Systematic Review and Meta-Analysis

Medicine

OPEN

The impact of Tanreqing injection on mucus hypersecretion and cough in bronchiectasis

A meta-analysis of randomized controlled trials

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Abstract

Background: Bronchiectasis clinically manifests airway mucus hypersecretion as mucopurulent sputum production and chronic cough. In the past decade, Tanreqing injection (TRQ) has been often used in clinical practice as an add-on treatment for bronchiectasis in China. Several in vivo studies have indicated that TRQ is effective in improving sputum expectoration and cough in acute exacerbation of bronchiectasis but results of individual studies are inconsistent. Therefore, systematically and critically evaluating the effectiveness and safety of TRQ on mucus hypersecretion and cough in bronchiectasis is necessary.

Methods: Randomized controlled trials examining the treatment of bronchiectasis with TRQ were systematically searched from databases including PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure, Vip Information Database, Wanfang data, and Chinese Biomedical Literature Database, based on a preregistered protocol and adhering to Cochrane methods. Pertinent data were taken out from the included studies and a methodological quality assessment was done. R language (version 4.4.1) was used to perform the meta-analysis.

Results: Twenty randomized controlled trials involving 1544 patients were analyzed. The results demonstrated that TRQ significantly improved mucus hypersecretion, shortened the duration of cough and phlegm, reduced symptom scores, and enhanced both forced expiratory volume in 1 second and forced vital capacity. Additionally, TRQ effectively lowered inflammatory markers, including C-reactive protein, procalcitonin, white blood cell count, neutrophil count, interleukin-6, and tumor necrosis factor-alpha. Moreover, TRQ increased the partial pressure of oxygen and decreased carbon dioxide pressure.

Conclusion: The findings suggest that TRQ positively impacts mucus hypersecretion and mucociliary clearance, leading to improvements in sputum production and cough during bronchiectasis exacerbations, without increasing the risk of adverse effects. TRQ may be considered a viable option for managing bronchiectasis and could serve as a novel mucus-modifying agent.

Abbreviations: CI = confidence intervals, CRP = C-reactive protein, CWM = conventional Western medicine, ESR = erythrocyte sedimentation rate, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IL-6 = interleukin-6, MD = mean differences, MUC5AC = Mucin 5AC, NEUT% = neutrophil percentage, $PaCO_2$ = carbon dioxide pressure, PaO_2 = partial pressure of oxygen, PCT = procalcitonin, PEF = peak expiratory flow, RCTs = randomized controlled trials, SMD = standard mean differences, TNF-α = tumor necrosis factor-alpha, TRQ = Tanreqing injection, WBC = white blood cell.

Keywords: bronchiectasis, cough, meta-analysis, mucus hypersecretion, Tanreqing injection

1. Introduction

Bronchiectasis is radiographically characterized by the permanent dilation of the bronchi and clinically by chronic cough, sputum production, and recurrent lung infections.[1] Since 2003, the prevalence has increased by 40%, with estimates reaching up to 566/100,000 population in the UK (2013) and 174/100,000 in China.[2–4] A recent prospective cohort study found that individuals with bronchiectasis experienced a median of 2 exacerbations per year (IQR 1–4), with 26.4%

The work was supported by the Special Project on Enhancing the Level of Evidence-Based Clinical Research in Traditional Chinese Medicine at Xiyuan Hospital, China Academy of Chinese Medical Sciences (No. XYZX0201-13).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Meta-analyses typically do not require ethical approval because they rely on publicly available data, do not involve original data collection, protect participant privacy, and involve no direct interventions or risk to participants' health or safety during the analysis process.

PROSPERO registration number: CRD42024564507 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=564507).

Supplemental Digital Content is available for this article.

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How to cite this article: Zhang J, Yang Z, Yuan S, Duan Y, Miao Q. The impact of Tanreqing injection on mucus hypersecretion and cough in bronchiectasis: A meta-analysis of randomized controlled trials. Medicine 2024;103:45(e40465).

Received: 23 September 2024 / Received in final form: 19 October 2024 / Accepted: 23 October 2024

http://dx.doi.org/10.1097/MD.0000000000040465

requiring hospitalization for exacerbations in the preceding year, significantly deteriorating their health status and escalating the healthcare burden.[5] However, the management of bronchiectasis remains challenging due to its heterogeneous etiology, diverse clinical manifestations, and complex pathophysiological mechanisms.[6] Notably, most treatments for bronchiectasis have been adapted from cystic fibrosis therapies rather than being specifically developed for bronchiectasis,[7] and there are currently no licensed treatments specifically for this condition.[8]

Patients suffering from bronchiectasis exacerbations manifest airway mucus hypersecretion as mucopurulent sputum production, cough, dyspnea, and respiratory failure.[9,10] Mucus hypersecretion represents a key pathophysiological feature and a treatable trait of the disease.[11] It is burdensome to patients and associated with lower forced expiratory volume in 1 second (FEV1), higher inflammatory markers, greater bacterial infection, poor quality of life, and higher risk of exacerbation, hospitalization, and mortality.[11–13] The relevant pharmacological and nonpharmacological treatments focus on enhancing mucus clearance, reducing airway inflammation, and tackling chronic bacterial infections, mainly based on the use of antimicrobials, bronchodilators, mucolytics, inhaled hyperosmolar agents, and airway clearance techniques.[6,14,15] Although effective airway clearance remains the cornerstone of its management, the availability and use of devices, mucoactive drugs and specialist chest physiotherapy are limited in many countries.[16] Consequently, these existing approaches provide only limited relief from airway mucus hypersecretion and its associated symptoms.

Chinese herbal expectorant preparations, such as Tanreqing injection (TRQ), may play a key role in reducing mucus secretion and enhancing its clearance. TRQ is an intravenous herbal preparation known for its anti-inflammatory,[17] antibacterial,[18] and expectorant properties.[19] It is derived from 5 Chinese medicines: Scutellariae Radix, Lonicerae Japonicae Flos, Forsythiae Fructus, bear bile powder, and goral horn.[20] The formulation has been approved by the National Drug Regulatory Authority of China (State Medical Permit No. Z20030054), and its quality is assessed using high-performance liquid chromatography.[21,22] It is primarily used to alleviate symptoms such as cough, fever, and excessive mucopurulent sputum production, and is widely utilized in China for treating various respiratory diseases, including acute bronchitis,[23] bronchiectasis,[18] chronic obstructive pulmonary disease,[24] pneumonia,[25] and even dengue fever.[17] Recently, some studies have shown that TRQ can improve mucociliary clearance,[26] against mucus hypersecretion and Mucin 5AC (MUC5AC) production,[19] alleviate cough symptoms, reduce airway inflammation and elevate lung function in patients with bronchiectasis.[27] However, the results of individual studies are inconsistent, and the efficacy and safety of TRQ in treating bronchiectasis with mucus hypersecretion are not yet fully established. Therefore, this study employs an evidence-based approach to systematically evaluate the efficacy and safety of TRQ on mucus hypersecretion and cough in bronchiectasis, thereby providing a foundation for clinical practice.

2. Materials and methods

2.1. Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024564507. The keywords utilized in this study included "Tanreqing injection," "TanReQing," "acute exacerbations of bronchiectasis," "acute exacerbations," "bronchiectasis," "mucus hypersecretion," "cough," and "Randomized Controlled Trials" as Chinese and English subject headings. A comprehensive computerized search was independently conducted by 2 authors across 8 databases: PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure, VIP Information Database, Wanfang Data, and Chinese Biomedical Literature Database. The search encompassed publications from the inception of each database up to June 2024. Medical Subject Headings and free-text terms were adapted as necessary for each database. The search was limited to randomized controlled trials (RCTs) published in English and Chinese, with no restrictions on publication year. Detailed search strategies and screening processes are provided in Appendix 1, Supplemental Digital Content, http://links.lww.com/MD/N878.

2.2. Inclusion criteria

(1) Study population: bronchiectasis exacerbation patients. The diagnosis of patients with adult bronchiectasis (≥18 years) was based on the European Respiratory Society/the British Thoracic Society guidelines. High-resolution computed tomography served as the gold standard for confirming bronchiectasis. The consensus definition of exacerbation is as follows: a person with bronchiectasis with a deterioration in 3 or more of the following key symptoms for at least 48 hours: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; hemoptysis and a clinician determines that a change in bronchiectasis treatment is required, generally referring to the prescription of antibiotics.
(2) Intervention and control
Both the control and experimental groups received conventional Western treatment, which included bronchodilators, anti-infection medications, mucolytics, continuous low-flow oxygen, and correction of water and electrolyte imbalances. In addition to conventional Western treatment, the experimental group was administered TRQ injection.
(3) Outcomes
Primary outcomes included time to symptom disappearance (including cough, sputum production, fever, lung rales), symptom scores (including breathlessness, cough, and sputum expectoration), and FEV1; secondary outcomes included forced vital capacity (FVC), peak expiratory flow (PEF), partial pressure of oxygen (PaO_2), carbon dioxide pressure ($PaCO_2$), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), neutrophil percentage (NEUT%), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α). Safety outcomes were assessed by evaluating adverse events.
(4) Study design: RCTs.

2.3. Exclusion criteria

(1) Studies not involving TRQ injection as the primary intervention; (2) non-randomized or observational studies; (3) studies with duplicate data; and (4) Studies with incomplete data, specifically those lacking outcome measures for symptom scores, lung function, inflammatory markers, or blood gas analysis.

2.4. Data collection process

The search criteria were implemented in 2 stages: initially, studies deemed clearly ineligible were excluded based solely on an abstract review. Subsequently, a thorough review of full manuscripts was conducted to ascertain final eligibility. Only studies meeting the specified inclusion criteria were incorporated. Furthermore, the ClinicalTrials.gov registry was queried using the term "bronchiectasis," and reference lists from pertinent

publications, prior meta-analyses, and relevant guidelines were examined to enhance the comprehensiveness of the search.

2.5. Data extraction

Two reviewers extracted data independently, and disagreements were settled by consensus. The following data were extracted from each study: (a) first author; (b) publication year; (c) patient characteristics; (d) sample size; (e) interventions and controls; (f) treatment duration; (g) outcome measures; (h) adverse events.

2.6. Risk of bias assessment

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool, which evaluates 6 domains: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting. The risk of bias for each study was categorized as "low risk," "high risk," or "unclear." Additionally, evidence quality was appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which classifies evidence into 4 levels: high, moderate, low, and very low. Evidence quality could be downgraded based on 5 factors: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Any discrepancies were addressed through discussion and resolved by consensus, with the involvement of a third party as necessary.

2.7. Data synthesis and analysis

The meta-analysis was conducted using RStudio, an integrated development environment for the R programming language (version 4.4.1). Continuous outcomes were reported as mean differences (MD) with 95% confidence intervals (CI), while dichotomous outcomes were reported as risk ratios with 95% CI. Heterogeneity among studies was evaluated using the I^2 statistic, with values exceeding 50% indicating significant heterogeneity. A random-effects model was employed to account for potential heterogeneity. In cases of low heterogeneity ($P \geq .05$, $I^2 < 50\%$), a fixed-effects model was utilized. Conversely, a fixed-effects model is used. Sensitivity analyses were performed to assess the robustness of the findings, and publication bias was investigated using funnel plots. For outcome indicators with more than 10 studies, funnel plots were specifically employed to detect publication bias. A z-test was conducted to determine whether TRQ as adjunctive therapy significantly outperformed Western medicine alone in the treatment of bronchiectasis. Statistical significance was set at $P < .05$.

3. Results

3.1. Selection and inclusion of studies

A comprehensive search across databases initially identified 675 potential studies. After removing duplicates, 336 studies remained. Of these, 290 studies were excluded since they were reviews, animal experiments, and conference papers. Based on the eligibility criteria, the full texts of 28 studies were meticulously screened. Ultimately, 20 RCTs were included for further quality assessment and meta-analysis. The results are shown in Figure 1.

3.2. Basic characteristics of the included studies

A total of 1544 patients were included across the 20 studies,[27,29–47] with 811 patients in the experimental group and 790 patients in the control group. No statistically significant differences in baseline characteristics were observed between the experimental and control groups (all $P > .05$). The studies, published from 2013 to 2024, were all conducted in China. Sample sizes varied between 48 and 126 participants, and the treatment durations ranged from 4 to 14 days. In terms of interventions, the control group in all 20 studies received conventional Western medicine (CWM), primarily consisting of β-lactam antibiotics. Routine therapies were administered as needed, including bronchodilators, cough suppressants, expectorants, postural drainage, and oxygen inhalation treatments. The experimental group received TRQ in combination with CWM. All studies were RCTs and were published in full text. The fundamental characteristics of the included studies are presented in Table 1.

3.3. Risk bias of included studies

The Cochrane Risk of Bias Assessment Tool was used to evaluate the quality of the 20 included studies. (1) Selection bias (random sequence generation and allocation concealment): 4 RCTs[31,35,42,47] grouped patients based on the time of admission, resulting in a "high risk" evaluation for selection bias. Seven RCTs[27,32–34,37,40,46] utilized randomization methods such as drawing lots or using random number tables, leading to a "low risk" evaluation for selection bias. The remaining RCTs mentioned random grouping but did not provide detailed methods, thus selection bias was assessed as "unclear risk." Due to the lack of information on allocation concealment, this aspect was also evaluated as "unclear risk." (2) Performance bias: none of the studies reported on blinding procedures, resulting in an "unclear risk" evaluation for performance bias. (3) Detection bias: blinding of outcome assessment was evaluated as "low risk" since the outcome indicators were objective measures. (4) Attrition bias: none of the included RCTs had incomplete data, so attrition bias was assessed as "low risk." (5) Reporting bias: for selective reporting, all data in the literature were complete and therefore rated as "low risk." (6) Other bias: this was evaluated as "unclear risk" due to insufficient information. The bias assessment of the included RCTs is shown in Figure 2.

3.4. Time to symptom disappearance

3.4.1. The time for the disappearance of cough and sputum. Five RCTs,[30,41,42,44,45] including a total of 409 patients, reported the time to disappearance of cough and sputum. The heterogeneity test revealed significant variability among the included studies ($I^2 = 83\%$, $P < .01$). Therefore, a meta-analysis was performed using a random-effects model. The results demonstrated that TRQ significantly reduced the time to symptom disappearance, including the duration for cough symptoms to subside and the time required for improvement in sputum production (standard mean differences [SMD] = −1.04, 95% CI (−1.25, −0.84), $P < .0001$, Fig. 3).

3.4.2. The time for defervescence. Five RCTs,[30,41,42,44,45] including 409 patients, reported the results of the time for defervescence. The heterogeneity test indicated high variability among the studies ($I^2 = 88\%$, $P < .01$), prompting the use of a random-effects model for the meta-analysis. The results revealed a statistically significant reduction in the time to defervescence in patients with bronchiectasis exacerbation following TRQ treatment compared to the control group (SMD = −1.22, 95% CI (−1.50, −0.94), $P < .0001$; see Fig. 4).

3.4.3. The time for the disappearance of lung rales. Five RCTs,[30,41,42,44,45] including 409 patients, reported the results of the time for the disappearance of lung rales. The heterogeneity test revealed substantial variability among the included studies ($I^2 = 89\%$, $P < .01$), necessitating the use of a random-effects model for the meta-analysis. The findings indicated a statistically significant reduction in the time for the disappearance of lung rales in patients with bronchiectasis exacerbation treated with

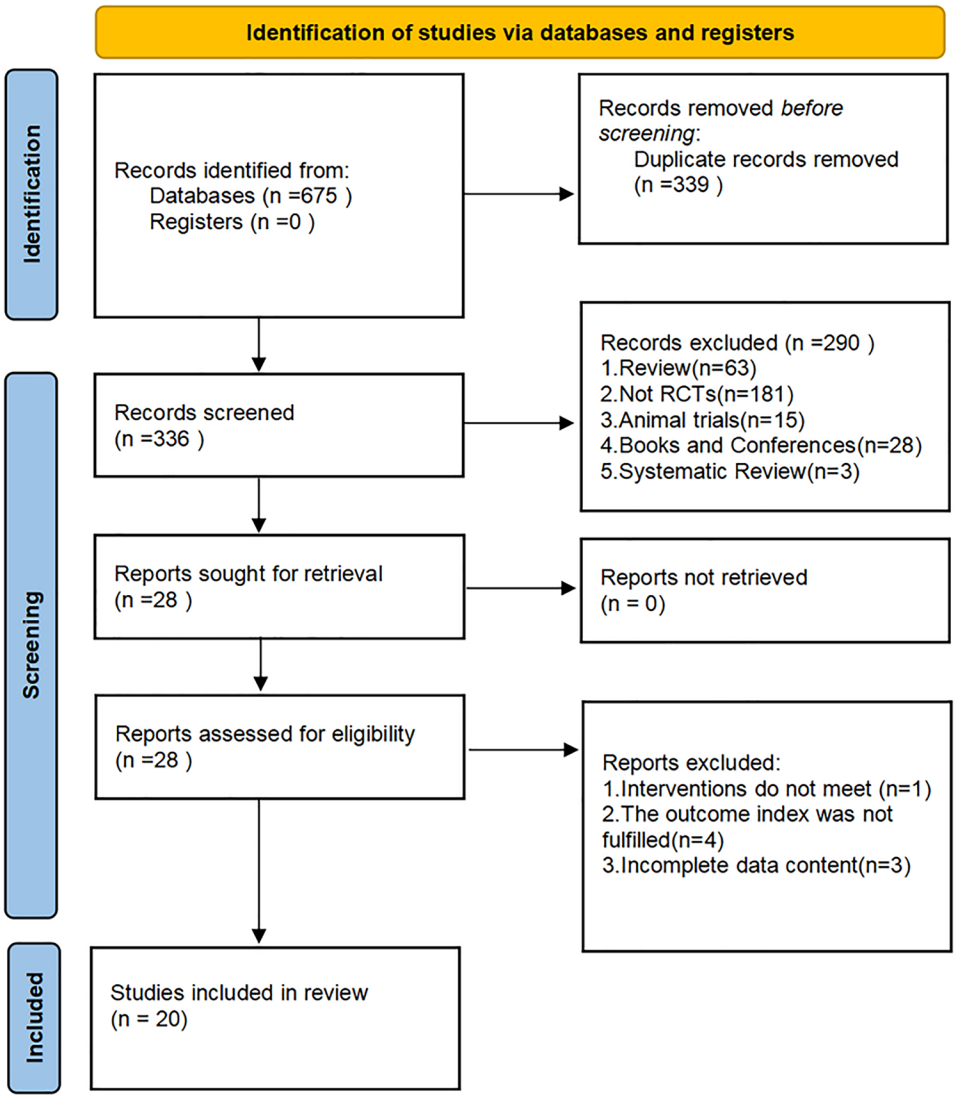

Figure 1. Flowchart for selection of randomized controlled trials.

TRQ, compared to the control group (SMD = −1.47, 95% CI (−1.69, −1.25), $P < .0001$, Fig. 5).

3.5. Symptom scores

3.5.1. Symptom score for cough. Five RCTs,[27,29,31,36,43] comprising 419 patients, reported data on cough symptom scores. Due to high heterogeneity ($I^2 = 95\%$, $P < .0001$), a random-effects model was employed for the analysis. The meta-analysis indicated that TRQ combined with CTM significantly reduced cough symptom scores compared to Western medicine alone (SMD = −1.48, 95% CI (−2.63, −0.34), $P = .01$, Fig. 6).

3.5.2. Symptom score for phlegm. Five RCTs,[27,29,31,36,43] encompassing a total of 419 patients, reported on the severity of phlegm-related symptoms. A test for heterogeneity revealed moderate heterogeneity among the included studies ($I^2 = 58\%$, $P = .05$). Consequently, a meta-analysis was conducted using a random-effects model. The findings demonstrated a statistically significant reduction in phlegm symptom scores in patients with bronchiectasis following treatment with TRQ compared to the control group (MD = −1.52, 95% CI (−1.72, −1.32), $P < .0001$, Fig. 7).

3.5.3. Dyspnea symptom score. Two RCTs,[27,43] involving 120 patients, reported on dyspnea symptom scores. The heterogeneity test indicated low heterogeneity between the included studies ($I^2 = 0\%$, $P = .49$), allowing for a meta-analysis using a fixed-effects model. The results showed no statistically significant difference in the dyspnea symptom scores between the treatment group and the control group (MD = −0.17, 95% CI (−0.40, 0.06), $P < .0001$, $P = .14$, Fig. 8).

3.6. Lung function

3.6.1. FEV1. Eight RCTs,[33,36–40,42,46] comprising a total of 653 patients, reported on FEV1. The heterogeneity analysis revealed significant variability among the included studies ($I^2 = 95.5\%$, $P < .0001$), necessitating the use of a random-effects model for the meta-analysis. The findings demonstrated a statistically significant improvement in FEV1 in patients with bronchiectasis following treatment with TRQ compared to the control group (SMD = 2.0, 95% CI (0.74, 3.25), $P = .002$, Fig. 9).

3.6.2. FVC. Six RCTs,[33,36–39,42] involving 465 patients, reported on FVC. The heterogeneity analysis indicated substantial variability among the included studies ($I^2 = 95\%$,

Table 1

Basic characteristics of the included studies.

Study	Sample (T/C)	Sex (male/female)		Average age (year)		Interventions		Treatment duration (day)	Outcome parameters	Adverse reactions
		T	C	T	C	T	C			
Guo (2017)	45/45	24/21	22/23	52.3 ± 10.4	51.8 ± 10.1	CWT + Tanreqing injection (ivgtt)	CWT	10	7, 17, 11, 15, 18	Not shown
Chen (A) (2017)	35/35	23/12	21/14	48.6 ± 3.3	48.2 ± 3.1	CWT + Tanreqing injection (bronchoalveolar lavage)	CWT	4	1, 2, 3, 10, 11, 13, 14	No adverse reaction
Li (A) (2019)	63/63	37/26	40/23	45.41 ± 6.40	45.10 ± 6.33	CWT + Tanreqing injection (ivgtt)	CWT	7	4, 5, 6, 10, 11, 13, 14, 17, 18	T: 6 cases had gastrointestinal symptoms, 2 cases felt xerostomia; C: 4 cases had gastrointestinal symptoms, 1 case had skin allergy, 1 case felt xerostomia
Zhang (2019)	42/42	23/19	25/17	45.09 ± 6. 27	44.73 ± 6.20	CWT + Tanreqing injection (ivgtt)	CWT	7	4, 5, 6, 10, 11, 12, 14, 15, 16, 17, 18	T: 5 cases had Gastrointestinal symptoms, 2 cases felt xerostomia; C: 3 cases had Gastrointestinal symptoms, 1 case experienced skin allergy, 1 case felt xerostomia
Yu (2021)	40/40	17/23	15/25	49. 2 ± 5. 7	50. 4 ± 5.9	CWT + Tanreqing injection (ivgtt)	CWT	10	7, 8, 10, 11, 14, 15, 16, 17, 18	Not shown
Gu (2017)	45/45	31/14	29/16	62.73 ± 3.08	52.23 ± 2.18	CWT + Tanreqing injection (inh)	CWT	7	7, 8, 9, 14	Not shown
Li (B) (2016)	30/30	18/ 12	15/15	60 ± 3.08	58.23 ± 2.18	CWT + Tanreqing injection (inh)	CWT	7	7, 14	No adverse reaction
Wu (A) (2018)	30/30	18/12	17/13	62.93 ± 0.64	62.28 ± 10.83	CWT + Tanreqing injection (inh + ivgtt)	CWT	14	10, 11, 13	T: 1 case experienced throat discomfort
Chen (B) (2023)	30/30	11/19	14/16	58.57 ± 11.40	62.60 ± 8.72	CWT + Tanreqing injection (ivgtt)	CWT	14	4, 5, 6, 10, 11, 13, 14	No adverse reaction
He (2024)	44/45	24/20	26/19	57.64 ± 8.47	56.51 ± 9.73	CWT + Tanreqing injection (ivgtt)	CWT	14	7, 8, 10, 11, 13	Not shown
Yang (2019)	49/49	24/25	25/24	66.5 ± 2.7	65.9 ± 2.4	CWT + Tanreqing injection (ivgtt)	CWT	14	7, 9, 17, 18	No adverse reaction
Ma (2019)	40/40	21/19	24/16	63.73 ± 10.31	60.46 ± 6.98	CWT + Tanreqing injection (ivgtt)	CWT	10	7, 8, 9, 10, 11, 13	Not shown
Liu (2020)	36/36	30/6	15/ 21	51.0 ± 1.2	52.3 ± 1.4	CWT + Tanreqing injection (ivgtt)	CWT	10	7, 8, 9, 10, 11	Not shown
An (2016)	25/25	14/11	15/10	50.9 ± 5.8	50.8 ± 6.2	CWT + Tanreqing injection (ivgtt)	CWT	10	7, 8, 9	Not shown
Zhu (A) (2018)	48/47	26/22	25/22	40.43 ± 1.95	40.57 ± 2.18	CWT + Tanreqing injection (ivgtt)	CWT	7	1, 2, 3	T: 6 case of hepatic function abnormalities; C: 2 case of hepatic function abnormalities
Wang (2016)	30/30	20/22	18/24	70. 1 ± 4. 5	69. 5 ± 5. 2	CWT + Tanreqing injection (ivgtt)	CWT	14	1, 2, 3, 7, 8, 9, 10, 12, 14, 17, 18	T: 1 case of nausea and loss of appetite
Zhu (B) (2014)	31/29	12/19	10/19	62.40 ± 7.95	60.76 ± 8.59	CWT + Tanreqing injection (bronchoalveolar lavage)	CWT	4	4, 5, 6, 10, 13	Not shown
Zhou (2014)	24/24	14/10	13/11	51.29 ± 5.62	51.28 ± 5.47	CWT + Tanreqing injection (ivgtt)	CWT	7	1, 2	Not shown
Deng (2013)	56/56	34/22	35/21	48.5 ± 3.2	48 ± 2.9	CWT + Tanreqing injection (ivgtt)	CWT	10	1, 2, 10, 11, 12, 13	Not shown
Wu (B) (2018)	30/30	18/12	17/13	62.93 ± 0.64	62.28 ± 10.83	CWT + Tanreqing injection (inh)	CWT	14	10, 11, 13	No adverse reaction

T is the experimental group, and C is the control group, which has not been reported. CWT is a conventional Western treatment. Outcome parameters: 1. The time for disappearance of cough and sputum, 2. The time for defervescence, 3. The time for the disappearance of lung rales, 4. Symptom score for cough, 5. Symptom score for phlegm, 6. Dyspnea symptom score, 7. FEV1, 8. FVC, 9. PEF, 10. WBC, 11. CRP, 12. ESR, 13. NEUT%, 14. PCT, 15. IL-6, 16. TNF-α 17. PaO_2, 18. $PaCO_2$.

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IL-6 = interleukin-6, NEUT% = neutrophil percentage, $PaCO_2$ = carbon dioxide pressure, PaO_2 = partial pressure of oxygen, PCT = procalcitonin, PEF = peak expiratory flow, RCTs = randomized controlled trials, SMD = standard mean differences, TNF-α = tumor necrosis factor-alpha, WBC = white blood cell.

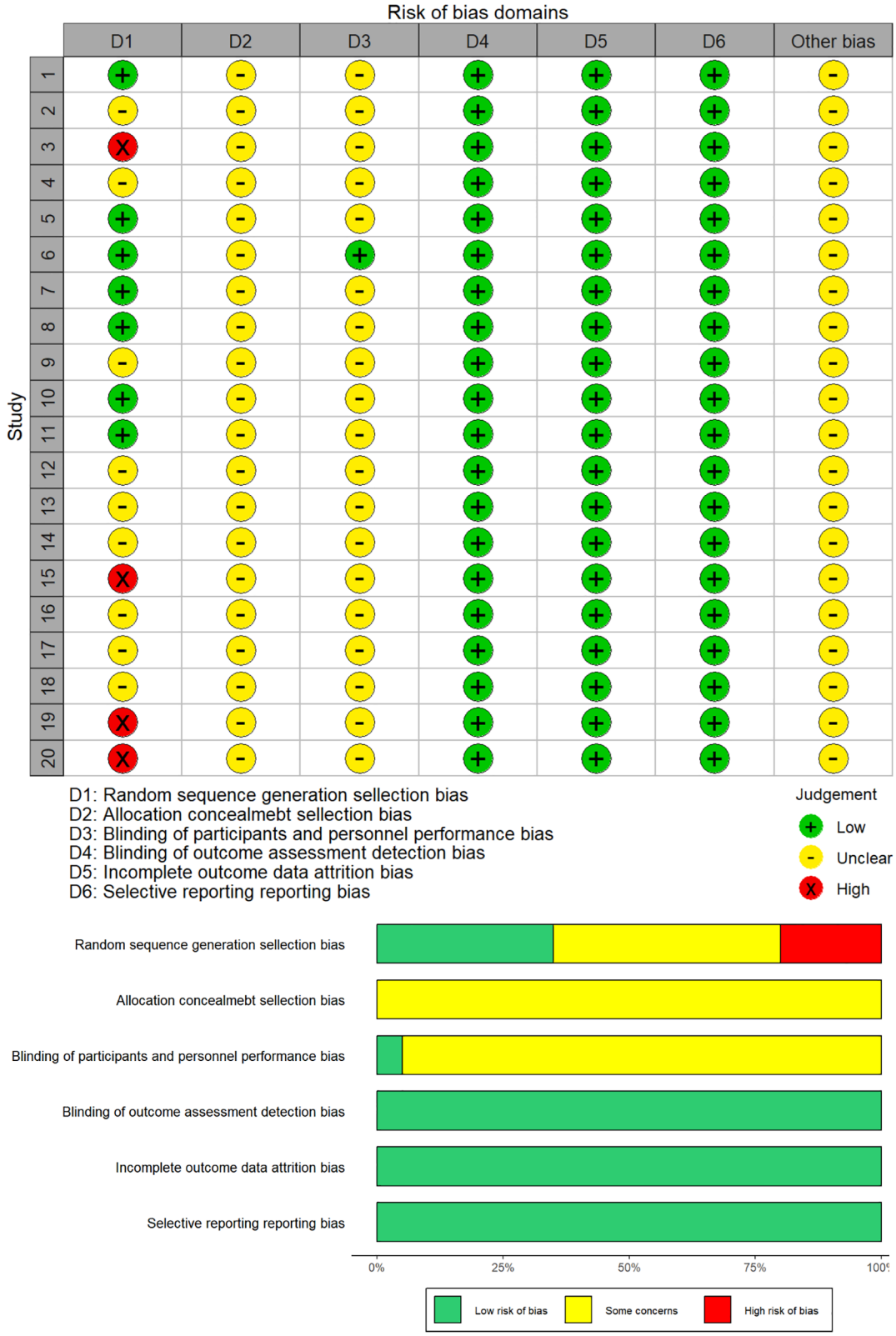

Figure 2. Risk of bias in the included studies.

$P < .0001$), leading to the application of a random-effects model for the meta-analysis. The results demonstrated a statistically significant improvement in FVC levels in bronchiectasis patients treated with TRQ compared to the control group (SMD = 1.87, 95% CI (0.72, 3.02), $P = .0015$, Fig. 10).

3.6.3. PEF. Six RCTs,[33,37–39,42,46] including 474 patients, reported PEF results. The heterogeneity analysis revealed substantial heterogeneity among the included studies ($I^2 = 97\%$, $P < .0001$), prompting the use of a random-effects model for the meta-analysis. The results demonstrated that combined TRQ with CWM showed no statistically significant difference in PEF

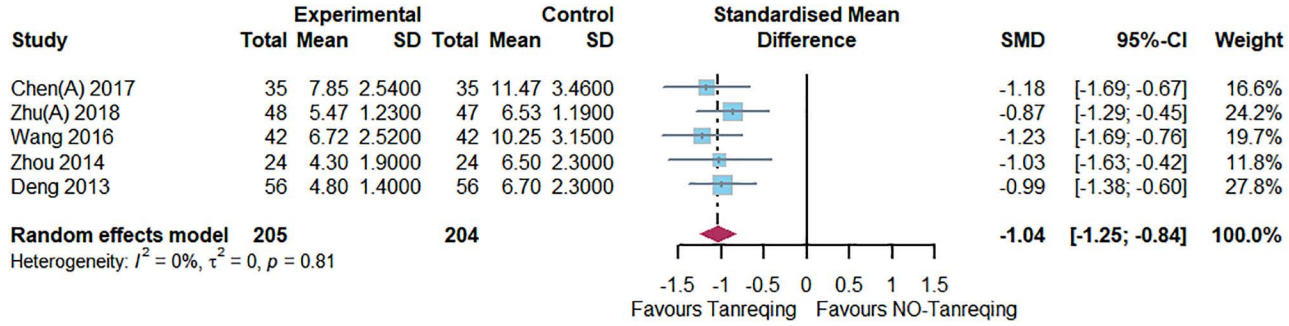

Figure 3. Meta-analysis of cough and sputum disappearance time.

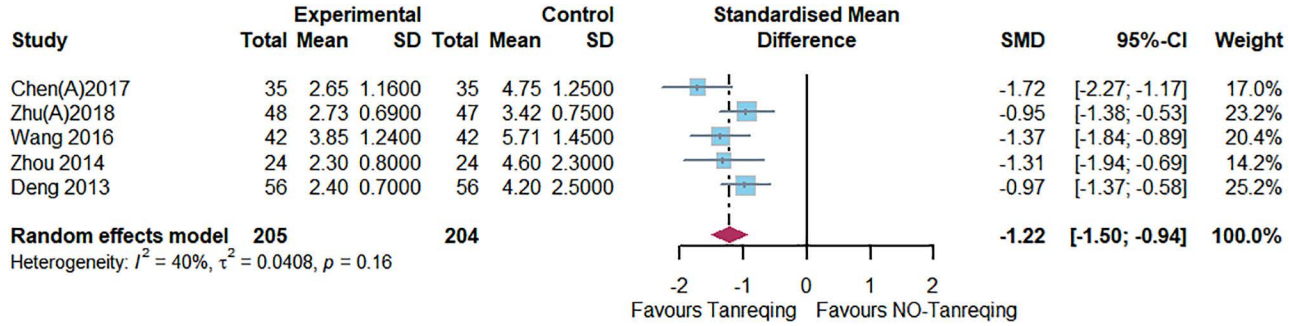

Figure 4. Meta-analysis of the time for defervescence.

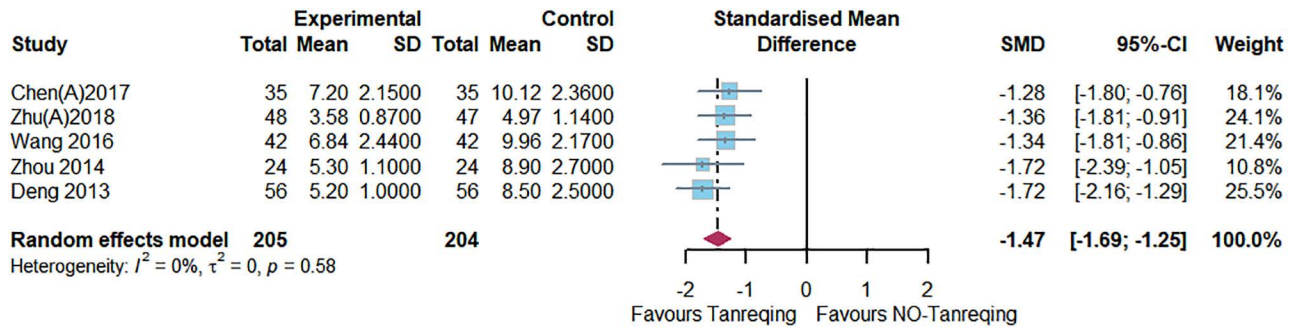

Figure 5. Meta-analysis of the time for lung rales disappearance.

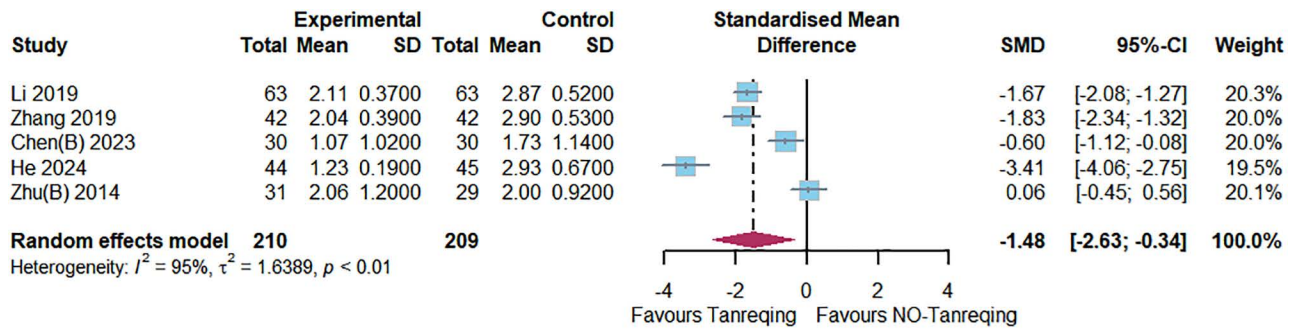

Figure 6. Meta-analysis of cough symptom score.

compared to CWM alone (SMD = 3.50, 95% CI (−0.40, 7.39), P = .079, Fig. 11).

3.7. Inflammation markers

3.7.1. WBC. Thirteen RCTs,[27,29–32,35–38,42,43,45,47] encompassing a total of 1037 patients, reported on WBC counts. The heterogeneity analysis indicated significant variability among the included studies (I^2 = 93%, P < .0001), leading to the use of a random-effects model for the meta-analysis. The results demonstrated a statistically significant reduction in WBC counts in bronchiectasis patients treated with TRQ compared to those in the control group (SMD = −1.21, 95% CI (−1.80, −0.62), P < .0001, Fig. 12).

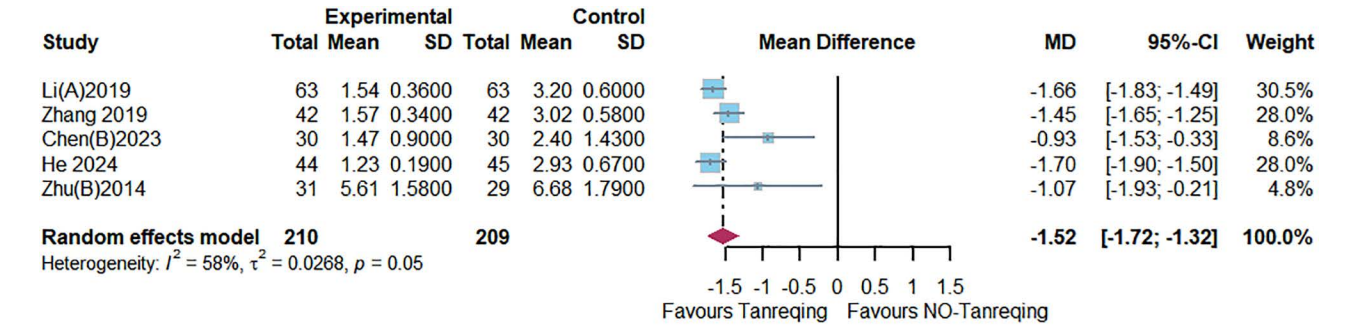

Figure 7. Meta-analysis of symptom score for sputum production.

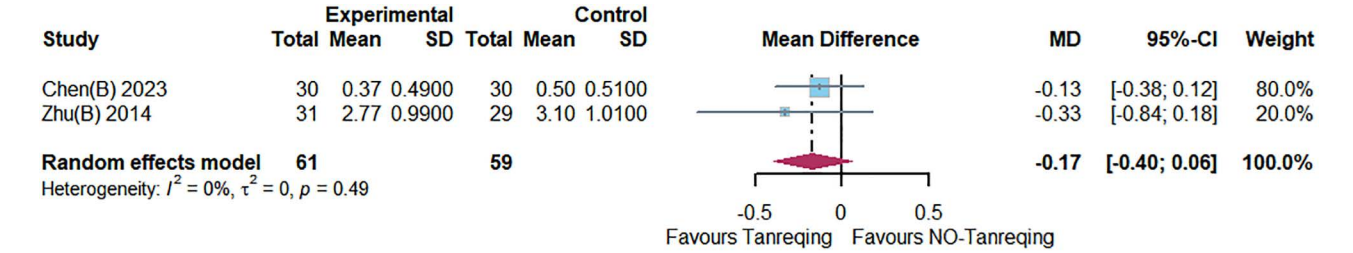

Figure 8. Meta-analysis of dyspnea symptom score.

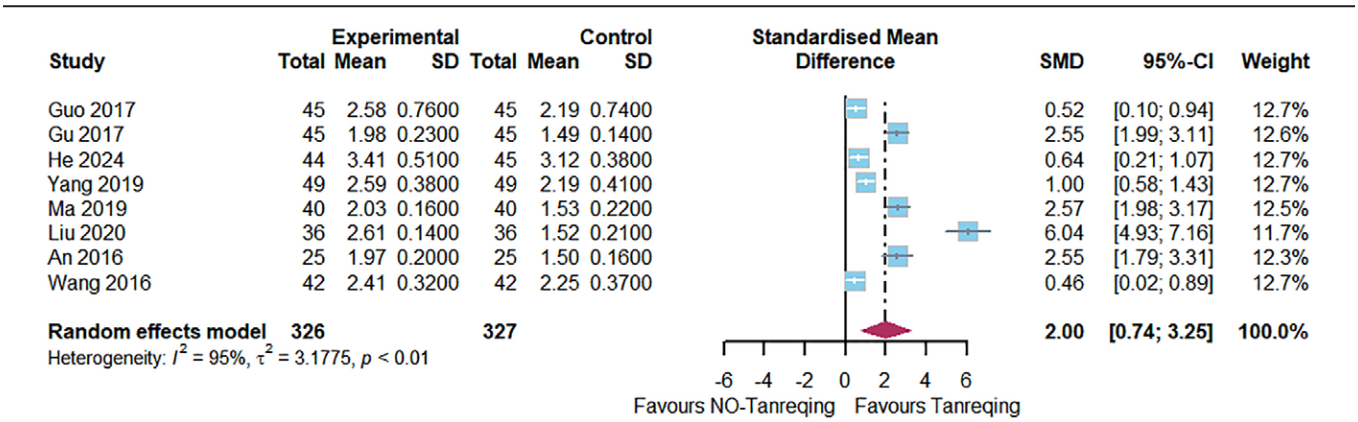

Figure 9. Meta-analysis of forced expiratory volume in 1 second.

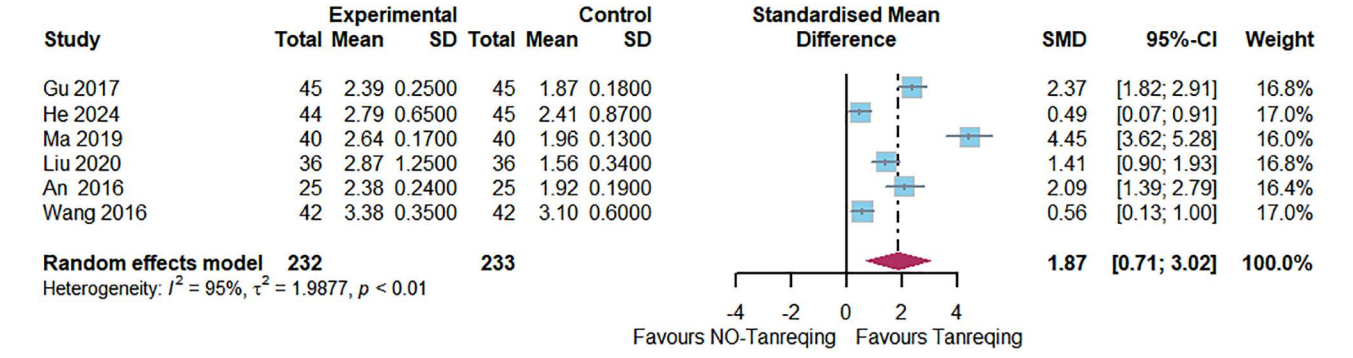

Figure 10. Meta-analysis of forced vital capacity.

3.7.2. CRP. Twelve RCTs,[27,29–32,35–38,40,45,47] involving 983 patients, reported on CRP levels. The heterogeneity analysis revealed considerable variability among the included studies (I^2 = 94.4%, P < .0001), necessitating the use of a random-effects model for the meta-analysis. The results indicated a statistically significant reduction in CRP levels in bronchiectasis patients treated with TRQ injection compared to the control group (SMD = −1.98, 95% CI (−2.72, −1.25), P < .0001, Fig. 13).

3.7.3. ESR. ESR was reported in an extractable format in the 4 trials (N = 406),[29,31,42,45] with significant heterogeneity (I^2 = 95.9%). The meta-analysis indicated that TRQ injection

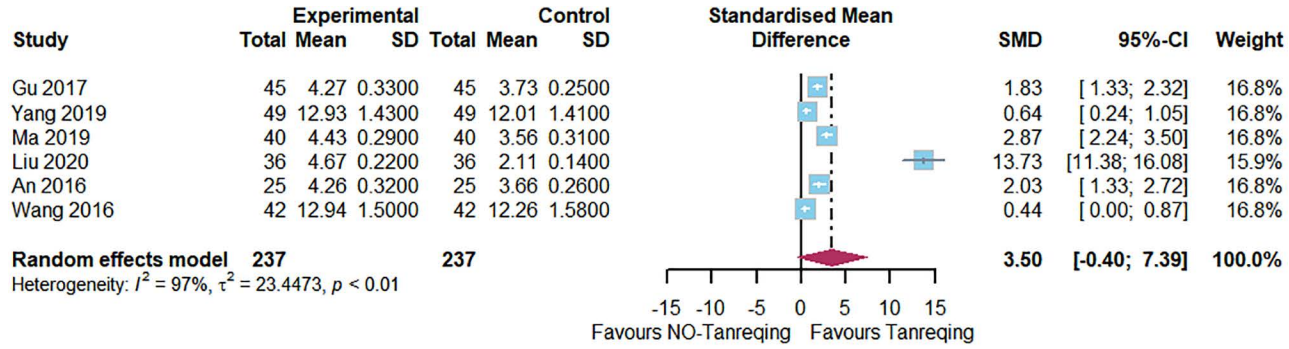

Figure 11. Meta-analysis of peak expiratory flow.

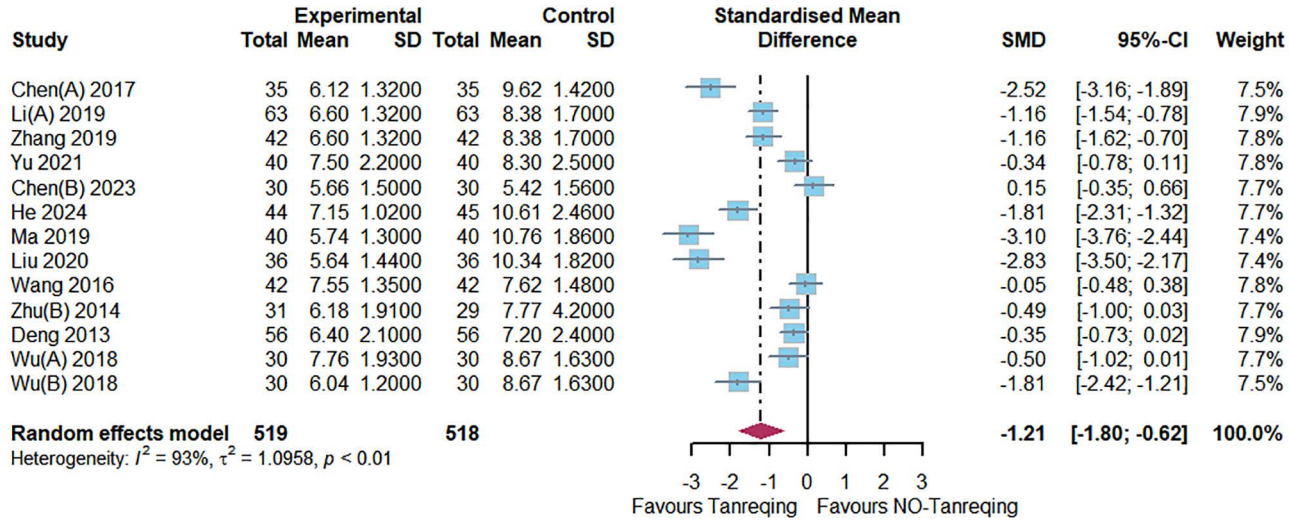

Figure 12. Meta-analysis of white blood cells.

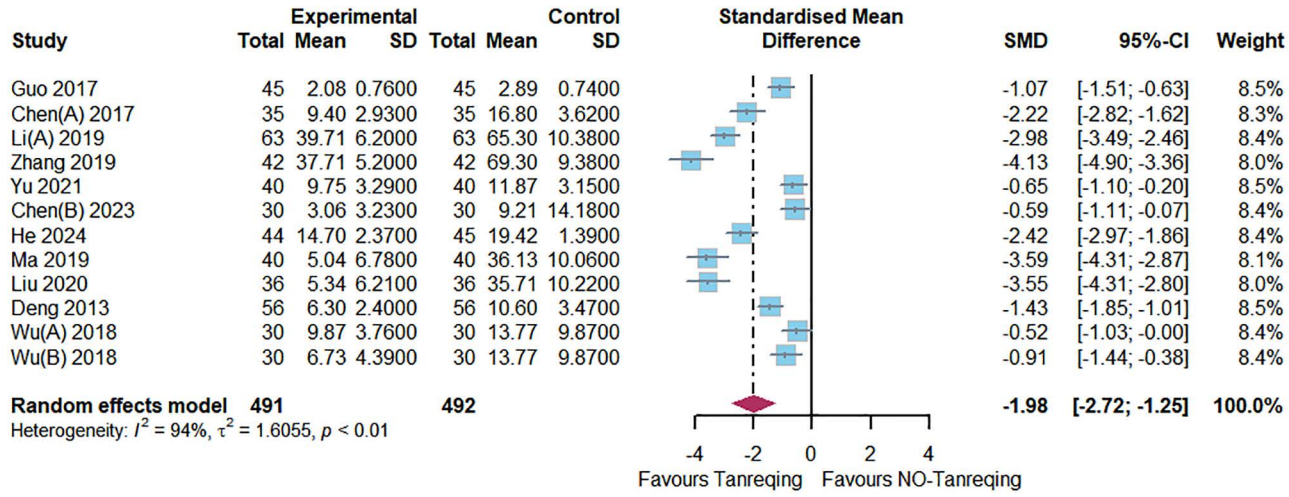

Figure 13. Meta-analysis of C-reactive protein.

significantly lowered ESR levels compared to the control group (SMD = −1.55, 95% CI (−2.70, −0.39), P = .009, Fig. 14).

3.7.4. NEUT%. NEUT% was reported in an extractable format in the 5 trials (N = 411),[27,30,36,37,45] with significant heterogeneity observed among the studies (I^2 = 95.8%, P < .01). The meta-analysis revealed that TRQ injection significantly reduced NEUT% levels compared to the control group (SMD = −1.91, 95% CI (−3.62, −0.21), P = .0281, Fig. 15), suggesting its potential anti-inflammatory effects.

3.7.5. PCT. Seven RCTs,[27,29–32,36,42] including 593 patients, reported the PCT results. Heterogeneity among studies was high (I^2 = 92%, P < .01), leading to a meta-analysis using a random-effects model. The analysis found that PCT improvement in bronchiectasis patients treated with TRQ preparation was

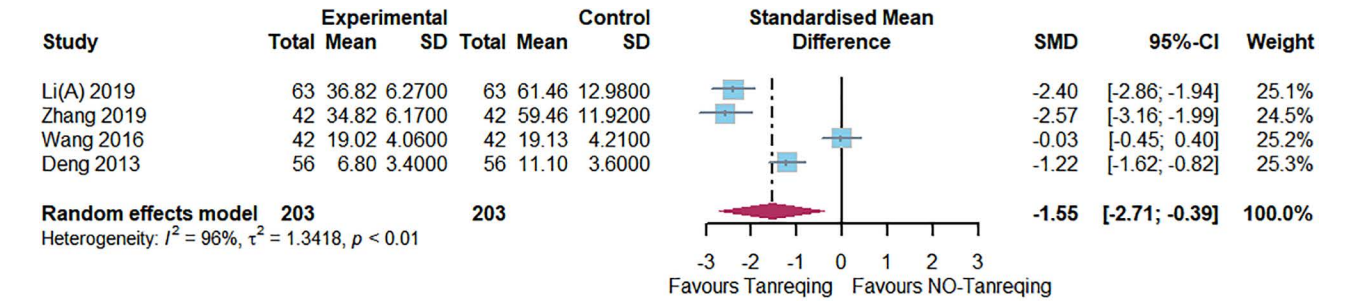

Figure 14. Meta-analysis of erythrocyte sedimentation rate.

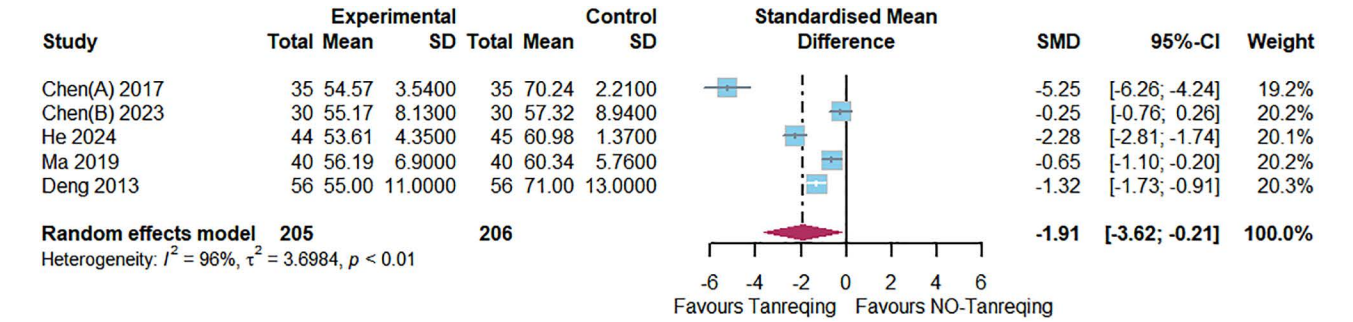

Figure 15. Meta-analysis of neutrophil percentage.

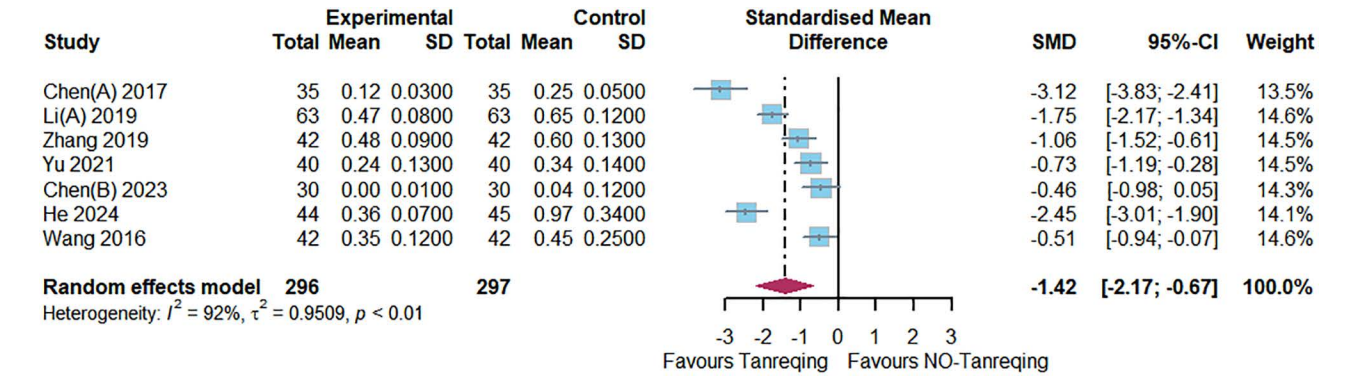

Figure 16. Meta-analysis of procalcitonin.

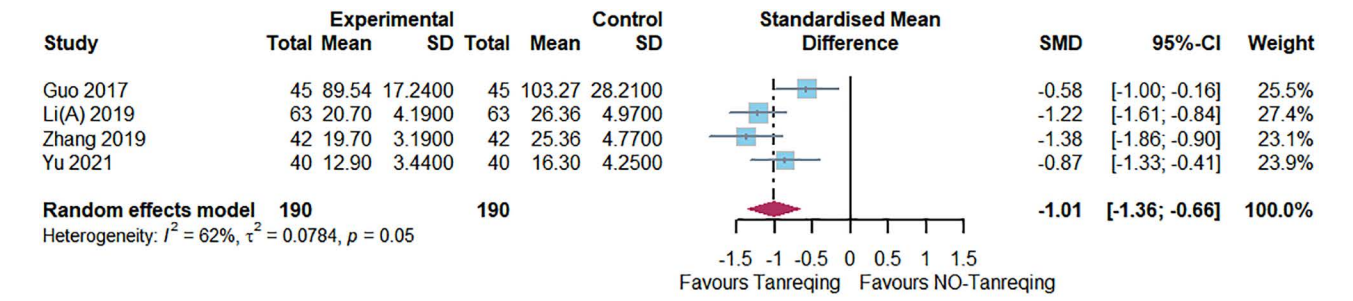

Figure 17. Meta-analysis of interleukin-6.

significantly better than in the control group (SMD = −1.42, 95% CI (−2.16, −0.67), P = .0002, Fig. 16).

3.8. Pro-inflammatory cytokines

3.8.1. IL-6. Four RCTs[29,31,32,40] with 380 patients reported IL-6 outcomes. A heterogeneity test indicated moderate variability (I^2 = 61.7%, P = .05), prompting a meta-analysis using a random-effects model. The analysis revealed that IL-6 improvement in bronchiectasis patients treated with TRQ preparation was significantly better than in the control group (SMD = −1.01, 95% CI (−1.36, −0.66), P = .0080, Fig. 17).

3.8.2. TNF-α. Three RCTs[29,31,32] with 290 patients reported TNF-α results. Heterogeneity was high (I^2 = 94.3%, P < .0001), necessitating a random-effects meta-analysis. The analysis

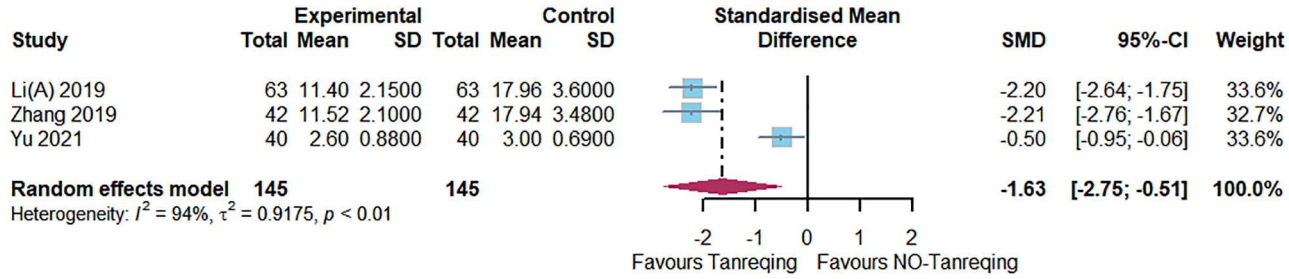

Figure 18. Meta-analysis of tumor necrosis factor-alpha.

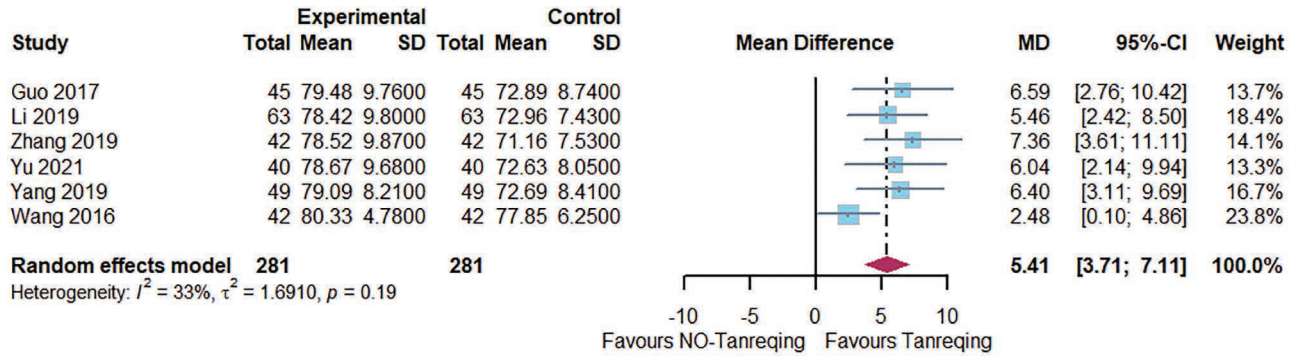

Figure 19. Meta-analysis of partial pressure of oxygen.

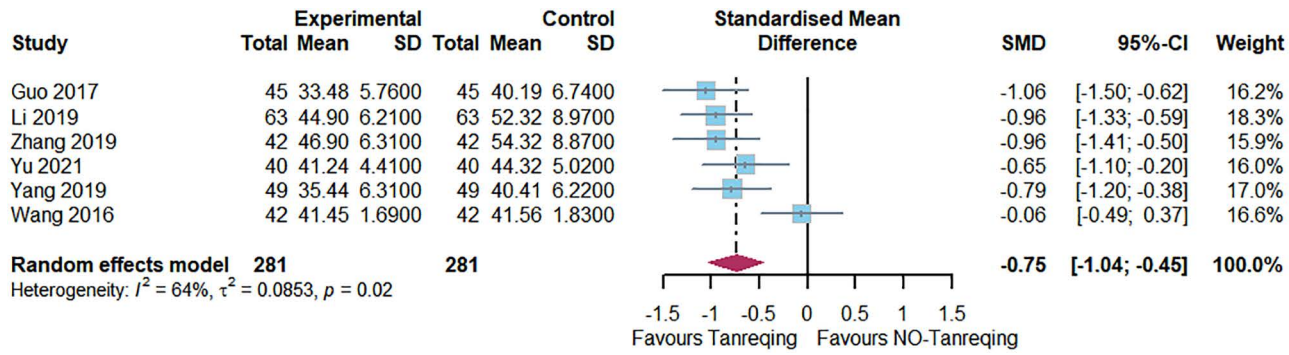

Figure 20. Meta-analysis of forced carbon dioxide pressure.

showed a significant reduction in TNF-α in bronchiectasis patients treated with TRQ preparation compared to the control group (SMD = −1.63, 95% CI (−2.75, −0.51), P < .004, Fig. 18).

3.9. Blood gas analysis

3.9.1. PaO_2. Six RCTs,[29,31,32,40,42,46] including 562 patients reported the results of PaO_2. The heterogeneity test indicated low variability (I^2 = 33%, P = .19), so a fixed-effects meta-analysis was used. The analysis showed a significant increase in PaO_2 in bronchiectasis patients treated with TRQ preparation compared to the control group (MD = 5.41, 95% CI (3.71, 7.11), P < .0001, Fig. 19).

3.9.2. $PaCO_2$. Six RCTs[29,31,32,40,42,46] involving 562 patients reported on $PaCO_2$ outcomes. The heterogeneity test indicated moderate variability among the studies (I^2 = 64%, P = .02), leading to the use of a random-effects model for the meta-analysis. The analysis demonstrated a statistically significant reduction in $PaCO_2$ in bronchiectasis patients treated with TRQ preparation compared to the control group (SMD = −0.74, 95% CI (−1.04, −0.46), P < .0001, Fig. 20).

3.10. Adverse reactions

Among the 20 included RCTs, 10 studies did not report adverse reactions,[32,33,36–41,44,45] while 10 studies documented adverse reactions.[27,29–31,34,35,41,42,46,47] Of these, 5 studies reported no adverse reactions, whereas 5 studies documented various adverse effects. Specifically, Ming Li's study[31] reported 6 cases of gastrointestinal symptoms and 2 cases of xerostomia; Yu Zhang's study[29] reported 5 cases of gastrointestinal symptoms and 2 cases of xerostomia; Jifeng Wu's study[35] reported 1 case of throat discomfort; Runlai Zhu's study[41] reported 6 cases of hepatic function abnormalities; and Chuanhai Wang's study[42] reported 1 case of nausea and loss of appetite in the treatment group. Statistical analysis revealed no significant difference in the incidence of adverse reactions between the experimental and control groups (P > .05), suggesting that TRQ preparation is generally safe for treating bronchiectasis with mucus hypersecretion.

3.11. Sensitivity analysis

A sensitivity analysis was conducted to evaluate the robustness of the meta-analysis results for TRQ's clinical efficacy in treating bronchiectasis. By sequentially excluding each study and comparing the

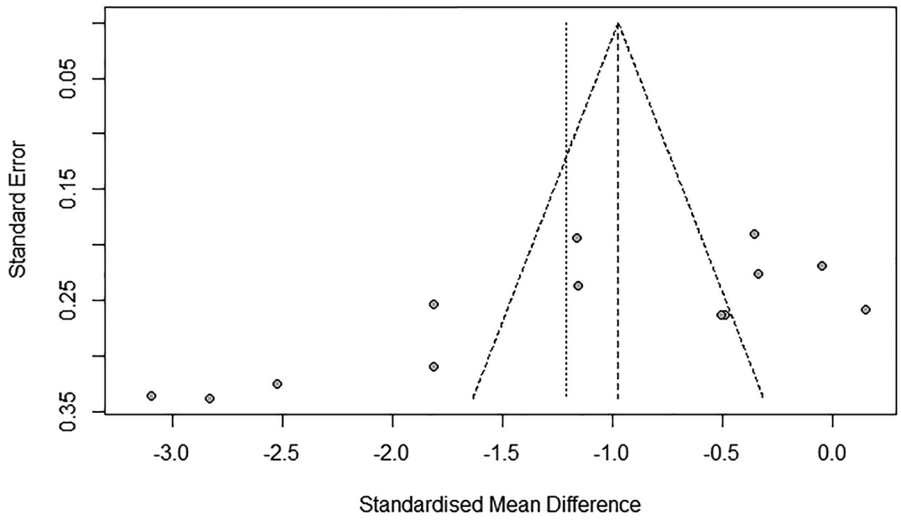

Figure 21. Funnel diagram of white blood cell count.

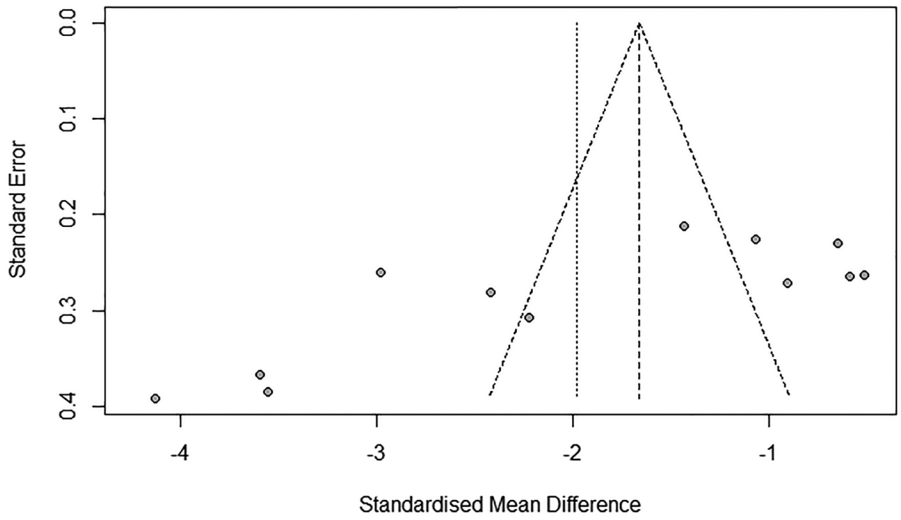

Figure 22. Funnel diagram of C-reactive protein.

results with those including all studies, we found that the overall outcomes remained consistent, indicating stability, and reliability in the analysis. However, excluding individual studies revealed significant reductions in heterogeneity: Chao Yu's study on TNF-α ($I^2 = 0\%$, $P = .59$), Chong Chen's study on time to defervescence ($I^2 = 0\%$, $P = .43$), and Chuanhai Wang's study on $PaCO_2$ ($I^2 = 0\%$, $P = .66$) markedly decreased heterogeneity. These findings suggest that these studies might have contributed to heterogeneity, potentially due to high bias risk, variations in sample size, age, administration route, treatment duration, or dosage. Detailed results are provided in Appendix 2, Supplemental Digital Content, http://links.lww.com/MD/N878.

3.12. Publication bias

Bias in the CRP and WBC analyses was assessed using funnel plot analysis. The plots, with the combined effect size SMD of CRP or WBC as the horizontal axis, exhibited noticeable asymmetry, suggesting the presence of publication bias (see Figs. 21 and 22).

3.13. The quality of the evidence

We assessed the quality of each outcome metric using the GRADE methodology. This evaluation indicated that the evidence quality was rated as "low" for the time to disappearance of lung rales, phlegm symptom score, PaO_2, and $PaCO_2$. Evidence quality was rated as "very low" for FEV1, FVC, PEF, WBC, CRP, ESR, NEUT%, PCT, IL-6, and TNF-α. The downgrades were attributed to factors such as a high risk of bias in the included studies, significant heterogeneity, small sample sizes, and potential publication bias. Detailed GRADE recommendations are provided in Table 2.

4. Discussion

4.1. Findings

This meta-analysis is the first to systematically evaluate the clinical efficacy and safety of TRQ for treating bronchiectasis exacerbations, incorporating 20 studies with a total of 1544 patients. The results demonstrated that TRQ, in combination with conventional Western therapy, significantly reduced overall symptom scores (cough and sputum production) and shortened the duration of cough, sputum production, and fever. Additionally, TRQ improved lung function, as evidenced by increases in FEV1 and FVC, and effectively reduced inflammation markers, including CRP, PCT, WBC, NEUT%, IL-6, and TNF-α. TRQ also enhanced PaO_2 and reduced $PaCO_2$, while not significantly affecting PEF and dyspnea scores.

Table 2

Quality of evidence for research outcome.

Certainty assessment Outcomes	Total (number of studies)	SMD/MD (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision 400	Other considerations	Certainty
The time for disappearance of cough and sputum	409 (5RCTs)	−1.04 (−1.25, −0.84)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
The time for defervescence	409 (5RCTs)	−1.22 (−1.50, −0.94)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
The time for the disappearance of lung rales	409 (5RCTs)	−1.47 (−1.69, −1.25)	Serious*	Not serious	Not serious	Not serious	Publication bias strongly suspected	⨁⨁◯◯ Low
Symptom score for cough	419 (5RCTs)	−1.48 (−2.63, −0.34)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
Symptom score for phlegm	419 (5RCTs)	−1.52 (−1.72, −1.32)	Serious*	Not serious	Not serious	Not serious	Publication bias strongly suspected	⨁⨁◯◯ Low
Dyspnea symptom score	120 (2RCTs)	−0.17 (−0.40, 0.06)	Serious*	Not serious	Not serious	Serious‡	Publication bias strongly suspected	⨁◯◯◯ Very low
FEV1	653 (8RCTs)	2.0 (0.74, 3.25)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
FVC	465 (6RCTs)	1.87 (0.72, 3.02)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
PEF	474 (6RCTs)	3.50 (−0.40, 7.39)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
WBC	1037 (13RCTs)	−1.21 (−1.80, −0.62)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
CRP	983 (12RCTs)	−1.98 (−2.72, −1.25)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
ESR	406 (4RCTs)	−1.91 (−3.62, −0.21)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
NEUT%	411 (5RCTs)	−0.88 (−1.15, −0.62)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
PCT	593 (7RCTs)	−1.42 (−2.16, −0.67)	Serious*	Serious†	Not serious	Not serious	Publication bias strongly suspected	⨁◯◯◯ Very low
IL-6	380 (4RCTs)	−1.01 (−1.36, −0.66)	Serious*	Not serious	Not serious	Serious‡	Publication bias strongly suspected	⨁◯◯◯ Very low
TNF-α	290 (3RCTs)	−1.63 (−2.75, −0.51)	Serious*	Serious†	Not serious	Serious‡	Publication bias strongly suspected	⨁◯◯◯ Very low
PaO_2	562 (6RCTs)	5.41 (3.71, 7.11)	Serious*	Not serious	Not serious	Not serious	Publication bias strongly suspected	⨁⨁◯◯ Low
$PaCO_2$	562 (6RCTs)	−0.74 (−1.04, −0.46)	Serious*	Not serious	Not serious	Not serious	Publication bias strongly suspected	⨁⨁◯◯ Low

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IL-6 = interleukin-6, NEUT% = neutrophil percentage, $PaCO_2$ = carbon dioxide pressure, PaO_2 = partial pressure of oxygen, PCT = procalcitonin, PEF = peak expiratory flow, RCTs = randomized controlled trials, SMD = standard mean differences, TNF-α = tumor necrosis factor-alpha, WBC = white blood cell.

* High risk of bias such as random error, allocation concealment, or blinding, as shown in Figure 2.

† Heterogeneity test ($I^2 > 80\%$) or less overlap of confidence intervals.

‡ Small study sample size (<400).

4.2. Dominance

The pathophysiology of bronchiectasis is best understood through the "vicious vortex" model, which highlights the complex interaction between impaired mucociliary clearance, chronic inflammation, airway infection, and progressive lung damage.[48] The mucociliary transport system is compromised

due to several potential factors: dehydration of the periciliary layer, absence of lubricative activity preventing mucus adhesion to airway surfaces, inherent ciliary defects, and immunodeficiencies, including cellular defects.[49] Any one of these may lead to a reduction in ciliary beat frequency and mucociliary clearance. Additionally, bronchiectasis airway secretions exhibit mucin hyperconcentration and increased osmotic pressure.[50] Compared to healthy individuals, patients with bronchiectasis have a higher proportion of solid components in their mucus, reflecting a state of dehydration.[51] This dehydrated mucus becomes viscous, sticky, and difficult to clear, resulting in mucus stasis and adhesion to airway surfaces, which in turn contribute to the critical infectious and inflammatory components of bronchiectasis.[50]

During exacerbations, airway mucus hypersecretion exacerbates difficulties in expectoration, airway inflammation, airflow obstruction, and bacterial adhesiveness.[52] These effects are driven by complex interactions involving inflammatory pathways, mucin gene regulation, oxidative stress, and ion channel dysfunction. Inflammatory mediators such as interleukin-8 (IL-8), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) upregulate mucin gene expression, particularly MUC5AC, and MUC5B, resulting in excessive mucus production.[53] Neutrophil elastase also enhances mucus production, activates cathepsins and matrix metalloproteases, and upregulates IL-8 and leukotriene B4, leading to increased neutrophil influx, airway obstruction, and tissue damage.[54] Notably, TRQ has shown significant potential in modulating these pathological mechanisms. A clinical study involving 60 bronchiectasis patients found that TRQ injection significantly reduced NE levels in the airways, promoted ciliary movement, and reduced mucus secretion.[55] In airway inflammation models, TRQ injection has been shown to reduce levels of TNF-α, IL-1β, IL-6, and IL-8, thereby mitigating mucus hypersecretion and inflammatory damage, potentially through the MAPK/NF-κB signaling pathways.[56] In vivo experiments further confirmed that TRQ significantly inhibits LPS-induced MUC5AC overproduction and reduces the expression of TNF-α, IL-6, IL-8, and IL-17A at both protein and mRNA levels, suggesting that its efficacy against mucus hypersecretion may be linked to the inhibition of pro-inflammatory cytokines.[19] Additionally, TRQ treatment for 24 hours has been shown to significantly reduce mucus hypersecretion and mucus cell hyperplasia by 30.5%.[19] High concentrations of TRQ accumulate in the respiratory tract, potentially blocking the secretion process of glands and goblet cells.[57] Furthermore, phenotypic analysis indicated that TRQ treatment completely inhibited phenazine pyocyanin production and moderately inhibited virulence factors like rhamnolipids, elastase, and alkaline protease, effectively protecting *Caenorhabditis elegans* from *Pseudomonas aeruginosa* lethality.[58] TRQ reduces the inflammatory burden and the risk of antibiotic resistance, showing promise in treating *P aeruginosa* infections.[59]

The primary meta-analysis demonstrated that the TRQ group outperformed the non-TRQ control group, showing significant improvements in various clinical parameters. These included reduced cough and sputum disappearance times, alleviation of cough and sputum symptoms, shortened lung rale disappearance time, and enhanced pulmonary function as indicated by FEV1 and FVC. Additionally, TRQ treatment led to improved blood gas parameters (PaO_2 and $PaCO_2$) and reductions in inflammatory markers such as white blood cell count, C-reactive protein, ESR, IL-6, TNF-α, NEUT%, and PCT levels. These findings suggest that TRQ not only acts as a mucus-modifying agent, effectively reducing mucus hypersecretion and cough but also exhibits potent anti-inflammatory effects. TRQ contains various ingredients with different pharmacologic properties that act on multiple targets. The main components, such as baicalin, chlorogenic acid, ursodeoxycholic acid, and goose deoxycholic acid, have anti-inflammatory, antioxidant, enhancing sputum clearance, and immunomodulatory properties.[60] By regulating the viscoelastic properties of mucus and facilitating sputum expectoration, TRQ may fundamentally reduce mucus secretion and resolve the vicious cycle, thus improving the outcomes of exacerbations. Furthermore, a population-based multicenter cohort study conducted in China, which included 30,322 inpatients from 90 hospitals, assessed the safety of TRQ. The incidence of adverse events and adverse drug reactions was found to be 1.4% and 0.3%, respectively. The most common adverse drug reactions were skin and subcutaneous tissue disorders, all of which were mild to moderate in severity, except for 1 serious case of anaphylactic reaction. These results suggest that TRQ is generally well-tolerated in the broader population.[61] However, it is contraindicated in individuals with hypersensitivity to any of its components.

4.3. Heterogeneity

We adhered strictly to the PICOS (Population, Intervention, Comparison, Outcome, Study Design) framework during literature screening to minimize research heterogeneity. Despite this, considerable heterogeneity persisted. Sensitivity analyses were performed to assess the robustness of our meta-analysis and to explore potential sources of heterogeneity, aiming to mitigate false-positive results. The findings confirmed that all outcome measures were stable and reliable, reinforcing the credibility of the research. Notably, heterogeneity significantly decreased ($I^2 = 0$) when 3 specific studies were excluded. We identified several potential sources of heterogeneity: First, none of the studies provided detailed sample size calculations, and 1 study had a relatively small sample size (44 cases). Additionally, variations in age across studies might contribute to heterogeneity. Second, treatment duration impacted the studies: 1 study had the shortest duration (4 days), while the others ranged from 7 to 14 days. For acute exacerbations of bronchiectasis, a treatment duration of less than 1 week may be insufficient to demonstrate the therapeutic efficacy of TRQ. Further research on the long-term efficacy of TRQ is needed. Third, the administration methods of TRQ preparations varied, including nebulization, alveolar lavage, and intravenous injection, produced by different manufacturers with inconsistent dosages. Even among injectable preparations, 2 dilution methods were used: glucose water and saline. The measurement of structural outcomes differed, and the speed of liquid titration was not clearly specified, potentially affecting the absorption rate and extent in the body, leading to uneven bias. Fourth, the severity index of bronchiectasis varied among the studies, which could influence the reliability of the results. These factors may introduce bias in efficacy evaluation, leading to a downgrade in evidence quality assessed using the GRADE methodology. Consequently, the conclusions should be considered as providing a reference for clinical use rather than definitive evidence.

4.4. Limitation

This study has several limitations. First, the inclusion of Chinese literature may introduce language bias, highlighting the need for research that includes a broader, more diverse population beyond just Chinese studies. Second, the quality of the included literature is relatively poor. Many clinical studies were not preregistered, had small sample sizes, and only 11 articles described specific randomization methods, with only 1 trial mentioning single blinding. Most trials had an unclear risk of bias, with none explicitly addressing allocation concealment. Additionally, the potential impact of patients' subjective psychological factors during drug administration could introduce bias, affecting the objective assessment of the drug's efficacy and safety. Third, inconsistencies in the administration methods of TRQ, manufacturers, dosages, injection solution configurations, intravenous

drip rates, treatment durations, and disease stages may result in heterogeneity bias. Addressing these discrepancies requires clearer categorization of TRQ and the establishment of more detailed research guidelines. Standardizing the administration route and dosage in future studies would help reduce variability and improve comparability between studies. Finally, inaccurate reporting in the included studies may have led to publication bias. This highlights the need for higher-quality clinical research to provide more reliable clinical evidence for the use of TRQ injections, enabling the international community to better assess their safety and efficacy.

5. Conclusion

In conclusion, this study showed that TRQ can significantly improve sputum production, alleviate cough, enhance pulmonary function, reduce hypoxia, and modulate the inflammatory microenvironment in patients with bronchiectasis. This suggests that TRQ is a promising therapeutic option for managing mucus hypersecretion in bronchiectasis, with potential benefits for a broader patient population. However, due to the limitations of this study, multicenter, large-sample, double-blinding design RCTs are needed to further verify the results.

Acknowledgments

We appreciate the efforts and cooperation of all research staff and patients involving this study.

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Supervision: Zi Yang.
Validation: Qing Miao.
Visualization: Jinzhi Zhang, Yuanyuan Duan.
Writing – original draft: Jinzhi Zhang, Shasha Yuan.
Writing – review & editing: Qing Miao.

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