventeen studies [5,8,11,12,16,20,21,28,36,38,42,47,49,53,60,61,66] reported the arterial blood PaO2 levels in the experimental and control groups. A total of 1388 patients were included, including 696 and 692 in the experimental and control groups, respectively. The heterogeneity test depicted that the heterogeneity among the studies was relatively high ($P < 0.01$, $I^2 = 95\%$). A sensitivity analysis was conducted, and it was found that removing any of the studies did not have a significant impact on the heterogeneity results. The result was stable, therefore, the random-effects model was used. Fig. 6 shows that the results are statistically different [*SMD* = 1.19, *95%CI* (1.06, 1.31), $P < 0.00001$], indicating that TRQI combined with conventional treatment is more efficacious than the control group in improving PaO2 in patients with COPD and RF.

3.1.7. FEV1/FVC%

Four studies [12,16,20,61] reported on the level of lung function in the experimental and control groups. There were 400 patients, including 200 in the experimental group and 200 in the control group. The heterogeneity test showed that $P = 0.0007$, $I^2 = 82\%$, therefore, the fixed-effects model was adopted. Fig. 7 shows that TRQI combined with conventional treatment significantly improved the lung function of the patients compared with that of the control group [*SMD* = 1.00, *95%CI* (0.79, 1.21)].

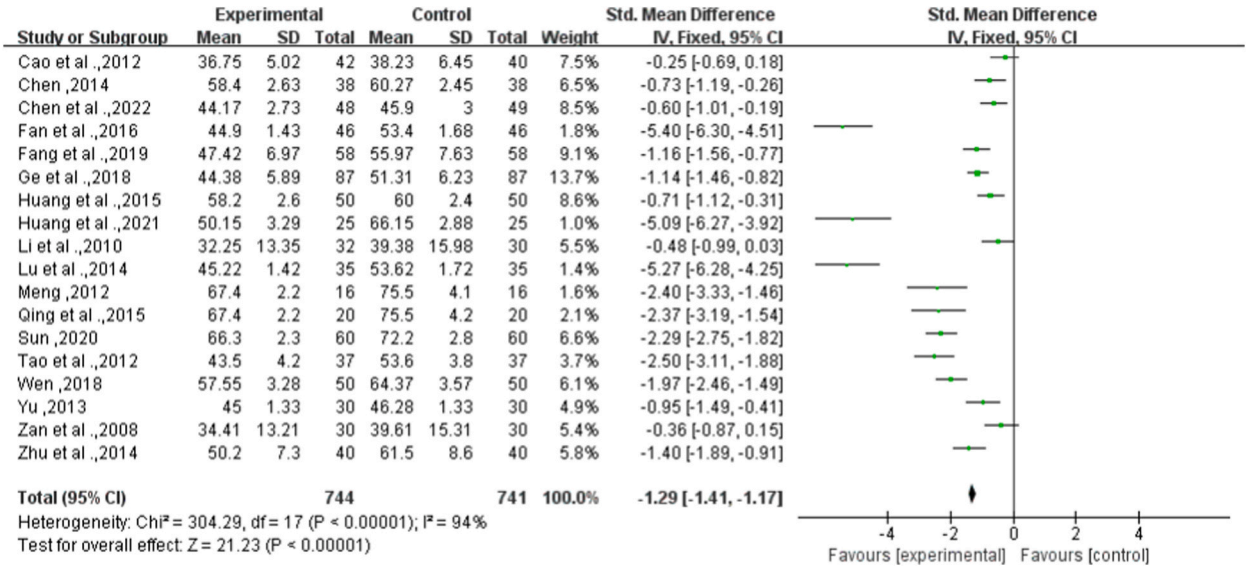


Fig. 5. Meta-analysis of $PaCO_2$ in included studies: forest plot of individual and overall effect of the experiment vs the control group on $PaCO_2$ outcome.

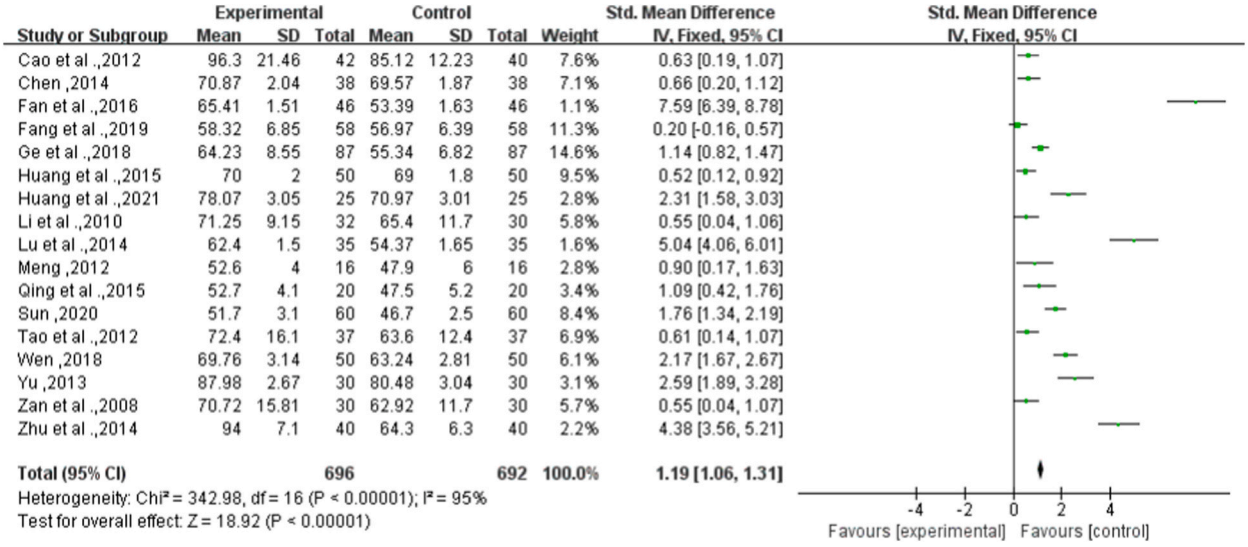


Fig. 6. Meta-analysis of PaO_2 in included studies: forest plot of individual and overall effect of the experiment vs the control group on PaO_2 outcome.

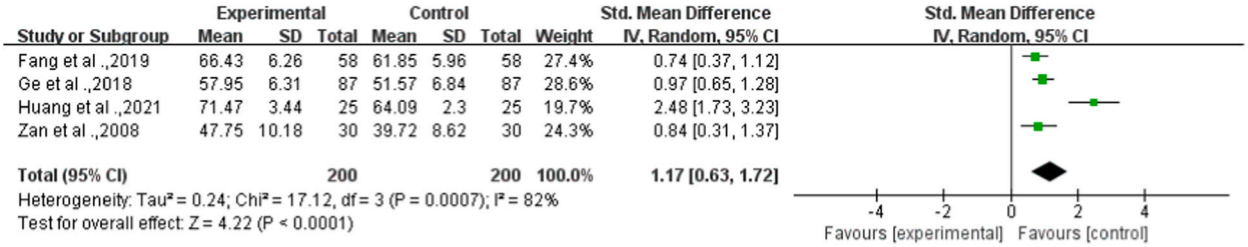


Fig. 7. Meta-analysis of pulmonary functions in included studies: forest plot of individual and overall effect of the experiment vs the control group on pulmonary functions outcome.

3.1.8. Mechanical ventilation time

Three studies [5,8,53] reported the mechanical ventilation time after treatment in the experimental and control groups. There were 258 patients, including 130 and 128 in the experimental and control groups, respectively. The heterogeneity test showed that $P = 0.0003$ and $I^2 = 88\%$, therefore, the random-effects model was adopted. Fig. 8 shows that TRQI has a positive effect on reducing the time of mechanical ventilation in patients with COPD combined with RF [*SMD* = −1.67, *95%CI* (−2.50, −0.84), $P < 0.00001$].

3.1.9. Adverse reactions

Of the 18 included studies, 3 studies [21,47,61] reported adverse reactions after medication in the control and treatment groups. Sun Hui [47] reported 5 cases of nausea, 18 cases of skin rash, and 9 cases of red blood cell decline in the control group; 2 cases of nausea, 10 cases of skin rash, and 4 cases of red blood cell decline in the treatment group. Huang Jie et al. [21] reported 8 cases of nausea, 22 cases of skin rash, and 15 cases of red blood cell decline in the control group; 2 cases of nausea, 10 cases of skin rash, and 3 cases of red blood cell decline in the treatment group. Zan Haifeng et al. [61] reported that one patient in the treatment group had a headache and mild chest tightness on the second day of medication. After slowing down the drug drip rate, the patient's headache and chest tightness symptoms spontaneously resolved without sequelae. The remaining 9 studies did not mention adverse reactions.

3.1.10. Publication bias

A funnel chart and Egger's regression chart were drawn for the total clinical effective rate of the included studies for publication bias analysis. As shown in Fig. 9, the corresponding points of the data are mainly concentrated at the top of the funnel, and the distribution was asymmetrical. Combined with the results of Egger's test ($t = 6.51$, $P < 0.05$), this suggests that the included studies may have a certain publication bias.

3.1.11. Evidence quality evaluation

The GRADE pro3.6.1 system was used to evaluate the quality of the outcome indicators. All RCTs default to the "high" level before proceeding to GRADE evidence level evaluation. In the evaluation process, the main consideration is whether to downgrade, and the factors that may lead to the decrease in the level of evidence are the five factors risk of bias, inconsistency, indirectness, accuracy, and publication bias [58]. The evaluation results showed that the outcome index (total effective rate, PaO2, PaCO2) of TRQI combined with conventional treatment was a "moderate" level; the level of evidence for lung function, mechanical ventilation time, and adverse reactions was "low" level. A detailed description of the evidence quality evaluation is presented in Table 2.

3.2. Results of network pharmacology

3.2.1. Potential targets for TRQI and COPD combined with RF

A total of 284 potential TRQI targets (after deduplication), 853 COPD genes, and 171 RF genes were gained after retrieval. We examined the interaction between the number of COPD and RF disease genes and the potential targets of TRQI. 19 common genes were acquired, that is, the potential targets of TRQI for COPD combined with RF (Fig. 10).

3.2.2. Construction of TRQI compounds-targets network

A total of 102 targets of baicalin, 74 targets of ursodeoxycholic acid, 109 targets of goose deoxycholic acid and 102 targets of chlorogenic acid were obtained by prediction (Table S3). The sorted "TRQI-active ingredient-target" Excel was entered into Cytoscape 3.9.0 to construct and visualize the compound-target protein network (Fig. 11.). The network has 4 compound nodes and 284 target protein nodes (after deduplication), with each compound acting on 71(284/4) targets on average, indicating that TRQI acts through multi-component multi-target.

3.2.3. Construction of PPI network

The 19 common targets obtained by mapping TRQI and COPD combined with RF in the Venny diagram were imported into the STRING database to construct a PPI network (Fig. 12A.) The PPI network was analyzed using Cytoscape 3.9.0 for network topology analysis, and the top 10 targets were screened according to the degree value, which was regarded to plays a vital role in the treatment of COPD combined with RF by TRQI. The top 10 targets according to degree ranking were TNF, TP53, SIRT1, SRC, CCND1, IL-10, NF-κB, MAPK14, STAT3, and SMAD3, and they were considered as possible core targets of TRQI for the treatment of COPD combined with

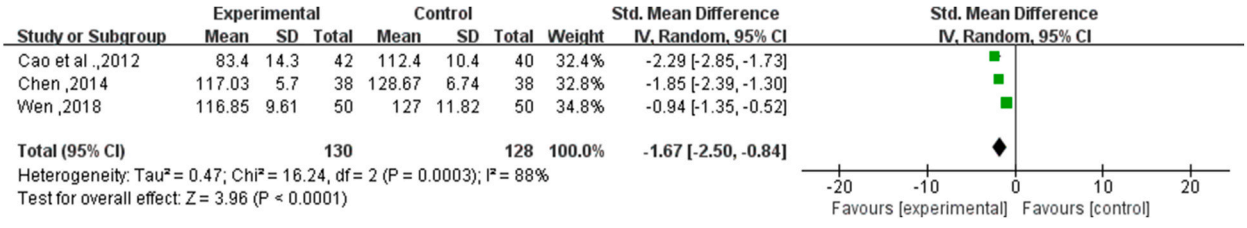
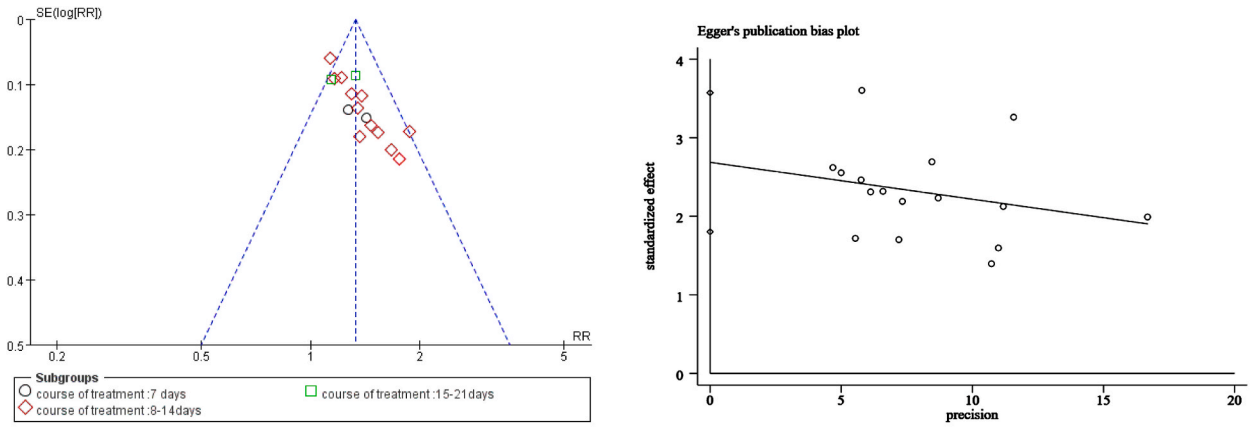


Fig. 8. Meta-analysis of the duration of ventilation in included studies: forest plot of individual and overall effect of the experiment vs the control group on the duration of ventilation outcome.



(A) Funnel plots for publication biases

(B) Egger's analysis chart

Fig. 9. Funnel plots for publication biases and Egger's analysis chart in included studies: A: Funnel plots for publication biases. B: Egger's analysis chart.

RF (Fig. 12B).

3.2.4. GO and KEGG analysis

GO enrichment analysis was conducted on 19 intersecting genes of TRQI for the treatment of COPD combined with RF, and $p < 0.05$, entries of biological function were gained, including 36 cell components, 93 molecular functions, and 905 biological processes. The top 10 rankings were selected for visualization and analysis (Table S5), as shown in Fig. 13A. These targets were entered into the David database for KEGG enrichment analysis, and a total of 56 entries with $p < 0.05$ were obtained, and the top 14 enrichment analysis pathways were screened (Table S6), which included the TNF, MAPK, IL-17, and NF-κB signaling pathways (Fig. 13B).

4. Discussion

COPD mainly affects the lungs and can also lead to extra-pulmonary multi-organ damage, eventually developing into RF and pulmonary heart disease as the disease worsens [51]. Respiratory tract infections are the main factor for patients with concurrent COPD. To prevent the development of the disease, anti-inflammatory drugs have become an option for long-term treatment of patients [41]; however, the incidence of broad-spectrum antibiotic resistance among anti-inflammatory drugs is increasing, leading to difficulty in coughing up sputum, deteriorating lung function, and increasing difficulty in infection control, which in turn leads to RF [59]. Adjunctive treatment with TRQI can improve microvascular injury in patients with COPD with RF, enhance the therapeutic effect and reduce the incidence of adverse effects [9,54].

Higher total clinical efficiency was observed in the treatment group compared to that of the control group. Subgroup analysis showed that the clinical efficiency of patients in the 7 day treatment group ($P = 0.57$, $I^2 = 0\%$) was more significant than that in the 8–14 day ($P = 0.04$, $I^2 = 45\%$) and 15–21-day ($P = 0.23$, $I^2 = 30\%$) treatment groups.

FEV1/FVC% is the ratio of the first second forceful expiratory volume to all expiratory volumes [44], and it is a sensitive indicator of obstructive ventilation dysfunction, and in the early stage [2]. Mechanical ventilation is used to maintain airway patency, improve ventilation and oxygenation, and prevent hypoxia and CO2 accumulation with the help of a ventilator [24], It is a more effective means of treating COPD combined with RF [19]. Both FEV1/FVC and mechanical ventilation time can reflect the respiratory function (2021). The results of the meta-analysis indicated that the treatment group significantly improved the level of FEV1/FVC% and reduced the time of mechanical ventilation significantly, which indicates that TRQI can improve the respiratory function of the patients.

For safety evaluation, no statistically significant difference was detected in the incidence of adverse reactions between the treatment and control groups, suggesting that the relevant adverse events were not significantly associated with the use of TRQI. Analysis of the relevant literature from a large sample size case series study suggests that TRQI-induced adverse reactions may be related to the solvents, dose used, drug-drug interactions, super-indication dosing, titration rate and individual differences [55,62]. Excessive concentration of the drug during clinical administration or too fast administration may lead to the occurrence of adverse reactions, such as pain at the injection site, dizziness, and irritant dermatitis [10]. Based on the above data, this study concluded that the combination of TRQI with conventional treatment has higher clinical safety.

Based on the results of the meta-analysis, we used network pharmacology to preliminarily explore the potential mechanism of TRQI in the treatment of COPD combined with RF. The results showed that the key active ingredients of TRQI, baicalin, chlorogenic acid, ursodeoxycholic acid, and chenodeoxycholic acid [26,31], could regulate factors, such as TNF, TP53, SIRT1, SRC, CCND1, IL-10, NF-κB, MAPK14, STAT3, SMAD3, and act on the relevant signaling pathways to achieve the effect of treating COPD combined with RF. GO and KEGG enrichment analyses revealed that TRQI treatment of COPD combined with RF mainly involved the activation of the TNF and MAPK signaling pathway, combating multiple viral infections, and modulation of cancer signaling pathways. The results

Table 2
GRADE Quality assessment of outcomes indicators.

Tanreqing Injection for COPD and respiratory failure

Patient or population: patients with COPD and respiratory failure
Settings:
Intervention: Tanreqing Injection

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Tanreqing Injection	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Partial pressure of carbon dioxide,PaCO2 Follow-up: mean 14 days		The mean partial pressure of carbon dioxide,paco2 in the intervention groups was **1.29 standard deviations lower** (2.18 to 1.17 lower)		1485 (18 studies)	⊕⊕⊕⊖ **moderate**[1,2]	SMD -1.63 (-2.18 to -1.08)
Partial pressure of oxygen,PaO2 Follow-up: mean 14 days		The mean partial pressure of oxygen,pao2 in the intervention groups was **1.19 standard deviations higher** (1.2 to 1.31 higher)		1388 (17 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD 1.8 (1.2 to 2.4)
total effective rates Follow-up: mean 14 days	**Study population**		**RR 1.33** (1.25 to 1.41)	1314 (16 studies)	⊕⊕⊕⊖ **moderate**[1]	
	670 per 1000	**891 per 1000** (838 to 945)				
	Moderate					
	688 per 1000	**915 per 1000** (860 to 970)				
Adverse reactions Follow-up: mean 14 days		The mean adverse reactions in the intervention groups was **5.81 standard deviations higher** (0.27 to 7.21 higher)		350 (6 studies)	⊕⊕⊖⊖ **low**[1,3]	
Lung function Follow-up: mean 14 days		The mean lung function in the intervention groups was **1 standard deviations higher** (0.27 to 1.21 higher)		400 (4 studies)	⊕⊕⊖⊖ **low**[1,3]	
Mechanical ventilation time Follow-up: mean 14 days		The mean mechanical ventilation time in the intervention groups was **1.67 standard deviations lower** (0 higher to 0.84 lower)		258 (3 studies)	⊕⊕⊖⊖ **low**[1,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Most trials had unclear risk，but the result had good robustness. The evidence was rated down by only one level
[2] Heterogeneity presented in them, and the results had good robustness. Not rated down
[3] The sample size for each outcome was fewer than 300 cases. Therefore, the evidence was rated down by one level

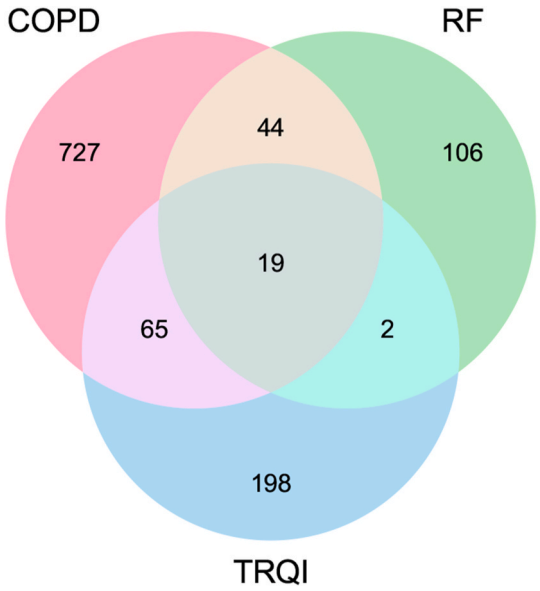


Fig. 10. The Venn diagram of TRQI and COPD combined with RF: The number of intersection targets of TRQI and COPD combined with RF.

confirmed that TRQI exerted its effects on the prevention and treatment of COPD combined with RF through the synergistic modulation of multi-component, target, and pathways.

TRQI comprises Jinyinhua (*Lonicera japonica Thunb.)*, Huangqin (*Scutellaria baicalensis Georgi*), Lianqiao (*Forsythia suspensa (Thunb.) Vahl*), Shanyangjiao (*Capra ibex Linnaeus*), and Xiongdanfen (*Fel Ursi Selenarctos thibetanus G.Cuvier Ursus arctos* L.). Its main chemical components are amino acids, cycloalkenes, terpenoids, flavonoids, phenolic acids, phenyl ethanol glycosides, lignans, steroids. Modern pharmacological studies have found that TRQI can attenuate inflammatory damage of lung tissue and can effectively regulate the release of IL-10, TNF-α, and MPO, which are involved in the whole process of COPD airway inflammation [52]. Among them, baicalin can act on a variety of immune cells, and can effectively inhibit the release of TNF-α, IL-1β, IL-6 by down-regulating NF-κB, MAPK, AKT, and other pathway-related proteins, with obvious anti-inflammatory effects [17]. Compounds, such as ursodeoxycholic acid, chenodeoxycholic acid, and chlorogenic acid can potentially act on the NF-κB, MAPK, JAK-STAT, and other cellular signaling pathways, thus effectively inhibiting the release of inflammatory factors [10]. Combined with the correlation value analysis in the PPI network, NF-κB, MAPK, and AKT belong to a class of factors in the pathogenesis of COPD, which further reveals that TRQI may play its role through signaling pathways such as TNF, MAPK, and NF-κB, etc.

Core targets are closely related to COPD-RF. For example, TNF is involved in the systemic inflammatory response in COPD [25], and cytokines such as TNF-α, IL-10, and IL-17, are upregulated when COPD continues to worsen [32]. TNF-α can disrupt epithelial cells as a physical barrier to airway inflammation and promote the release of inflammatory factors, such as IL-6 and IL-8 in bronchial epithelial cells, and high levels of IL-6 are associated with decreased lung function. TNF-α usually activates JNK, NF-κBp65, and p38 MAPK after promoting the production of many inflammatory mediators to further aggravate the inflammatory response in airway epithelial cells [57]. Activation of MAPK and NF-κB signaling pathways can upregulate inflammatory genes in airway epithelial cells. In patients with COPD combined with RF, NF-κB is highly activated, and NF-κB is the main transcription factor of pro-inflammatory factors in inflammation-related diseases, which is mainly dependent on the stimulation of pro-inflammatory cytokines (IL-1β and TNF-α) [27]. NF-κB is activated and released in large amounts and translocated into the nucleus, eventually leading to the transcription of pro-inflammatory genes. Sirtuin-1(SIRT1) is a protein-dependent deacetylase, is involved in coordinating a variety of isolated cellular functions, such as cell cycle, response to DNA damage, metabolism, apoptosis, and autophagy, which can be actively regulated by RPS19BP1 protein to mediate p53/TP53 deacetylation and thus inhibit p53/TP53-mediated transcriptional activity [56]. Moreover, SIRT1 reduces airway inflammation, is associated with reduced NF-κB(p65) acetylation, and that prevents particulate matter-induced airway inflammation [6].

The results of KEGG enrichment analysis depicted multiple signaling pathways, among which inflammation-related pathways, such as the TNF, MAPK, IL-17, and NF-κB signaling pathways, function in interconnections with each other. Furthermore, the TNF signaling pathway, as an important cytokine, can induce a variety of intracellular signaling pathways and may be a potential therapeutic target for TRQI in the treatment of COPD combined with RF [3]. Activated TNF binds to its receptors (TNFR1, TNFR2), and TNFR1 signaling induces the activation of many genes, which are mainly controlled by two different pathways, the NF-κB pathway, the MAPK cascade response, or apoptosis and necroptosis [25]. TNFR2 signaling activates NF-κB pathways, including the PI3K-dependent NF-κB and JNK pathways. The IL-17 family plays a crucial role in both acute and chronic inflammatory responses, signaling through its corresponding receptors and activating downstream pathways, including NF-κB, MAPKs, to induce cytokine and chemokine factor expression [32]. TNF, MAPK, and NF-κB signaling pathways are associated with COPD, which is consistent with the results of our enrichment analysis [1,34,35].

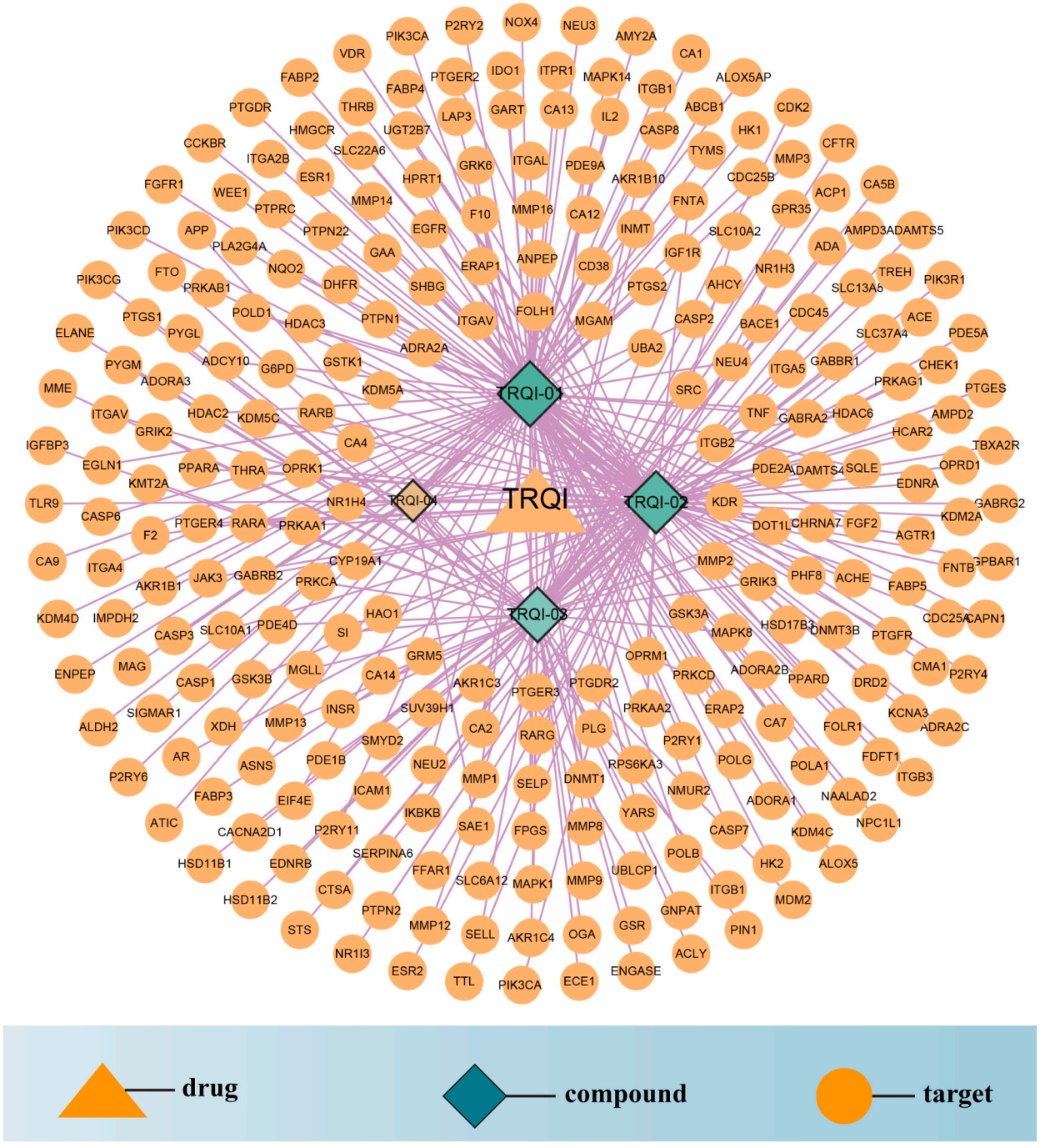


Fig. 11. TRQI compounds-targets network: The diamonds in the network diagram represent the four compound components of TRQI and the circles represent their targets obtained by prediction.

5. Limitation

In this study, we conducted literature screening and quality evaluation, according to predefined inclusion and exclusion criteria, and found some potential publication bias in the included studies by drawing funnel plots and Egger's regression plots, Other limitations include: (1) The randomized trials in this study had methodological flaws in reporting blinding and allocation concealment. (2) The included studies were all small sample trials of 30–90 participants, and there was heterogeneity in some of the outcome indicators. (3) All included studies were conducted in China, and there was geographical bias. (4) There is a need to improve other assessment

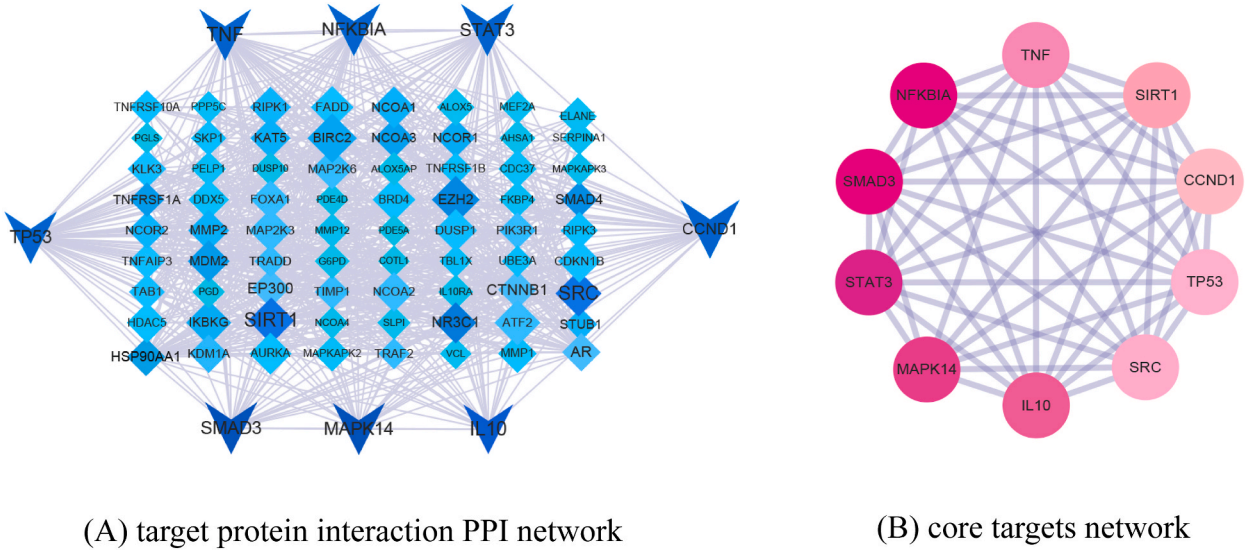


Fig. 12. PPI network of TRQI for COPD combined with RF: A: target protein interaction PPI network; B: core targets network.

indicators, such as the 6-minute walking test, the modified British medical research council dyspnea questionnaire, the COPD self-assessment test which is a symptom assessment test. (5) Network pharmacology is a research technology based on molecular network data and computer simulation analysis, which needs to be verified by in vitro and in vivo experiments in the future.

6. Conclusion

Based on meta-analysis and network pharmacology techniques, this study comprehensively evaluated the efficacy of TRQI combined with conventional chemotherapy in the treatment of COPD combined with RF and preliminarily explored its potential mechanism of action. The meta-analysis results demonstrated that adjuvant treatment of COPD with RF using TRQI was better than conventional treatment alone in terms of improving the total clinical efficiency, increasing PaO2, lowering PaCO2, improving lung function, and reducing the duration of mechanical ventilation. Through network pharmacology analysis, 284 potential TRQI targets, 19 common targets, and 56 related pathways were identified, mainly involving the TNF, MAPK, IL-17, NF-κB signaling pathways. Therefore, TRQI may act through multiple targets and pathways in the treatment of COPD combined with RF.

Declarations

Author contribution statement

Dan Wang and Di Han: Performed the experiments; Wrote the paper. Tongxing Huang: Contributed reagents, materials, analysis tools or data. Yong Xu: Analyzed and interpreted the data. Xianmei Zhou: Conceived and designed the experiments.

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Data availability statement

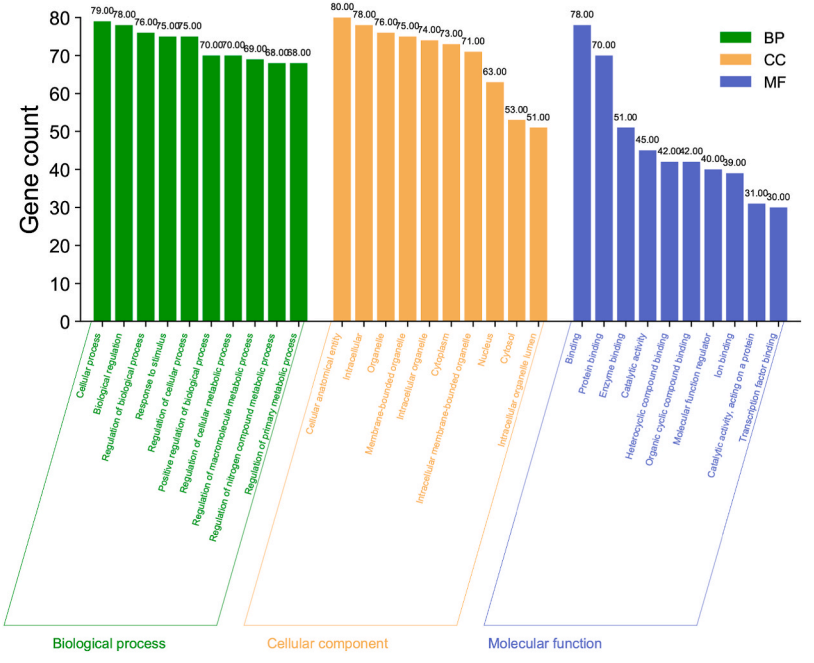
Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

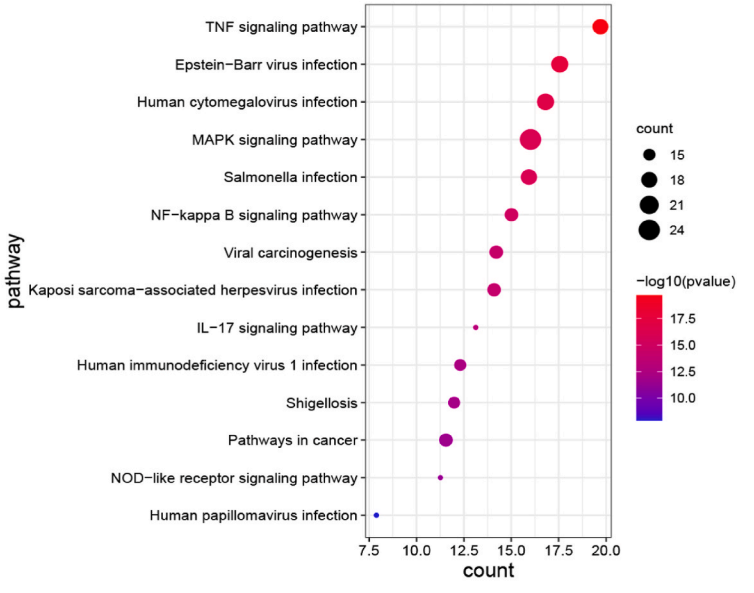
The authors declare no conflict of interest.

Abbreviation

TRQI Tanreqing injection. COPD Chronic obstructive pulmonary disease. RF Respiratory failure. PaO2 Partial pressure of dioxide. PaCO2 Partial pressure of carbon dioxide. COPD-RF COPD combined with RF. RCTs Randomized controlled trials CBM China Biology Medicine Database. CNKI China National Knowledge Infrastructure. VIP Weipu Chinese Journal Database. Wanfang Wanfang Digital



(A) GO enrichment analysis



(B) KEGG enrichment analysis

Fig. 13. GO and KEGG enrichment analysis: A: GO enrichment analysis of treating COPD combined with RF; B: KEGG enrichment analysis of treating COPD combined with RF.

Full-text Journal Database MD mean difference. RR relative risk SMD standardized mean difference. 95% CI 95% confidence interval PPI Protein-protein interaction. GO Gene Ontology KEGG Kyoto Encyclopedia of Genes and Genomes. BG Blood gas analysis TNF Tumor necrosis factor. TP53 Cellular tumor antigen p53 NF-κB Nuclear factor NF-kappa-B. SIRT1 NAD-dependent protein deacetylase sirtuin-1 CCND1 G1/S-specific cyclin-D1. SRC Proto-oncogene tyrosine-protein kinase Src IL-10 Interleukin-10. MPO Myeloperoxidase MAPK14 Mitogen-activated protein kinase 14. STAT3 Signal transducer and activator of transcription 3. IL-6 Interleukin-6. AKT threonine-protein kinase. SMAD3 Mothers against decapentaplegic homolog 3. STAT Signal transducer and activator of transcription. IL-17 Interleukin-17A. JNK c-jun n-terminal kinase. RPS19BP1 Ribosomal protein s19 binding protein 1. TNFR1 Tumor necrosis factor receptor 1. TNFR2 Tumor necrosis factor receptor 2. 6MWT 6-minute walking test CAT COPD Assessment Test. mMRC modified British medical research council.

Additional information

Supplementary content related to this article has been published online at.

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e13513.

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