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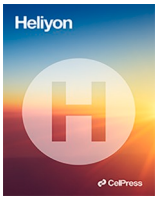

Research article

Efficacy and safety of integrated traditional Chinese and Western medicine for rheumatoid arthritis-interstitial lung disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To systematically evaluate the efficacy and safety of integrated traditional Chinese and Western medicine(TCM-WM) for the treatment of rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Materials and methods: An independent search of electronic databases (PubMed, Excerpta Medica Database, Cochrane Central Register of Controlled Trials, OVID Medline, China National Knowledge Infrastructure, WanFang Data, VIP Data databases, and China Biology Medicine disc) from inception to June 25, 2024 was performed to identify studies treating RA-ILD that used combined Chinese and Western medicine treatment compared to Western medicine. Two researchers independently audited each article, and the quality was assessed using the Cochrane Risk of Bias Assessment Tool 2 and the modified Jadad. Meta-analyses were performed using Review Manager 5.4 and Stata 16.0 software to analyze data. Sample certainty and conclusiveness of evidence were assessed using the Grading of Recommendations Assessment, Development, and Evaluation Profiler (GRADEPRO) and trial sequential analysis(TSA) 0.9.5.10 beta.

Results: Eighteen randomised controlled trials (RCT), including 1353 patients, were abstracted. Integrated traditional Chinese and Western medicine was significantly more effective than Western medicine in improving lung function in patients with rheumatoid arthritis-associated interstitial lung disease, including forced vital capacity (FVC) (Standardized Mean Difference (SMD) = 1.44, 95 % CI 0.93 to 1.95, $P < 0.00001$), diffusion capacity for carbon monoxide of the lung (DLCO) (SMD = 1.20, 95 % CI: 0.57 to 1.84, $P = 0.0002$), and total lung capacity (TLC) (SMD = 1.29, 95 % CI: 0.81 to 1.76, $P < 0.00001$). There were significant differences between the two groups in the reduced high-resolution Computed Tomography scores (Mean Difference(MD) = −1.92, 95 % CI: 2.73 to −1.10, $P < 0.00001$). Significantly reduced inflammatory markers, combined Chinese and Western medical treatments for RA-ILD were substantially better than Western treatments, including erythrocyte sedimentation rate(ESR) (MD = −7.89, 95 % CI: 12.40 to −3.39, $P < 0.00001$), C-reactive protein(CRP) (MD = −4.75, 95 % CI: 8.61 to −1.34, $P = 0.006$), rheumatoid factor(RF) (MD = −41.76, 95 % CI: 66.95 to −16.56, $P = 0.001$). Combination therapy improved clinical effectiveness (odds ratio (OR) = 3.69, 95 % CI: 2.68 to 5.07, $P <$

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0.00001). Simultaneously, trial sequential analysis indicated that the results demonstrating the superiority of integrated traditional Chinese and Western medicine over Western medicine alone in the treatment of rheumatoid arthritis-associated interstitial lung disease are robust.
Conclusion: Current evidence shows that combined traditional Chinese medicine is effective and safe for rheumatoid arthritis-associated interstitial lung disease compared with Western medicine alone. The sample size for inclusion concerns may require the inclusion of more randomised trials in the future to validate our results.

Abbreviations

RA	Rheumatoid Arthritis
ILD	Interstitial Lung Disease
PF	Pulmonary Fibrosis
CHM	Chinese Herbal Medicine
TCM	Traditional Chinese Medicine
WM	Western Medicine
CNKI	China National Knowledge Infrastructure
Wanfang	Wanfang Data Knowledge Service platform
VIP	Chinese Scientific Journal Database
CBM	China Biological Medicine Database
MeSH	Medical subject headings
RCTs	Randomized Controlled Trials
MD	Mean Difference
95 % CI	95 % Confidence Interval
OR	Odds Ratio
TSA	Trial Sequential Analysis
GC	Glucocorticoid
ISD	Immunosuppressive Drug
AFD	Antifibrotic Drug
NASID	Non-steroidal Anti-inflammatory Drugs
TD	Theophylline Drugs
CRP	C-reactive Protein
FVC	Forced Vital Capacity
SMD	Standardised Mean Difference
ESR	Erythrocyte Sedimentation Rate
HRCT	high-resolution Computed Tomography
RF	Rheumatoid Factor
FVC	Forced Vital Capacity
TLC	Total Lung Capacity
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
TwHF	*Tripterygium wilfordii* Hook
ADRs	adverse reactions
GRADE	Grading of Recommendations, Assessment, Development and Evaluation

1. Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterised by joint damage and persistent systemic inflammation. Its multisystem involvement significantly elevating mortality rates [1–4]. Notably, the increased prevalence of interstitial lung disease (ILD) among patients with RA is a major contributor to this heightened mortality [5]. ILD refers to various lung conditions that cause extensive inflammation or fibrosis of the interstitium, impair lung function, and lead to respiratory distress or failure [6,7]. A clinical study indicated that rheumatoid arthritis-associated interstitial lung disease (RA-ILD) patients with usual interstitial pneumonia (UIP) have a median survival of 3.2 years, much lower than the 6.6 years observed in non-UIP patterns [8]. Moreover, the presence of ILD in patients with RA is linked to a 13 % increase in mortality compared to the general population [9,10]. More than 30 % of patients with RA-ILD exhibit early symptoms such as dry cough and dyspnoea, which are frequently misdiagnosed as other pulmonary diseases [11], and approximately 20 % of patients with RA-ILD present no noticeable clinical symptoms [12,13]. Early identification and diagnosis of RA-ILD are particularly challenging because of its heterogeneous presentation and diagnostic

NO.	Search Items(Chinese)	NO.	Search Items(English)
1	"类风湿关节炎" + "类风关" + "类风湿性关节炎" + "关节炎" + "类风湿"	1	("Arthritis, Rheumatoid"[Mesh]*) OR ("Caplan Syndrome"[Mesh]*) OR ("Felty Syndrome"[Mesh]*) OR ("Rheumatoid Nodule"[Mesh]*) OR ("Rheumatoid Vasculitis"[Mesh]*) OR ("Sjogren's Syndrome"[Mesh]*) OR ("Still's Disease, Adult-Onset"[Mesh]*)
2	"间质性肺病" + "肺间质病" + "肺纤维化" + "纤维化间质性肺疾病" + "肺间质纤维化"	2	("Lung Diseases, Interstitial"[Mesh]*) OR (Diffuse Parenchymal Lung Disease[Title/Abstract]) OR (Interstitial Lung Diseases[Title/Abstract]) OR (Diffuse Parenchymal Lung Diseases[Title/Abstract]) OR (Interstitial Lung Disease[Title/Abstract]) OR (Interstitial Pneumonia[Title/Abstract]) OR ("Pulmonary Fibrosis"[Mesh]*) OR (Fibrosis, Pulmonary[Title/Abstract]) OR (Alveolitis, Fibrosing[Title/Abstract]) OR (Idiopathic Diffuse Interstitial Pulmonary Fibrosis[Title/Abstract])
3	"中医药" + "中西结合" + "中草药" + "中药复方" + "中成药" + "汤" + "方" + "剂" + "散" + "颗粒"	3	("Drugs, Chinese Herbal"[Mesh]*) OR (Chinese Drugs, Plant) OR (Chinese Herbal Drugs) OR (Chinese Plant Extracts) OR ("Medicine, Chinese Traditional"[Mesh]*) OR (Chung I Hsueh) OR (Hsueh, Chung I) OR (Zhong Yi Xue)) OR (Traditional Tongue Diagnosis) OR (Traditional Tongue Assessment)
4	"随机" + "随机对照" + "随机试验" + "RCT" + "对照"	4	randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]
5	#1*#2*#3*#4	5	#1 AND #2 AND #3 AND #4

Fig. 1. PubMed and CNKI database retrieval strategy.

ambiguity. These factors significantly complicate the early diagnosis and treatment efforts of clinicians treating RA-ILD.

The pathogenesis of RA-ILD remains unclear but is inseparable from chronic persistent inflammation and pulmonary fibrosis induced by the immune milieu. A disturbed immune system damages the tissues within the lungs, and large numbers of fibroblasts accumulate abnormally, damaging the alveolar structure and ultimately leading to loss of lung function, irreversible fibrosis, abnormal lung function, and even respiratory failure [14,15]. Although the pathogenesis of RA-ILD is not completely understood, it is certain that RA-mediated systemic immune inflammation plays a crucial role in the early stages of ILD development. Although the pathogenesis of RA-ILD is not completely understood, RA-mediated systemic immune inflammation plays a crucial role in the early stages of ILD development. Glucocorticoids and immunosuppressive agents are the main components of the disease. Glucocorticoids are used for symptomatic relief, conventional synthetic disease-mitigating antirheumatic drugs (csDMARDs), targeted synthetic DMARDs, and biological DMARDs for ongoing treatment [16,17]. High-dose prednisone is recognised as a first-line option for RA-ILD treatment [18], and studies have shown that long-term hormones may cause patients to develop disease disorders or induce ILD [19]. Extensive clinical studies have shown that some RA patients treated with methotrexate have develop lung damage in some patients [20]. Studies on leflunomide have found that it is not desirable for use in patients with RA-ILD and may exacerbate the disease while inducing the emergence of a new ILD [21]. Anti-fibrotic drugs such as Pirfenidone and Nidanib are also permitted for use in RA-ILD [22,23]. However, no large body of clinical research has supported the effectiveness and safety of this treatment. Moreover, the high cost of drugs for long-term treatment adds to the treatment difficulty. Given the current treatment dilemma, there is an urgent need to develop safer and more effective complementary therapies.

The World Health Organization has recognised herbal medicines as traditional and complementary [24]. New strategies emphasise the use of herbal medicines, herbal compounds and natural active ingredients of herbs, to combat diseases and strengthen traditional medicine prevention and treatment to protect human health [24–26]. Its high efficacy and low incidence of safety events have garnered significant attention from scholars. In China, RA-ILD falls under the category of "Bi syndrome," with a common pathogenesis of phlegm and blood stasis obstruction, leading to impaired circulation in the collaterals. In the "Huangdi Neijing," it is stated that "When the five viscera are affected by Bi syndrome, the skin, flesh, tendons, bones, and vessels are obstructed, and further invasion by pathogenic factors leads to the internal lodging of the five viscera." This results in Bizheng of the five viscera, indicating that Bizheng is chronic and difficult to cure, prone to recurrent attacks, and over time, can affect the lungs, causing "Fei Bi". In classical Chinese medicine theory, the lungs govern qi, and the kidneys receive qi, aiding in the circulation of qi and blood throughout the body. Tonifying lung qi, assisting kidney qi absorption, and eliminating pathogenic factors to unblock the meridians are key treatments in traditional Chinese medicine for RA-ILD [27]. Studies have utilized traditional Chinese medicine combined with methotrexate to treat early-stage RA-ILD. After six months of treatment, high-resolution Computed Tomography (HRCT) scans of the lungs demonstrated a significant reduction in the area of inflammatory lesions without any safety concerns [28]. Despite randomized studies showing that traditional Chinese medicine (TCM) can effectively improve lung function and inflammatory markers in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD), there is no direct evidence-based medical evidence confirming its efficacy for RA-ILD. This lack of evidence has led to controversy regarding its therapeutic effectiveness. Therefore, to further clarify the application value of TCM in the treatment of RA-ILD, we conducted this meta-analysis. Our aim was to analyze reliable evidence from various studies to confirm the efficacy and safety of TCM combined with Western medicine in the treatment of RA-ILD, thereby providing an evidence-based foundation for future clinical treatments.

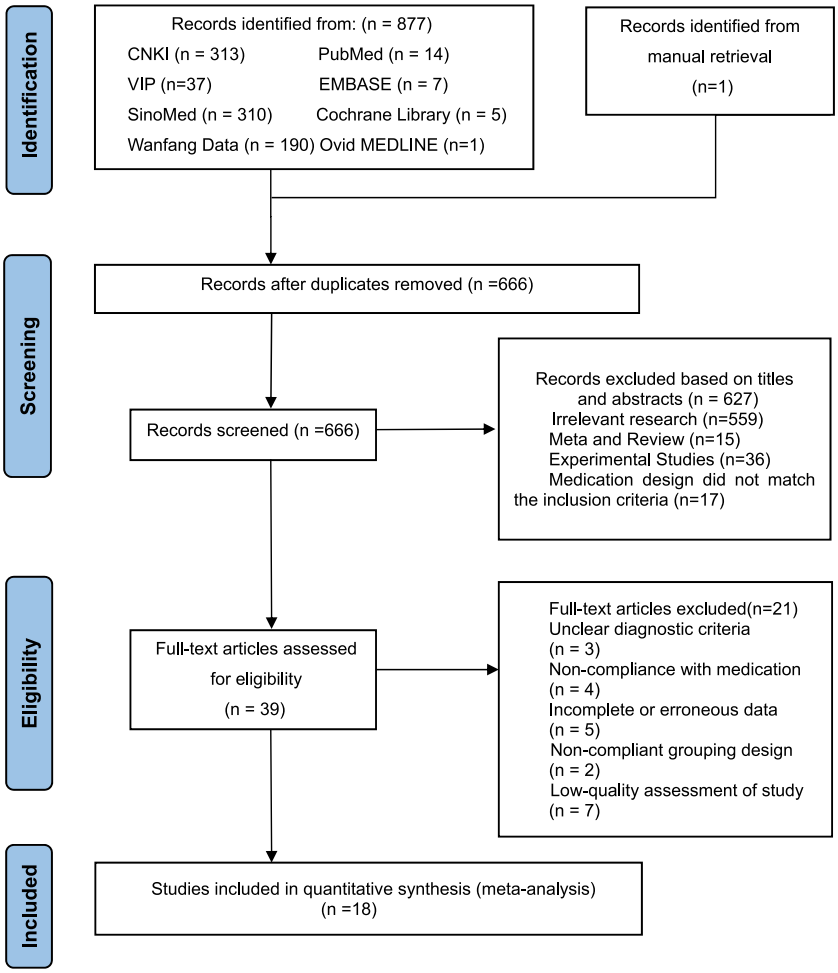

Fig. 2. Flow diagram of study selection and identification (PRISMA).

2. Material and methods

2.1. Registration of protocols

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 checklist (Supplementary Information) [29,30]. This meta-analysis was registered with PROSPERO (registration number: CRD42022329715). The PRISAM list was filled out according to the specific situation of the review, and all were completed, See Attachment.

2.2. Database search strategy

We searched PubMed, Excerpta Medica Database, Cochrane Central Register of Controlled Trials, OVID Medline, China National Knowledge Infrastructure(CNKI), Wanfang Data, VIP Data databases(VIP), and the China Biology Medicine disc(CBM) from the time of construction to 2024 25nd of June. Relevant content was searched for on ClinicalTrials.gov. Match Medical Subject Headings (MeSH) and free words with search terms such as “rheumatoid arthritis”, “interstitial lung disease,” " traditional Chinese medicine”, and “randomized”. Complementing studies were missed when manual search strategies were used. The specific search strategies for PubMed and CNKI (Fig. 1). Specific searches for other databases are provided in Attachment 1.

2.3. Selection criteria

Following the preferred reporting items described in the systematic review and meta-analysis [29], study inclusion should be consistent with the following: 1)Participants: Patients with a definite diagnosis of rheumatoid arthritis combined with interstitial lung disease; 2)Intervention: Intervention group was treated with TCM combined with Western medicine (WM), and the dosage forms of the

Table 1
Characteristics of included literature.

Studyyear region	Number of participants (M/F)	Average age (SD)	CHM Formula (efficacy)	Diagnostic standards	Treatment measures	Duration of disease (SD)	Therapy duration	Outcomes	Total score of the Jadad scale
Li 2011 China	I: 23(5/18) C:22(4/18)	I: 56.34 ± 5.71C:55.64 ± 8.92	Fangxian Decoction (Replenishing qi and yin-tonifying, resolving phlegm and stasis)	RA: ACR (1987) ILD: ATS/ERS (2000)	I: CHM + GC + ISD C: GC + ISD	I: 6–30C:6~29	3 months	a, d, e, f, g, h, I, j	4
Xie 2011 China	I: 32(14/18) C:32(15/17)	I: 58.5 ± 15.5C:60.29 ± 15.21	Bufei Tongluo Wan (Activating blood and resolving stasis, dredging collaterals lung collateral, treating with both elimination and reinforcement)	RA: ACR (1987), EULAR (2009) ILD: ATS/ERS (2000), Guidelines for the diagnosis and treatment of IPF (Chinese Medical Association Respiratory Disease Society 2002).	I: CHM + NASID + ISD C: NASID + ISD	I: 5.12 ± 4.63C:5.08 ± 4.73 (ILD duration)	6 months	a, b, c, d, e	3
Zhang 2014 China	I: 26(14/12) C:26(13/13)	I: 50.5 ± 15.5C:50.29 ± 15.21	Shengxian Bolus (Tonifying lung qi, activating blood, and dredging collaterals.)	RA: ACR (1987) ILD: ATS/ERS (IPF, 2002)	I: CHM + ISD C: ISD	I: 5.12 ± 4.32C:5.08 ± 4.73 (ILD duration)	12 months	a, b, c, d, e, f, g, h, j	3
Tang 2017 China	I: 31(5/26) C:31(4/27)	I: 64.1 ± 7.6C:58.1 ± 10.7	Chenshi Qingfei Decoction (Tonifying and replenishing lung kidney, resolving phlegm and dispelling stasis, dredging lung collateral)	RA: ACR (1987) ILD: ATS/ERS (2000) TCM Diagnostics: the Guideline for clinical research of new traditional Chinese medicine and TCM syndrome diagnosis. Dimostrazione: Chuanzheng, Cough.	I: CHM + GC C: GC	I:9.8 ± 4.5C:8.8 ± 4.5	3 months	d, e, f, g, i	4
Wang 2017 China	I: 60(18/42) C:60(20/40)	I: 57.1 ± 8.9C:56.8 ± 9.4	Yiqi Yangyin Tongbi Prescription (Tonifying and replenishing lung-kidney, replenishing qi and nourishing yin, resolving phlegm, and resolving stasis.)	RA: Chinese guideline for diagnosing and treating rheumatoid arthritis (Chinese Rheumatology Association, 2010.) ILD: ATS/ERS (IPF, 2000.)	I:CHM + GC + NASID + ISD C: GC + NASID + ISD	I:9.3 ± 2.5C:9.1 ± 2.2	6 months	a, b, c, d	4
Huang 2018 China	I: 40(16/24) C:40(18/22)	I: 58.60 ± 7.69 C:58.48 ± 7.63	Yangyin Tongbi Formula (Blood-activating and dredging collaterals, and tonifying the kidney yin)	RA: Chinese guideline for the diagnosis and treatment of rheumatoid arthritis (Chinese Rheumatology Association, 2010) TCM Diagnostics: Instructional principle of the latest Chinese herbal medicine	I: CHM + GC + ISD C: GC + ISD	I:9.75 ± 1.42C:9.82 ± 1.46	6 months	a, b, d, e, i	3

(*continued on next page*)

Table 1 (*continued*)

Studyyear region	Number of participants (M/F)	Average age (SD)	CHM Formula (efficacy)	Diagnostic standards	Treatment measures	Duration of disease (SD)	Therapy duration	Outcomes	Total score of the Jadad scale
				to Clinical Research (2002)					
Duan 2019 China	I:38(5/33) C:38(4/34)	I:45.32 ± 11.48C:44.89 ± 11.36	Total Glucosides of White Paeony Capsules (emolliating liver to relieve pain, dredging collaterals the blood vessels.)	RA: Chinese guideline for diagnosing and treating rheumatoid arthritis (Chinese Rheumatology Association, 2010.)	I: CHM + ISD C: ISD	I:6.35 ± 1.35C:6.28 ± 1.26	3 months	b, e, f, g, h, j	3
Li 2019 China	I:30(10/20) C:30(14/16)	I: 36.81 ± 6.44 C:37.13 ± 6.97	Huoxue Tongluo decoction (Activating blood and resolving stasis, expelling wind, and dredging collaterals.)	RA: Chinese guideline for the diagnosis and treatment of rheumatoid arthritis (Chinese Rheumatology Association, 2010) ILD: ATS/ERS (IPF, 2002)	I: CHM + GC C: GC	I: 3.13 ± 5.24C:4.33 ± 5.57	3 months	a, b, c, e, f, g	3
Liu 2020 China	I:30(10/20) C:30(12/18)	I: 46.7 ± 8.9C:47.1 ± 7.5	Tongbi Granules (replenishing qi, tonifying blood, resolving phlegm, and dispelling stasis.)	RA: ACR and EULAR (2010) ILD: ATS/ERS/ JRS/ALAT (2011).	I: CHM + GC + ISD C: GC + ISD	I: 8.5 ± 3.5C:9.3 ± 4.1	3 months	a, b, d, e, f, g	4
Wang 2020 China	I:30(21/9) C:26(20/6)	I:52.8 ± 8.9C:50.3 ± 8.6	Bufei Huaxian Decoction (Replenishing qi and tonifying blood, resolving phlegm, and dredging collaterals.)	RA: ACR and EULAR (2010) ILD: ATS/ERS (IPF, 2000) TCM Diagnostics: Guiding Principles for Clinical Research of New Traditional Chinese Medicine. (2002)	I: CHM + AFD C: AFD	None	3 months	c, d, h	3
Zhang 2021 China	I:47(27/20) C:47(29/18)	I: 63.45 ± 5.29 C:63.34 ± 5.33	Huoxue Huayu, Buyi Pishen Recipe (activating blood circulation to dissipate blood stasis and invigorate the spleen-kidney)	RA/ILD: Internal Medicine (9th edition). TCM Diagnostics: Chinese Internal Medicine	I: CHM + GC C: GC	I: 14.42 ± 5.36C:14.29 ± 5.41	4 weeks	b, e, f, g, h	4
Chen 2022 China	I:55 (34/21) C:55 (32/23)	I:51.3 ± 10.3C:49.2 ± 7.3	Tetrandrine(dispelling wind and dampness, moving qi and relieving pain,water-draining and swelling-dispersing)	RA: ACR (2010) ILD: Bronchoscopic lung aspiration biopsy was performed and pathologically diagnosed as unusual interstitial pneumonia, excluding other etiologies.	I: CHM + ISD C: ISD	NM	6 months	b, c, e, i	3
Liu 2022 China	I:25 (15/10) C:25 (14/11)	I: 51.22 ± 3.84 C:50.36 ± 4.03	Huoxue Huayu Decoction(Activating blood and resolving stasis, dredging collaterals and blood-activating analgesic, ventilating lung, and relieving cough.)	RA and ILD: Criteria for Diagnosis and Determination of Efficacy in Clinical Disease (2010.) TCM Diagnosis: Guiding Principles for Clinical Research of New Chinese Medicines, paralysis	I: CHM + GC + TD C: GC + TD	I: 5.11 ± 1.32C:5.27 ± 1.18	3 months	a, b, c, j	4

(*continued on next page*)

Table 1 (*continued*)

				syndrome due to blood stasis (2002.)					
Yao 2022 China	I: 33 (13/20) C:33 (12/21)	I: 65.30 ± 9.41 C:65.97 ± 8.28	Qingfei Huayu Decoction (Taking care of both tip and root, clearing lung and resolving stasis, dredging collaterals, and removing toxins)	RA: ACR, EULAR (2010) ILD: The diagnostic criteria for PF-ILD proposed by Cotton (2018) TCM Diagnostics: Diagnostic and therapeutic criteria for traditional Chinese medicine syndromes (State Administration of Traditional Chinese Medicine, 1994)	I: CHM + AFD C: AFD	I: 123.65 ± 115.44C:122.73 ± 121.91 (months)	6 months	b, d, e, f	4
Wang 2023 China	I:30 (8/22) C:30 (9/21)	I: 52.77 ± 10.30C:53.67 ± 10.96	Kangxian decoction (Tonifying and replenishing lung-kidney, activating blood and dredging collaterals, reinforcing healthy qi, and dispelling evil spirits.)	RA: Guidelines for diagnosing and treating rheumatoid arthritis (Rheumatology Branch of the Chinese Medical Association, 2016). ILD: Consensus of Chinese Experts on the Diagnosis and Treatment of IPF (Interstitial Pulmonary Disease Group, Respiratory Branch, Chinese Medical Association, 2016). TCM Diagnostics: Syndrome of qi deficiency with blood stasis.	I: CHM + GC C: GC	I: 12.17 ± 3.53C:12.83 ± 3.64	3 months	a, b, c, e, i	4
Li 2023 China	I:45 (15/30) C:45 (17/28)	I: 49.18 ± 5.67 C:49.33 ± 4.81	Tripterygium glycosides (Main active ingredients of Tripterygium wilfordii. Dispelling wind and dampness, activating blood, and dredging collaterals.)	RA: ACR (2010). ILD: AST/ERS (2015).	I: CHM + ISD C: ISD	I: 6.11 ± 1.71C:6.02 ± 2.32	12 weeks	a, b, c, d, f, h, I, j	4
Shao 2024 China	I:41 (27/14) C:41 (26/15)	I: 63.49 ± 6.03C:63.03 ± 6.27	Canxiong Tongbi Decoction((Tonifying and replenishing lung-pi, activating blood and dredging collaterals.)	RA: 2018 Chinese Diagnosis and Treatment Guidelines for Rheumatoid Arthritis(Rheumatology Branch of the Chinese Medical Association 2002). ILD: AST/ERS (2015).	I: CHM + GC + ISD + NASID C:GC + ISD + NASID	I: 13.84 ± 5.03C:13.57 ± 5.29	3 months	a, c, e	4
Qin 2024 China	I:63 (23/40) C:63 (21/42)	I: 44.06 ± 7.82C:43.87 ± 7.76		RA: Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis. ILD: Interpretation of the 2011 New Evidence-Based Guidelines for the Diagnosis and Treatment of Idiopathic Interstitial Fibrosis.	I: CHM + GC C:GC	I: 8.07 ± 1.26C:7.98 ± 1.23	3 months	a, b, c, e, j	4

Abbreviations: I: Intervention group; C: Control group; M: Male; F: Female; NM: not mentioned; GC: Glucocorticoids; ISD: Immunosuppressive drug; NASID: non-steroidal anti-inflammatory drugs; TD: Theophylline drugs; AFD: antifibrotic drug.
Notes: Result code a: TLC; b: FVC; c: DLCO; d: HRCT integral; e: Clinical efficiency; f: ESR; g: CRP; h: RF.

drugs used in WM were the same as those in the control group; TCM was not restricted to the dosage forms, dosages and formulations of the drugs; 3)Comparison: Western medicine (WM) therapy alone, such as glucocorticoids, immunosuppressants, antifibrotic drugs, etc.; usage and dosage must be the same as in the intervention group; 4)Outcome: Primary outcomes were improvement in lung function (FVC, DLCO, TLC) and change in HRCT score; secondary outcomes were clinical effectiveness and improvement in inflammatory markers; 5)Literature type: Studies of randomized trials combining Chinese and Western medicine in the treatment of RA-ILD versus Western medicine only were published in Chinese or English.

2.4. Exclusion criteria

Exclusion criteria of the evaluation literature were as follows: 1) the literature studies did not conform to randomized controlled trials; 2) neither published conference papers nor graduate studies were included in the evaluation; 3) data were duplicated in the

Table 2
CHM in the included studies.

Study Year region	CHM Formula (Dosage, frequency)	CHM Components	Placebo (Dosage, frequency)	Adverse event
Li 2011 China	**Fangxian Decoction** (One dose daily, morning and evening, 200 ml)	Root of *Astragalus membranaceus* (Fisch.) Bunge 20 g, Processed products of *Atractylodes macrocephala* Koidz. 12 g, Root of *Adenophora stricta* Miq. 15 g, Root of *Ophiopogon japonicus* (L. f.) Ker Gawl. 15 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 10 g, Root of *Rehmannia glutinosa* (Gaert.) Libosch. Ex Fisch. et Mey. 10 g, Root of *Angelica sinensis* (Oliv.) Diels 10 g, Rhizomes of *Spatholobus suberectus* Dunn 30 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 30 g, Rhizomes of *Fritillaria cirrhosa* D. Don 15 g, Root bark of *Morus alba* L. 15 g, Dry body of *Pheretima aspergillum* (E.Perrier) 15 g, Dry body of *Beauveria bassiana*(Bals.) Vuillant 15 g, *Centella asiatica* (L.) Urb. 30 g, Root of *Tripterygium wilfordii* Hook. f. 10 g	Prednisone (0.5 mg/kg/d at around 7 a. m., with regular tapering.) Cyclophosphamide injection (400 mg in 100 ml of 0.9 % saline, IV drip, once every two weeks.)	I: Leukopenia(n = 1) C: Leukopenia(n = 5), Colds (n = 4), Dizziness (n = 3), Hepatic impairment (n = 3)
Xie 2011 China	**Bufei Tongluo Wan** (Water-honeyed pills, 10 g each time, two times daily.)	Root of *Astragalus membranaceus* (Fisch.) Bunge 20 g, Root of *Glehnia littoralis* F. Schmidt ex Miq. 20 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 20 g, Processed products of *Paeonia lactiflora* Pall. 20 g, Roots of *Sophora flavescens* Aiton 20 g, the part of the sclerotium with pine roots of *Wolfiporia cocos* (F.A. Wolf) Ryvarden & Gilb. 30 g, Root of *Ophiopogon japonicus* (L. f.) Ker Gawl. 10 g, Dried fleshy scaly leaves of *Lilium brownii* var. *viridulum* Baker 10 g, Fruits and seeds of *Lycium chinense* Miller 10 g, Dried mature seeds of *Prunus persica* (L.) Batsch 10 g, Dry flowers of *Carthamus tinctorius* L. 10 g, Dry body of *Whitmania* Pigra Whitman 10 g, Dry body of *Pheretima aspergillum* (E.Perrier) 10 g, Tail of *Angelica sinensis* (Oliv.) Diels 10 g, Underground bulb of *Fritillaria thunbergii* Miq. 10 g Shoots of *Cinnamomum cassia* (L.) D. Don 10 g, Processed products of *Atractylodes macrocephala* Koidz. 10 g, Dry seeds of *Prunus armeniaca* L. 10 g, Root bark of *Houpoea officinalis* (Rehder & E. H. Wilson) N. H. Xia & C. Y. Wu 10 g, Dry outer peel of *Citrus reticulata* Blanco 10 g, Processed products of *Pinellia ternata* (Thunb.) Ten. Ex Breitenb. 10 g.	Methotrexate (2.5 mg per tablet, 5–10 mg each time, once a week) Celecoxib capsule (200 mg per capsule, 200 mg each time, 1 to 2 times a day, orally) (according to RA condition)	I: Gastrointestinal reaction (n = 1), Elevated alanine aminotransferase (n = 2) C: Gastrointestinal reaction (n = 2), Elevated alanine aminotransferase(n = 1)
Zhang 2014 China [42]	Shengxian Bolus (Water-honeyed pills, 8 g each time, three times daily.)	Root of *Astragalus membranaceus* (Fisch.) Bunge 18 g, Root of *Anemarrhena asphodeloides* Bunge 9 g, Root of *Bupleurum longiradiatum* Turcz. 6 g, Root of *Platycodon grandiflorus* (Jacq.) A. DC. 6 g, Root of *Actaea cimicifuga* L. 6 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g, Dried mature seeds of	Basal therapy, CTX shock therapy (each dose of 10–16 mg/kg, added to 0.9 % NaCl solution 250 ml IV, single dose longer than 1 h, every four weeks, after six treatments change to every three months, after 6–8 g, discontinue the drug)	I: Gastrointestinal reaction (n = 16), transaminase elevation (n = 2) C: gastrointestinal reaction (n = 17), transaminase elevation (n = 2)

(*continued on next page*)

Table 2 (*continued*)

Study Year region	CHM Formula (Dosage, frequency)	CHM Components	Placebo (Dosage, frequency)	Adverse event
		Prunus persica (L.) Batsch 12 g, Dry flowers of *Carthamus tinctorius* L. 12 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 9 g.		
Tang 2017 China [43]	Chenshi Qingfei Decoction (One dose daily, morning and evening, 150 ml)	Root of *Pseudostellaria heterophylla* (Miq.)Pax ex Pax et Hoffm. 30 g, Root of *Ophiopogon japonicus* (L. f.) Ker Gawl. 30 g, Root of *Adenophora stricta* Miq. 30 g, *Salvia chinensis* Benth. 30 g, Root of *phragmitis rhizoma* 30 g, Root of *Taraxacum mongolicum* Hand.-Mazz. 30 g Dried mature seeds of *Prunus persica* (L.) Batsch 9 g, Root of *Curcuma phaeocaulis* Valeton 30 g, Dry pseudobulbs of *Cremastra appendiculata* (D. Don) Makino 9 g, Dry bulb of *Fritillaria thunbergii* Miq. 9 g, Dry body of *Beauveria bassiana* (Bals.)Vuillant 15 g, Root of *Benincasa hispida* (Thunb.) Cogn. 15 g.	Prednisone (5 mg per tablet, 10–30mg/dose, once daily, given by morning).	I: Diarrhea (n = 12), Leukopenia(n = 2), transaminases elevation (n = 2) C: Gastrointestinal reaction (n = 2), Leukopenia (n = 2), transaminase elevation (n = 3)
Wang 2017 China [44]	Yiqi Yangyin Tongbi Prescription (One dose daily, morning and evening, 200 ml)	Root of *Panax ginseng* C. A. Mey. 10 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 30 g, Processed products of *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey. 30 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 6 g, Root of *Aster tataricus* L. f. 10 g, Root bark of *Morus alba* L. 12 g, Root of *Angelica sinensis* (Oliv.) Diels 10 g, Dry aboveground parts of *Eclipta prostrata* L. 20 g, Root of *Adenophora stricta* Miq. 20 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 20 g, Root of *Curcuma longa* L. 12, Dry outer peel of *Citrus reticulata* Blanco 15 g, Processed products of *Glycyrrhiza uralensis* Fisch. 6 g.	Celecoxib capsule (0.2 g/dose, two times/d, orally). Cyclophosphamide tablets (100 mg/dose, 1 time/every other day, orally). Prednisolone tablets (30 mg/dose, one time/d, in the morning, after the onset of effect, according to the regular reduction of dosage).	NM
Huang 2018 China [45]	Yangyin Tongbi Formula (One dose daily, morning and evening, 150 ml)	Root of *Codonopsis pilosula* (Franch.) Nannf. 30 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 30 g, Processed products of *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey. 30 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 20 g, Root of *Aster tataricus* L. f. 20 g, Root of *Angelica sinensis* (Oliv.) Diels 20 g, Dry aboveground parts of *Eclipta prostrata* L. 20 g, Root of *Adenophora stricta* Miq. 15 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g.	Cyclophosphamide (50 mg per tablet, 100 mg/dose, once every two days, orally). Prednisone (5 mg per tablet, 30 mg/dose, once daily, orally).	NM
Duan 2019 China [37]	Total Glucosides of Paeony (Week 1: 0.3 g/d, three times/d; Week 2–4: 0.6 g/d, two times/d, one month as a course of treatment.)	Effective extracts of root of *Cynanchum otophyllum* Schneid. (Week 1: 0.3 g/d, three times/d; Week 2–4: 0.6 g/d, two times/d, one month as a course of treatment.)	Methotrexate (5 mg/dose, 1 time/d, orally.) Leflunomide (50 mg/dose every other day on days 1–3, 20 mg/dose every other day after that.)	NM
Li 2019 China [46]	Huoxue Tongluo decoction (One dose daily, morning and evening, 200 ml)	Roots and rhizomes of *Salvia miltiorrhiza* Bunge 12 g, Dry Flowers of *Carthamus tinctorius* L. 12 g, Processed products of *Paeonia lactiflora* Pall. 15 g, Root of *Angelica sinensis* (Oliv.) Diels 15 g, Dried mature seeds of *Prunus persica* (L.)	Prednisone (0.5–1 mg/kg/day, Po.)	No adverse reactions occurred during treatment

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Table 2 (*continued*)

Study Year region	CHM Formula (Dosage, frequency)	CHM Components	Placebo (Dosage, frequency)	Adverse event
		Batsch 10 g, Rhizomes of *Spatholobus suberectus* Dunn 10 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 10 g, Shoots of *Cinnamomum cassia* (L.) D. Don 10 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 10, Root of *Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow 6 g, Rhizome of *Ligusticum sinense* 'Chuanxiong' 6 g, Dry mature fruits of *Ziziphus jujuba* Mill. 5 piece, Dry body of *Scolopendra subspinipes mutilans* L. Koch 2 strip.		
Liu 2020 China [47]	Tongbi Granules (6 g per sachet, one sachet each time, twice a day.)	Root of *Astragalus membranaceus* (Fisch.) Bunge, Tail of *Angelica sinensis* (Oliv.) Diels, Root of *Cynanchum otophyllum* Schneid., Rhizome of *Ligusticum sinense* 'Chuanxiong,' Dry body of *Beauveria bassiana* (Bals.) Vuillant, Dry body of *Buthus martensii* Karsch, Dry resins of *Boswellia carterii* Birdw., Dry resins of *Commiphora myrrha* Engl., Hoots of *Cinamomum cassia* (L.) D. Don, Dry bark of *Phellodendron chinense* Schneid., Processed products of *Glycyrrhiza uralensis* Fisch.	Methylprednisolone tablets (20 mg each time, once a day, gradually reduce the dosage after the onset of effect), Cyclophosphamide tablets (100 mg every other day).	I: epigastric discomfort (n = 2), C: epigastric discomfort (n = 1).
Wang 2020 China [48]	**Bufei Huaxian Decoction** (One dose daily, morning and evening, 150 ml)	Root of *Astragalus membranaceus* (Fisch.) Bunge 30 g, Processed products of *Atractylodes macrocephala* Koidz. 10 g, Root of *Ophiopogon japonicus* (L. f.) Ker Gawl. 15 g, Processed products of *Pinellia ternata* (Thunb.) Ten. ex Breitenb. 10 g, Root of *Codonopsis pilosula* (Franch.) Nannf. 10 g, Rhizome of *Ligusticum sinense* 'Chuanxiong' 10 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g, Root of *Rhodiola rosea* L. 15 g, Dry leaves of *Morus alba* L. 10 g, Rhizomes of *Fritillaria cirrhosa* D. Don 10 g, Dry mature fruit of *Luffa cylindrica* (L.) Roem. 10 g, Pericarp sinews of *Citrus reticulata* Blanco 6 g, Dry ripe fruit of *Cullen corylifolium* (Linnaeus) Medikus 10 g, Processed products of *Glycyrrhiza uralensis* Fisch. 3 g.	Pirfenidone capsules (100 mg per capsule, two tablets each time, three times daily by mouth. Take for one week; after the second week, take for four weeks; from week 6, continue).	NM
Zhang 2021 China [49]	Huoxue Huayu, Buyi Pishen Recipe (Take one daily dosage twice with lukewarm water.)	Dry seeds of *Prunus armeniaca* L. 10 g, Root of *Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm. 30 g, Rhizome of *Ligusticum sinense* 'Chuanxiong' 15 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 30 g, Root bark of *Morus alba* L. 15 g, Fruits and seeds of *Lycium chinense* Miller 20 g, Root of *Cynanchum otophyllum* Schneid. 15 g, Root of *Angelica sinensis* (Oliv.) Diels 20 g, Root of *Paeonia lactiflora* Pall. 15 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 20 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 15 g, Root of *Rehmannia glutinosa* (Gaert.) Libosch. Ex Fisch. et Mey. 15 g, Root of *Ophiopogon japonicus* (L. f.) Ker Gawl. 15 g, Processed products of *Glycyrrhiza uralensis* Fisch. 3 g.	Prednisone Acetate Tablets (5 mg per tablet, two tablets/dose, three times/day)	NM

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Table 2 (*continued*)

Chen 2022 China [38]	Tetrandrine(20 mg per tablet, three tablets each, three times daily, Po.).	Effective extracts of root of *Stephania tetrandra* S. Moore(20 mg per tablet, three tablets each time, three times a day, Po.)	Cyclophosphamide (0.2 g per dose at 600 mg/m2 (BSA), I.V., every four weeks for six doses).	I: Respiratory infection (n = 1), granulocytopenia (n = 2), gastrointestinal reaction (n = 5). C: Respiratory infection (n = 6), granulocytopenia (n = 3), hepatic impairment (n = 1), gastrointestinal reaction (n = 5).
Liu 2022 China [50]	Huoxue Huayu Decoction (One dose daily, morning and evening, 200 ml)	Root of *Astragalus membranaceus* (Fisch.) Bunge 30 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g, Root of *Paeonia lactiflora* Pall. 15 g, Rhizomes of *Spatholobus suberectus* Dunn 15 g, Root of *Angelica sinensis* (Oliv.) Diels 10 g, Shoots of *Cinnamomum cassia* (L.) D. Don 10 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 10 g, Dry mature seeds of *Prunus persica* (L.) Batsch 10 g, Dry flowers of *Carthamus tinctorius* L. 10 g, Rhizome of *Ligusticum sinense* 'Chuanxiong' 6 g, Dry body of *Buthus martensii* Karsch 3 g, Dry body of *Scolopendra subspinipes mutilans* L.Koch 2 strip.	Prednisone acetate tablets (5 mg per tablet, 10–15 mg each time, once a day, Po.) Aminophylline tablets (0.1 g per tablet, 0.2 g each time, two times a day, Po.)	NM
Yao 2022 China [51]	Qingfei Huayu Decoction (One dose daily, morning and evening, 200 ml)	Root of *Rehmannia glutinosa* (Gaert.) Libosch. Ex Fisch. et Mey. 30 g, Dry Whole Grass of *Centella asiatica* (L.) Urb. 30 g, Dry mature seeds of *Prunus persica* (L.) Batsch 15 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 9 g, Root of *Scutellaria baicalensis* Georgi 9 g, Rootstock of *Curculigo orchioides* Gaertn. 12 g, Dry leaf of *Epimedium brevicornu* Maxim. 12 g, Dry root of *Dipsacus asper* Wall.12 g, Processed products of *Glycyrrhiza uralensis* Fisch. 6 g.	RA Remission regimen + pirfenidone (200–400 mg/dose, three times/d, orally, gradually increasing the dosage as tolerated by the patient.)	I: Hepatic Insufficiency (n = 1), mild abdominal distension, diarrhea (n = 2). C: Hepatic Insufficiency (n = 2), mild abdominal distension, diarrhea (n = 2)
Wang 2023 China [52]	Kangxian decoction (One dose daily, morning and evening, 200 ml)	Root of *Codonopsis pilosula* (Franch.) Nannf. 15 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 15 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g, Rhizomes of *Spatholobus suberectus* Dunn 15 g, Dry the inside of sand bladder of *Gallusgallusdomesticus* Brisson 15 g, Root of *Adenophora stricta* Miq. 10 g, Root of *Angelica sinensis* (Oliv.) Diels 10 g, Rhizome of *Ligusticum sinense* 'Chuanxiong' 10 g, Dry fruit of *Perilla frutescens* (L.) Britt. 10 g, Dry fleshy bulb of *Lilium brownii* var. viridulum Bake9 g, Dry capitulum of *Inula japonica* Thunb. (cover decoction) 9 g, Dry ripe fruit of *Amomum villosum* Lour. (decoct later) 9 g, Processed products of *Glycyrrhiza uralensis* Fisch. 6 g.	Prednisone (5 mg per tablet, 0.5 mg/kg, once daily, Po.)	No adverse reactions occurred during treatment
Li 2023 China [39]	Tripterygium glycosides(10 mg per tablet, 20 mg each time, three times a day, Po.)	Effective extracts of root of *Tripterygium wilfordii* Hook. f.(10 mg per tablet, 20 mg each time, 3 times a day, Po.)	Leflunomide (10 mg per tablet, one tablet once daily).	I: Leukopenia (n = 2), abnormal liver function (n = 1), mouth ulcer (n = 1). C: abnormal liver function (n = 2), leukopenia (n = 1).
Shao 2024 China	Canxiong Tongbi Decoction(One dose per day, morning and evening, 150 ml)	Rhizome of *Ligusticum sinense* 'Chuanxiong' 15 g, Dry body of *Pheretima aspergillum* (E.Perrier) 15 g, Dry body of *Beauveria bassiana*(Bals.) Vuillant 15 g, Dry vine stems of *Sinomenium acuturn*(Thunb.)Rehd.et Wils. 15 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 15 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 15 g, Dry seeds of *Prunus armeniaca* L. 10 g, Underground	Prednisone (5 mg per tablet, 0.5 mg/kg, once daily, Po.) + Cyclophosphamide tablets (100 mg every other day)	NM

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Table 2 (*continued*)

Qin 2024 China	Huoxue Huayu Decoction(One dose per day, morning and evening, 150 ml)	bulb of *Fritillaria cirrhosa* D. Don 10 g, Root of *Codonopsis pilosula* (Franch.) Nannf. 10 g, Processed products of *Glycyrrhiza uralensis* Fisch. 6 g. Dry body of *Scolopendra subspinipes mutilans* L.Koch 2 strip, Dry mature fruits of *Ziziphus jujuba* Mill. 5piece, Rhizome of *Ligusticum sinense* 'Chuanxiong' 6 g, Root of *Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow 6 g, Rhizomes of *Spatholobus suberectus* Dunn 10 g, Fruit of *Schisandra chinensis* (Turcz.) Baill. 10 g, Dried mature seeds of *Prunus persica* (L.) Batsch 10 g, Shoots of *Cinnamomum cassia* (L.) D. Don 10 g, Root of *Astragalus membranaceus* (Fisch.) Bunge 10 g, Dry Flowers of *Carthamus tinctorius* L. 12 g, Roots and rhizomes of *Salvia miltiorrhiza* Bunge 12 g, Root of *Angelica sinensis* (Oliv.) Diels 15 g, Processed products of *Paeonia lactiflora* Pall. 15 g.	Prednisone (5 mg per tablet, 0.5 mg/kg, once daily, Po.)	I: Vomiting (n = 2), headache (n = 1), nausea (n = 2) C: Vomiting (n = 4), headache (n = 2), nausea (n = 2)

Abbreviations: CHM: Chinese medicine prescription; I: Intervention group; C: Control group; NM: not mentioned.

Table 3
Frequency of traditional Chinese medicine Use(≥2).

Name of Chinese Medicine	Frequency
Astragalus membranaceus (Fisch.) Bunge; *Salvia miltiorrhiza* Bunge	13
Angelica sinensis (Oliv.) Diels	10
Schisandra chinensis (Turcz.) Baill.; *Ligusticum sinense* 'Chuanxiong'	8
Prunus persica (L.) Batsch	7
Adenophora stricta Miq.; *Ophiopogon japonicus* (L. f.) Ker Gawl.; *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey.; *Spatholobus suberectus* Dunn; *Paeonia lactiflora* Pall.; *Carthamus tinctorius* L.;	5
Glycyrrhiza uralensis Fisch.	6
Morus alba L.; *Cinnamomum cassia* (L.) D. Don; *Codonopsis pilosula* (Franch.) Nannf.	4
Atractylodes macrocephala Koidz.; *Citrus reticulata* Blanco; *Cynanchum otophyllum* Schneid.; *Fritillaria cirrhosa* D. Don; *Pheretima aspergillum* (E.Perrier); *Prunus armeniaca* L. ; *Scolopendra subspinipes mutilans* L.Koch	3
Beauveria bassiana(Bals.)Vuillant; *Centella asiatica* (L.) Urb.;*Tripterygium wilfordii* Hook. f. ;*Lilium brownii* var. viridulum Baker; *Lycium chinense* Miller; *Fritillaria thunbergii* Miq.; *Pinellia ternata* (Thunb.) Ten. ex Breitenb.; *Aster tataricus* L. f.; *Eclipta prostrata* L.; *Buthus martensii* Karsch; *Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow; *Ziziphus jujuba* Mill.; *Beauveria bassiana* (Bals.) Vuillant	2

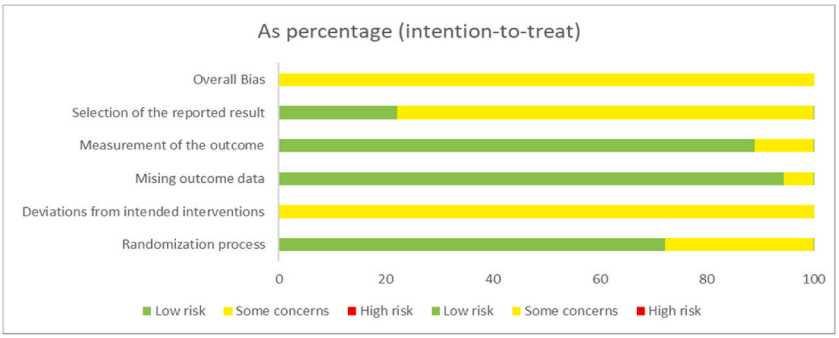


Fig. 3. Risk of bias graph.

publication or the information was incomplete and the full text was unavailable; 4) the treatment group and the control group did not conform to whether it was a traditional Chinese medicine (TCM) treatment or not; 5) the treatment of the control group was not consistent with the treatment group; and 6) the quality of the literature was assessed to be low (the modified Jadad scale score was ≤3, for detailed screening criteria, please refer to the supplementary materials.).

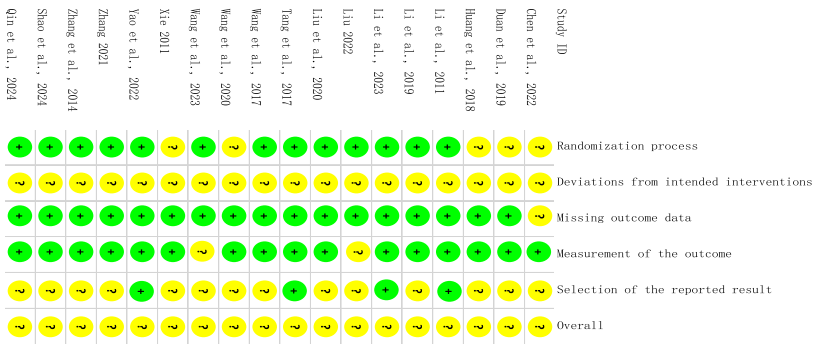


Fig. 4. Risk of bias summary.

2.5. Screening of studies and data extraction

Two researchers (Lu and Li) assessed each other's titles for inclusion in the literature, and the data were extracted and cross-checked. Any differences in the course were resolved through debate by a third researcher (Bin Liu). The full texts of eligible articles were summarised to filter the information. Basic information extracted from the articles included essential study characteristics (author, year of publication, place of publication, and study type), baseline patient characteristics (sample size, age, disease duration, and sex), intervention controls, outcome indicators, and adverse reactions(ADRs).

2.6. Quality evaluation

Two researchers (Lu and Li) independently assessed the methodological quality of each study using the Cochrane Collaboration Risk of Bias tool [31,32]. Disagreements were resolved through mutual discussions or involvement of a third reviewer (Bin Liu). The items assessed included Randomization process, Deviations from intended interventions, Missing outcome data, Measurement of the outcome, Selection of the reported result, Overall. The quality of the included studies was assessed using the modified Jadad scale [33].

2.7. Data analysis

Meta-analyses of the outcomes were summarised using Review Manager (RevMan) software version 5.4, as recommended by the Cochrane Collaboration. Continuous results were presented as mean difference (MD) or standardised mean difference (SMD), and dichotomous data were presented as odds ratios (ORs) and 95 % confidence intervals (95 % CI). Heterogeneity of the pooled results was analysed using the I^2 statistic. An $I^2 > 75$ % indicated firm heterogeneity and was analysed using a random effects model [34]; low heterogeneity ($I^2 < 50$ % or $P > 0.05$) was examined using a fixed-effects model [35,36]. Subgroup analyses were conducted to determine the reasons for high heterogeneity. Sensitivity analyses were performed by excluding the effects of individual studies on the results, on a case-by-case basis. Funnel plots were drawn for publication bias ($P > 0.05$) and calculated using the Stata 16.0 Egger test. The stability of the results was evaluated using trial sequential analysis (TSA) 0.9.5.10 Beta software. Grading of Recommendations Assessment, Development, and Evaluation Profiler (GRADE Pro)-Evidence Assessment Quality of Primary Outcome Evidence.

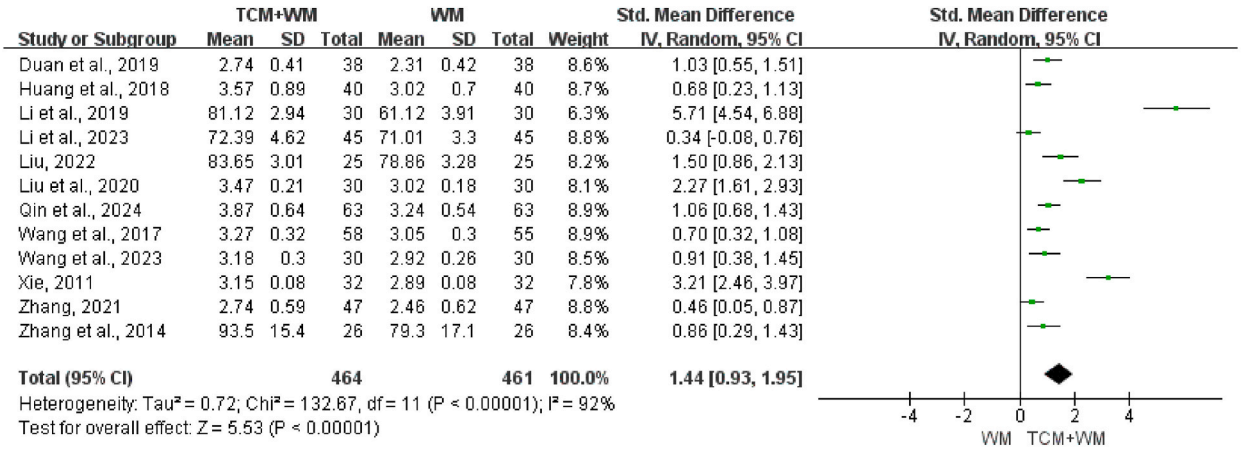
3. Results

3.1. Select results

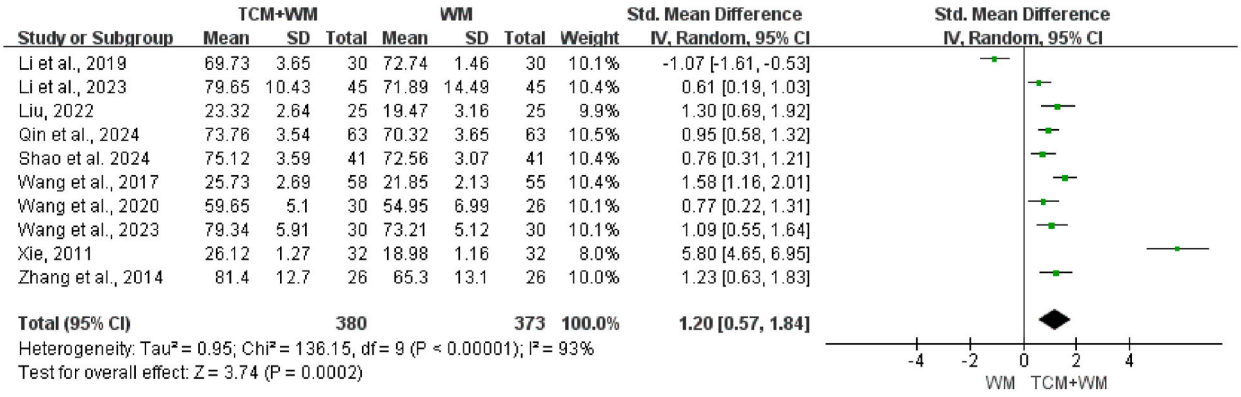
Aggregated 877 relevant studies from 8 database searches and one manually searched relevant literature in the literature reading. Eight hundred and seventy-eight studies were retrieved and imported, and 212 duplicates were excluded by duplicate checking using EndNote X9 software. Next, from the title and abstract of the search entries, 627 items that did not meet the inclusion criteria were excluded. The final 39 studies were assessed by reading the complete text, and 21 were excluded. Ultimately, 18 RCTs [37–54] were included in this meta-analysis. Detailed screening is shown in Fig. 2.

3.2. Research characteristics

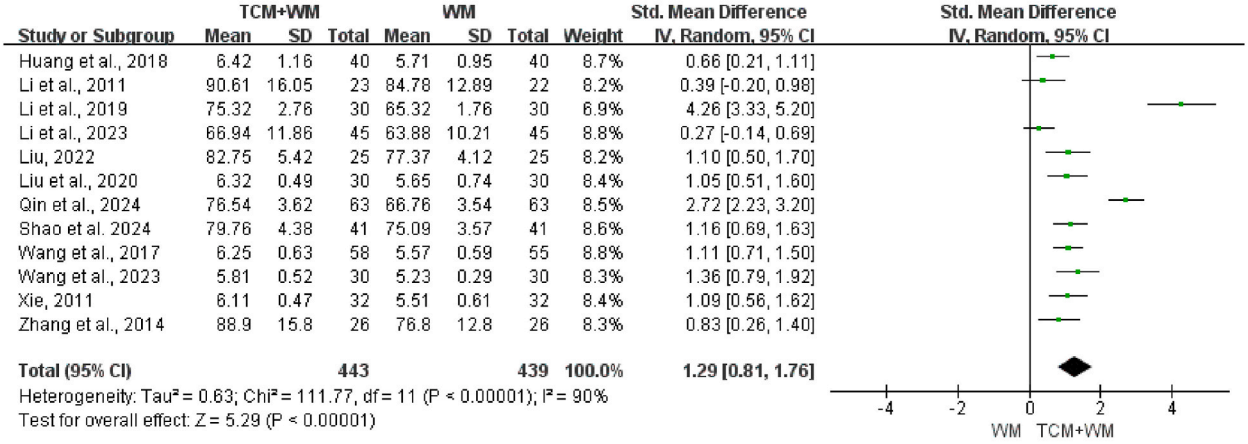
Two researchers independently extracted data from 18 papers. These studies will be published between 2011 and 2024, all in China. A thousand of three hundreds fifty-three patients were included in the study, divided into an intervention group (679 participants) and a control group (674 participants), with no statistically significant difference between the two groups at baseline. Aside from three studies [37–39]that utilized herbal compound medications, the remaining studies employed traditional Chinese medicine formulations. And provided a detailed description of the basic characteristics of the included studies(Tables 1–3).



a) FVC



b) DLCO



c) TLC

Fig. 5. Forest plot of lung function:
a) FVC; b) DLCO; c) TLC.

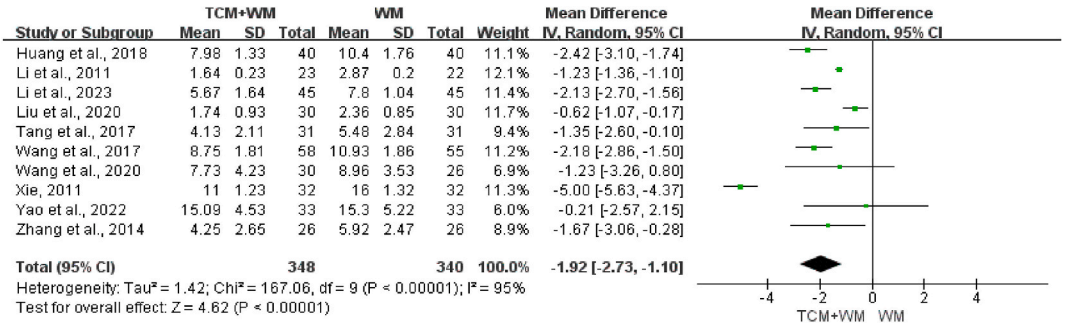


Fig. 6. HRCT integral forest plot.

3.3. Quality of data and risk of bias assessment

Eighteen studies mentioned randomization and only 12 [39,40,42–44,47,49–54] mentioned using random number tables to generate sequences. The inclusion of 18 studies did not clearly indicate whether the subjects were informed in advance, and thus were judged as "unclear risk." Data from one study could not determine whether it would impact the outcome measures, and was also judged as "unclear risk." Four studies demonstrated accurate outcome detection methods and were rated as "low risk." Supplementary assessment of literature quality was performed using a modified Jadad scale (Table 1). The details are shown in Figs. 3 and 4.

3.4. Evaluation analysis

3.4.1. Improvement of lung function

Regarding FVC, the results were reported in 12 studies [37,39,41,42,44–47,49,50,52,53] involving 925 patients (TCM + WM: 464; WM: 461). Summarised DLCO results from ten studies [39,41,42,44,46,48,50,52–54], and 12 studies [39–42,44–47,50,52–54] reported improved TLC outcomes with treatment, involving a total of 882 patients (TCM + WM: 443, WM: 439). Higher heterogeneity of the three indicators($P < 0.00001$, $I^2 = 92$ %); ($P < 0.00001$, $I^2 = 93$ %); ($P < 0.00001$, $I^2 = 90$ %) was observed, and a random-effects model was used. Results showed that combined Chinese and Western medicine treatment for RA-ILD has significant advantages in improving lung function(FVC: SMD = 1.44, 95 % CI 0.93 to 1.95, $P < 0.00001$; Fig. 5a), (DLCO: SMD = 1.20, 95 % CI: 0.57 to 1.84, $P = 0.0002$; Fig. 5b), (TLC: SMD = 1.29, 95 % CI: 0.81 to 1.76, $P < 0.00001$; Fig. 5c).

3.4.2. HRCT score

HRCT score results [39–45,47,48,51] were reported in 10 studies that were analysed for heterogeneity($I^2 = 95$ %, $P < 0.00001$) using a randomised model. Forest plot results: combination drug therapy slows inflammation scores(MD = −1.92, 95 % Cl: 2.73 to −1.10; $P < 0.00001$; Fig. 6).

3.4.3. Clinical efficacy

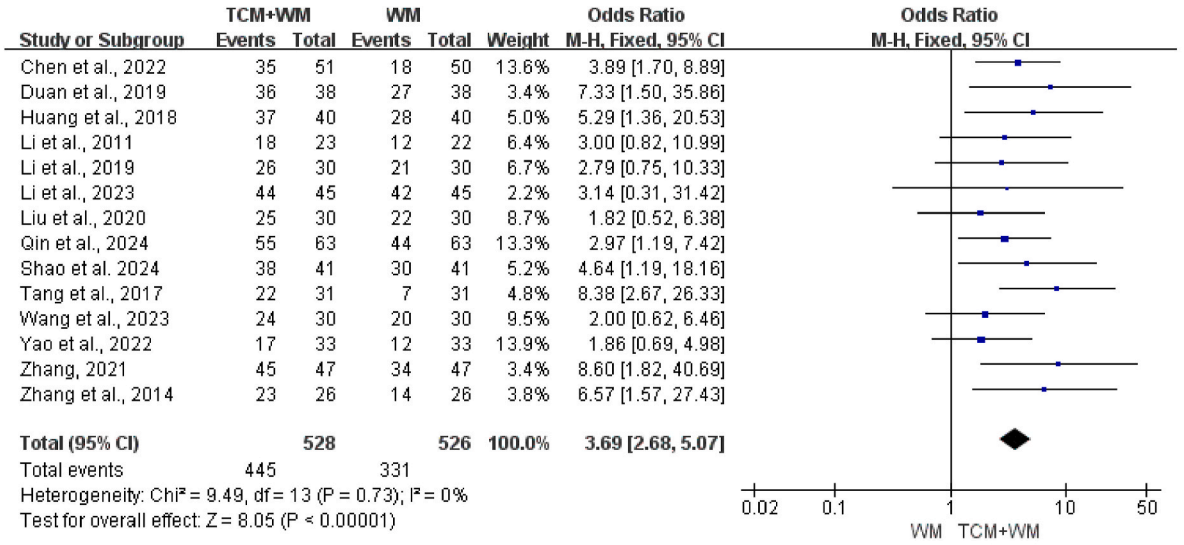
Fourteen studies [37–40,42,43,45–47,49,51–54]involving 1054 cases (TCM + WM: 528, WM: 526) reported the overall efficiency of TCM + WM treatment. Heterogeneity was not tested; therefore, a fixed-effects model was used($I^2 = 0$ %, $P = 0.73$). Forest map summary results (OR = 3.69, 95 % CI: 2.68 to 5.07, $P < 0.00001$; Fig. 7a). Treatment data were classified into an ordered hierarchy of effects. Forest plots show that combination medication is more effective than treatment alone (OR 2.83, 95 % CI: 2.24 to 3.58; $P = 0.617$, $I^2 = 0$ %; Fig. 7b).

3.4.4. Indicators of inflammation

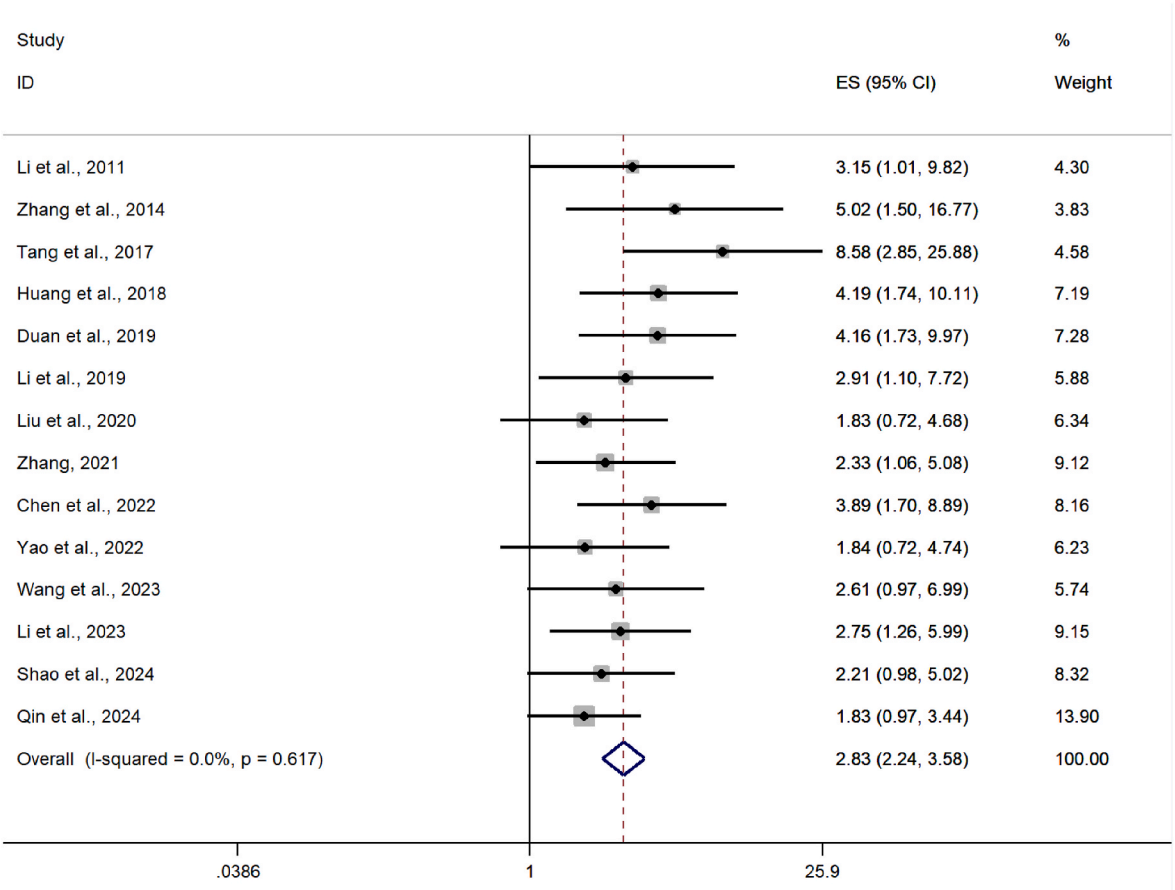
Eight studies [37,39,40,42,46,47,49,51] reported ESR, seven [37,39,40,42,46,47,49] reported CRP and six [37,39,40,42,48,49] reported results on RF improvement. The meta-analysis was highly heterogeneous ($I^2 = 97$ %, $P < 0.00001$), ($I^2 = 98$ %, $P < 0.00001$), and ($I^2 = 97$ %, $P < 0.00001$), and a random-effects model was used. Pooling showed that TCM combined with WM treatment effectively reduced inflammatory ESR, CRP, RF levels, which was superior to the effect of WM alone (MD = −7.89, 95 % CI: 12.40 to −3.39, $P < 0.00001$; Fig. 8a); (MD = −4.75, 95 % CI: 8.61 to −1.34, $P = 0.006$; Fig. 8b); (MD = −41.76, 95 % CI: 66.95 to −16.56, $P = 0.001$; Fig. 8c).

3.4.5. Adverse reactions

Among the 18 randomised trials enrolled, two studies [46,52]explicitly described the occurrence of no significant adverse reactions during the trial period. Seven studies [37,44,45,48–50,54] had an unspecified adverse reaction profile and nine studies [38–43,47,51,53] reported adverse reactions (Table 2). Patients with adverse events were mildly ill, and most symptoms resolved spontaneously. Several studies have not mentioned the occurrence or non-occurrence of security incidents. Therefore, this evaluation does not assess security incidents.

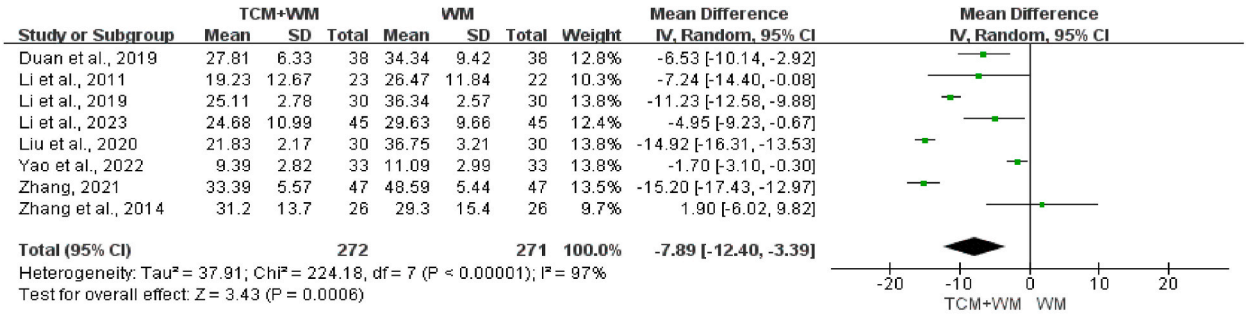


a) Clinical Efficacy

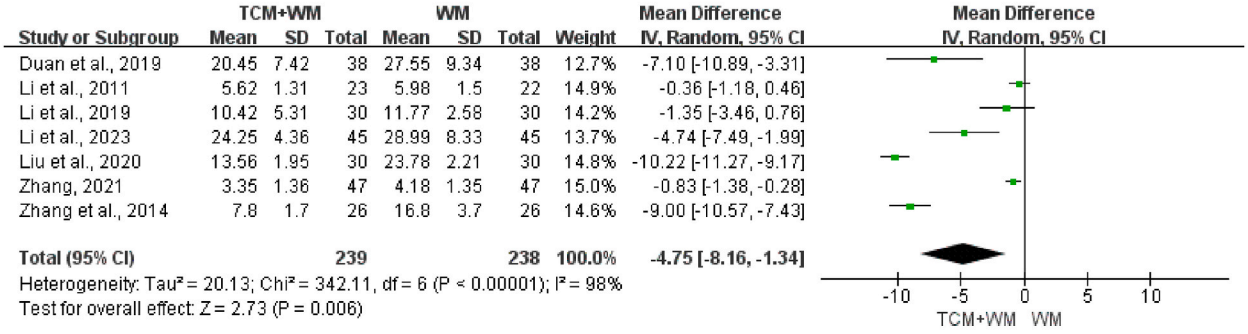


b) Orderly Grade Clinical Effectiveness

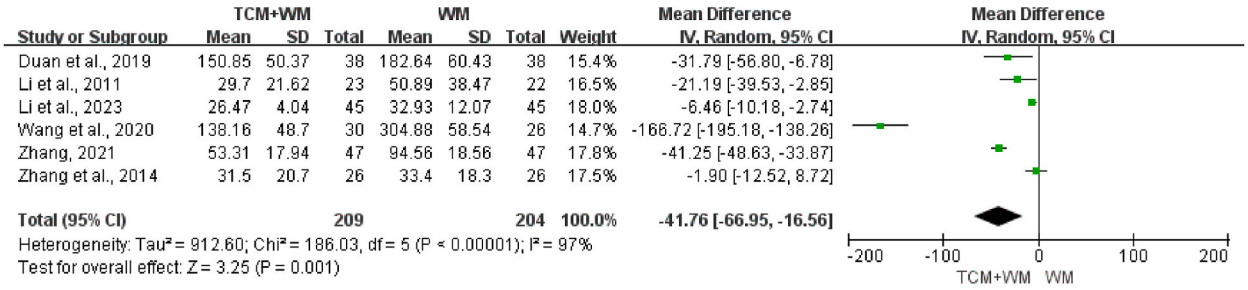
Fig. 7. Forest plot of clinical efficacy:
a) Clinical Efficacy; b) Orderly Grade Clinical Effectiveness.



a)ESR



b)CRP



c)RF

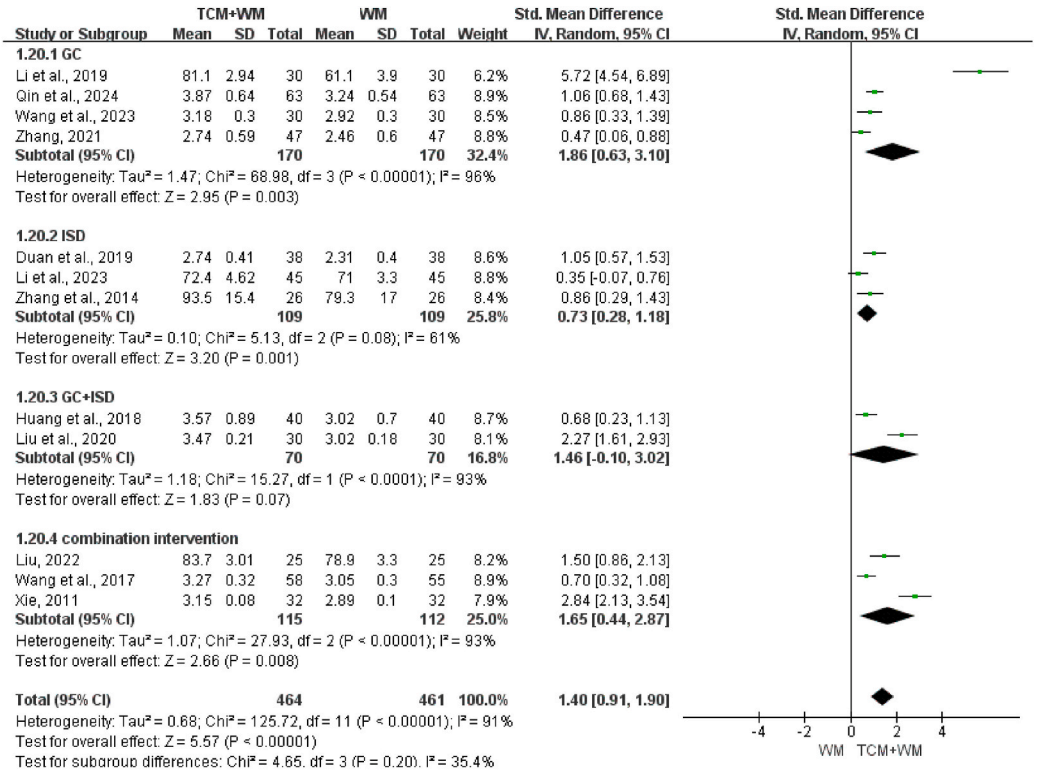
Fig. 8. Forest plot of inflammation indicators:
a) ESR; b) CRP; c) RF.

3.5. Subgroup analysis

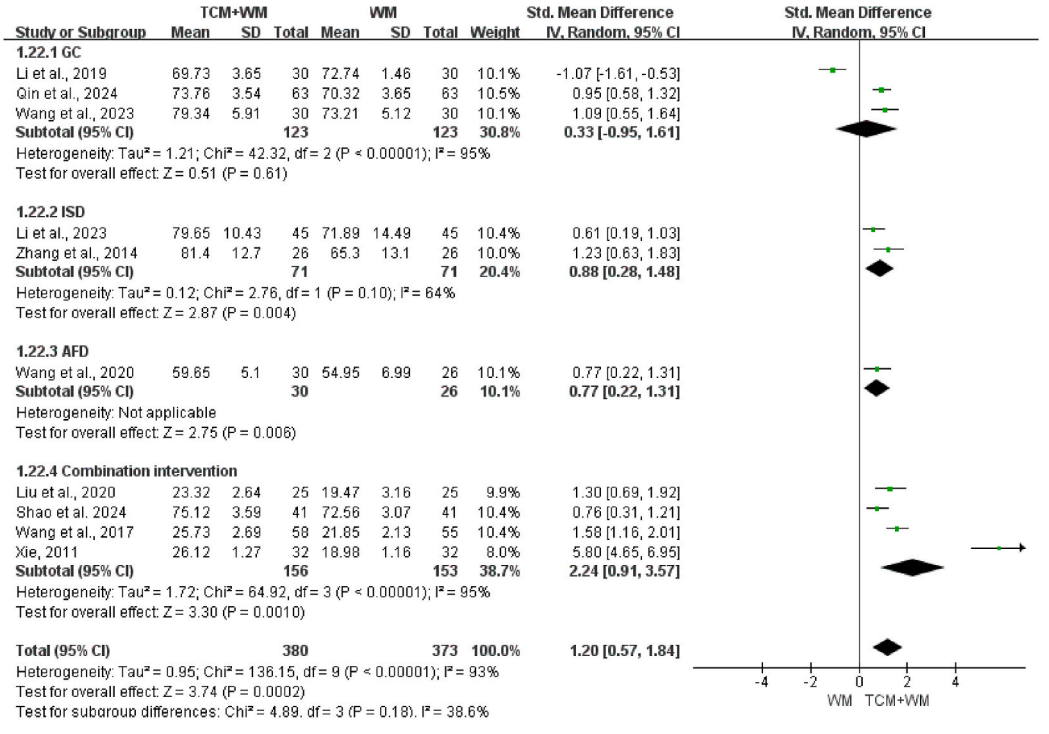
The meta-analysis results showed high heterogeneity in lung function parameters and HRCT scores; thus, we conducted subgroup analyses to determine the possible causes of heterogeneity. Based on the use of Western drugs, these were categorised into GC, ISD, AFD, and combined interventions. The results of the subgroup analysis (Fig. 9) showed that the subgroup using ISD alone had no heterogeneity in the four categories of FVC(Fig. 9a), DLCO(Fig. 9b), TLC(Fig. 9c), and HRCT scores(Fig. 9d), which may have accounted for some heterogeneity. Heterogeneity in TLC was eliminated in both the GC + ISD and ISD subgroups(Fig. 9c). The use of the AFD eliminated heterogeneity in the HRCT scores on the AFD(Fig. 9d). In addition, for both FVC and HRCT scores, the sample size may have contributed to high heterogeneity (Supplementary Tables1, 2 and 3).

3.6. Sensitivity analysis

The high heterogeneity of the FVC results may affect the reliability of the outcome, and we performed a sensitivity analysis with one-by-one exclusion. The results showed (Fig. 10) that the individual studies did not affect the products, indicating that this meta-

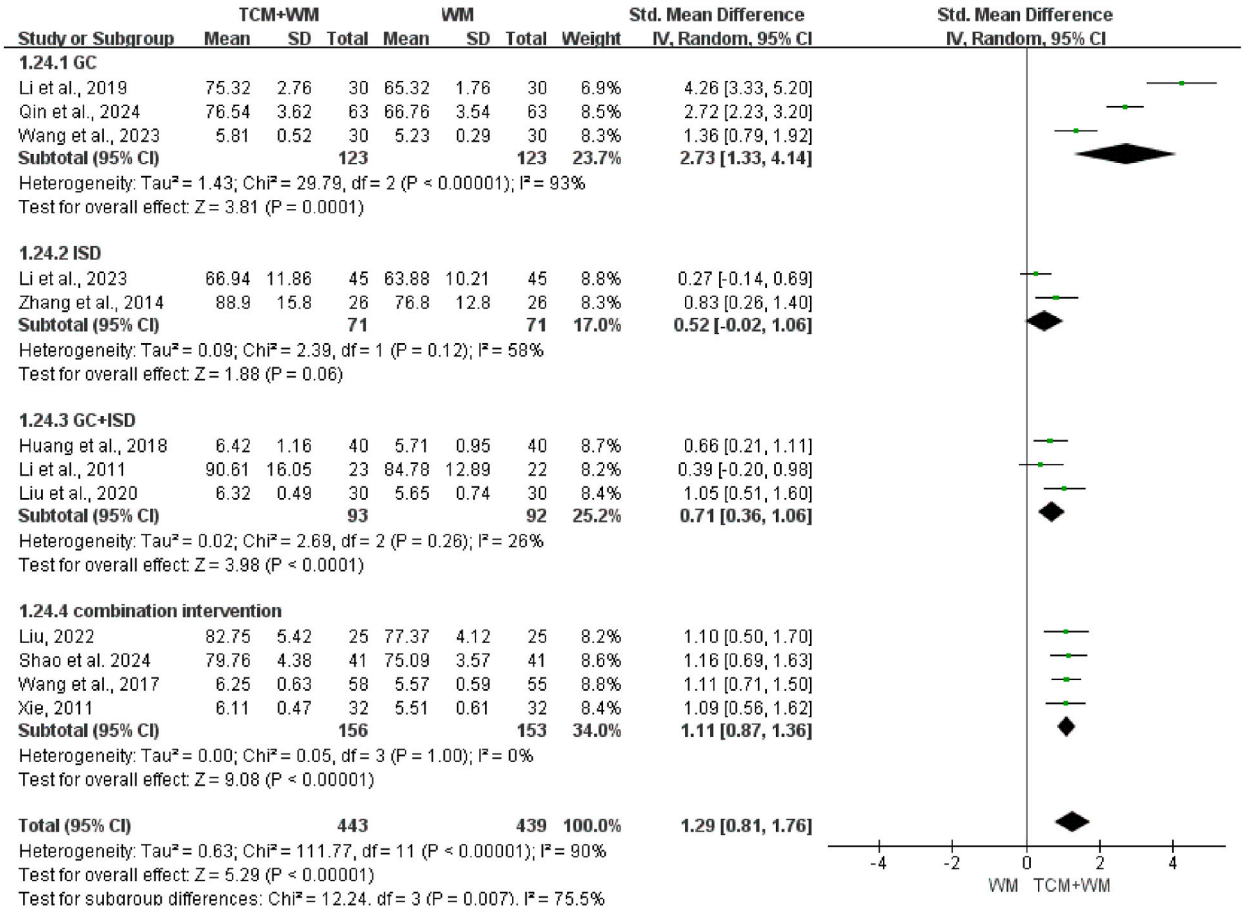


a) FVC

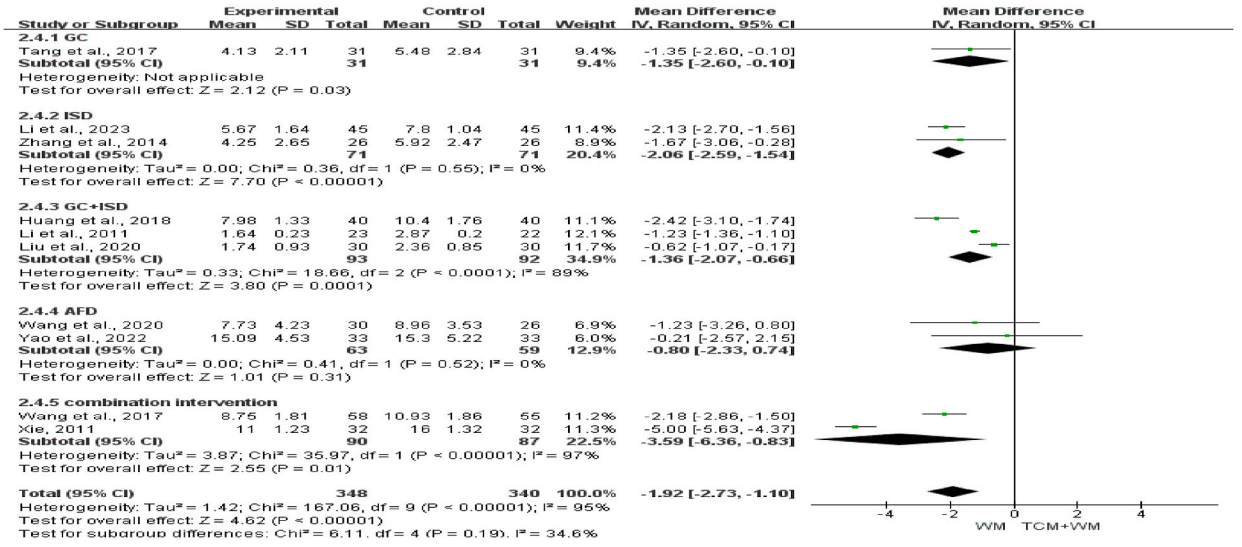


b) DLCO

Fig. 9. Forest plot subgroup comparisons according to the type of intervention in WM: a) FVC; b) DLCO; c) TLC; d) HRCT.



c) TLC



d) HRCT

Fig. 9. (*continued*).

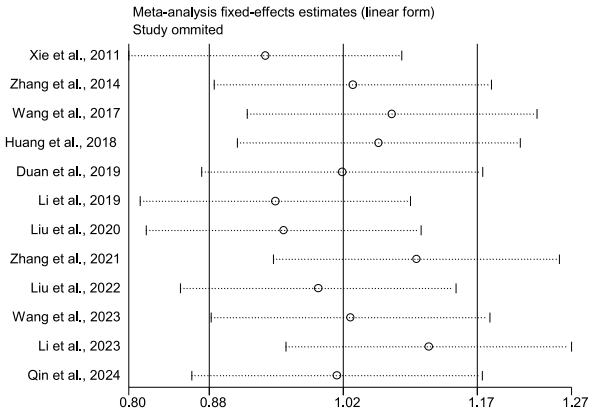


Fig. 10. Sensitivity analysis plots of FVC.

analysis was stable. The Supplementary Material (Supplementary Sensitivity analysis Figure A, B, C, and D) presents sensitivity analyses of the remaining indicators.

3.7. Evaluation of publication bias

Funnel plot analysis using the HRCT scores was not symmetrical (Fig. 11a). Therefore, Egger's test ($P = 0.267 > 0.05$) was used (Fig. 11b), indicating that there was no publication bias. Furthermore, contour-enhanced funnel plots showed no missing studies (Fig. 11c).

3.8. Trial sequential analysis (TSA)

Bilateral Z-curve values were calculated using O'Brien-Fleming in the fixed-effects model ($\alpha = 0.05$, $\beta = 0.2$), and the relative risk reduction rate (RRR = 33.93 %) and the event rate for the control group ($Pc = 62.93$ %, based on the metadata), with the sample sizes used as the expected value (RIS). The results show(Fig. 12a) that the Z-curve crosses the TSA cutoff value when the fourth study is included, and the inclusion of the 10th study achieved the expected results(RIS = 768), indicating that the overall clinical efficacy rate is recognised. After penalised statistical analysis(Fig. 12b), the penalised Z-curve (green) crosses the traditional threshold value ($Z = \pm 1.96$), affirming that the results of the combination are stable and reliable (Fig. 12).

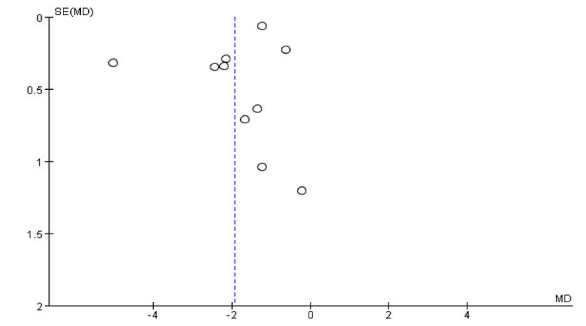
3.9. GRADE assessment of evidence

GRADE Pro assessed the summary quality of the included outcome metrics, such as HRCT score, lung function metrics, and overall clinical effectiveness. The results showed that the DLCO outcome indicator was rated very low owing to adverse effects, while the other relevant factors were rated moderate or low (Table 4).

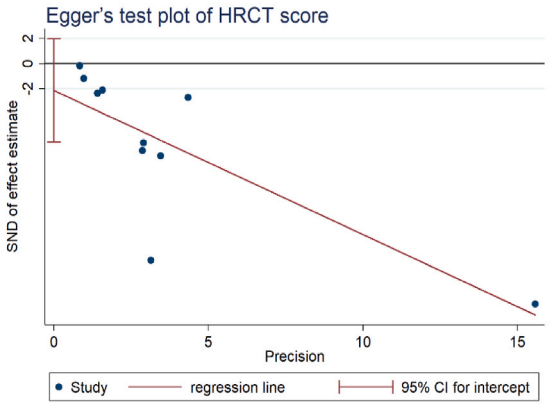
4. Discussion

This study systematically evaluated the efficacy and safety of integrated traditional Chinese and Western medicine for the treatment of RA-ILD. These results are generally consistent with our expectations. Compared to Western medicine alone, the combined use of TCM effectively improved the pulmonary function of patients with RA-ILD, including increases in FVC, DLCO, and TLC. In terms of HRCT, the integrated treatment showed a significantly better improvement in imaging inflammation scores than Western medicine alone. When comparing inflammatory markers such as RF, ESR, and CRP, the integrated treatment significantly reduced these values, thereby ameliorating the condition of patients with RA-ILD. Additionally, in the evaluation of overall clinical efficacy, the total effective ratio of the integrated TCM and Western medicine was significantly superior to that of Western medicine alone. Table 2 shows the occurrence of safety events reported in the 16 included studies. Owing to the diverse reporting methods used in these studies, a meta-analysis of safety events was not feasible; however, a summary of relevant safety events is provided. It can be observed that the combined use of TCM and Western medicine does not increase the burden on RA-ILD patients. Further precise results are required for validation. Based on the above results, an integrated approach of traditional Chinese and Western medicine may be an effective and safe method for improving the condition of patients with RA-ILD.

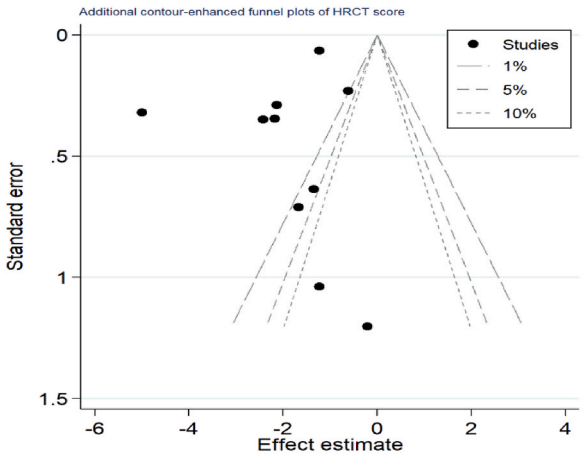
Evaluating the diagnostic status and disease progression or severity in patients with RA-ILD using pulmonary function tests and HRCT is strongly endorsed [55]. Changes in FVC and DLCO [56], along with HRCT inflammation scores [57], are effective in assisting clinicians in diagnosing the disease, assessing its severity, and guiding treatment decisions. Research has confirmed that traditional Chinese medicine can alleviate the condition of patients with RA-ILD by improving lung function, reducing HRCT inflammation scores, regulating collagen deposition in lung tissue, and reducing inflammatory indicators such as rheumatoid factors [26,58]. This finding is



a) Funnel plot of HRCT



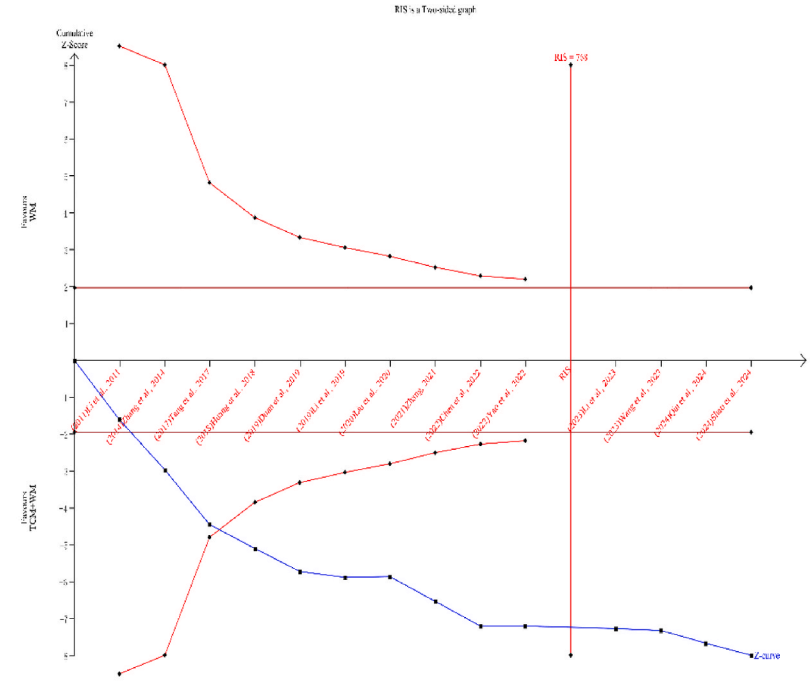
b) Egger's test plot of HRCT



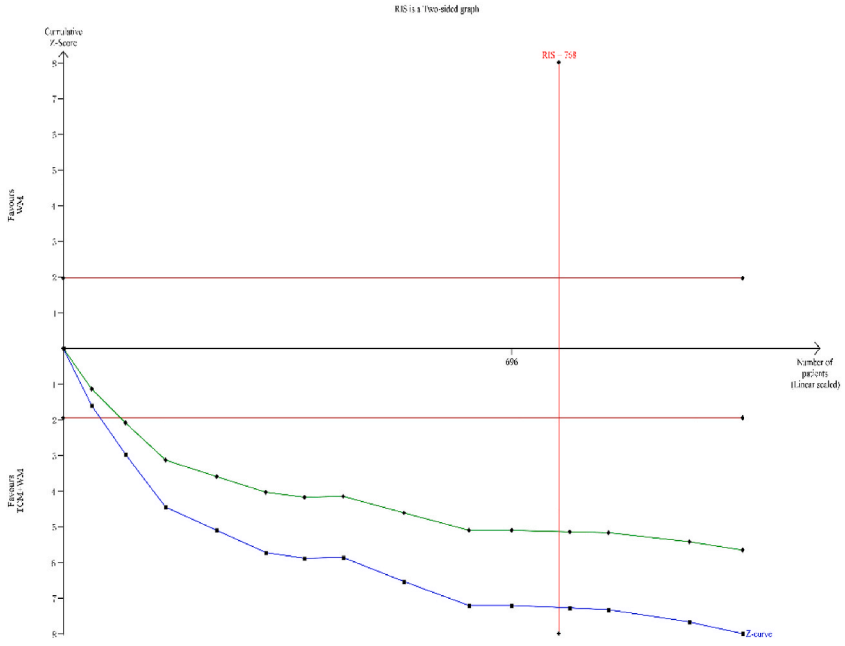
c) Additional contour funnel plot of HRCT

Fig. 11. Publication bias plots of:
a) Funnel plot of HRCT; b) Egger's test plot of HRCT; c) Additional contour funnel plot of HRCT.

consistent with the results of the present meta-analysis. Similarly, experimental studies have also confirmed that traditional Chinese medicine can inhibit the activation of PI3K/Akt, cell apoptosis, and TNF - α signalling pathway in mouse lung tissue, inhibit the expression of inflammatory factors, significantly improve lung pathology and collagen deposition [59,60]. At present, the clinical treatment of RA-ILD can improve the condition of patients with RA-ILD to some extent by using immunosuppressive agents, steroid drugs, or anti fibrotic drugs to suppress rheumatism. However, studies have shown that the use of methotrexate can actually worsen ILD diseases [61] The use of high-dose prednisone can significantly improve FVC in patients, but is accompanied by a large number of



a) TSA analysis of clinical effective rate



b)Analysis of penalty statistics

Fig. 12. a) TSA analysis of clinical effective rate; b)Analysis of penalty statistics.

adverse reactions [62] Among patients receiving TNFi treatment, the proportion of deaths caused by RA-ILD was higher [63]. Prednisone is a corticosteroid used to treat RA-ILD. It can rapidly improve the clinical symptoms of patients with RA-ILD. However, high doses or prolonged use may lead to adverse reactions such as osteoporosis and gastrointestinal ulcer bleeding [64]. The advantage of adding traditional Chinese medicine in the treatment of RA-ILD with immunotherapy or hormone therapy is that it can reduce the

Table 4
Evidence for GRADE evaluation of lung function, HRCT score, and clinical efficacy.

Quality assessment							Number of participants		Pooled result (95 % CI)		Quality
Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	intervention	control	OR	SMD/MD	
FVC	12 RCTs	Serious2	Serious2	no serious indirectness	no serious indirectness	none	464	461	–	SMD 1.44 higher (0.93–1.95 higher)	⊕⊕OO LOW
TLC	12 RCTs	serious1	serious1	no serious indirectness	no serious indirectness	none	443	439	–	SMD 1.29 higher (0.81–1.79 higher)	⊕⊕OO LOW
DLCO	10 RCTs	very serious3	serious3	no serious indirectness	no serious indirectness	none	380	373	–	SMD 1.2 higher (0.57–1.84 higher)	⊕OOO VERY LOW
HRCT score	10 RCTs	serious1	serious1	no serious indirectness	no serious indirectness	none	348	340	–	MD 1.92 lower (2.73–1.1 lower)	⊕⊕OO LOW
Clinical effective rate	14 RCTs	serious1	no serious indirectness	no serious indirectness	no serious indirectness	none	445/528 (84.3 %)	331/526 (62.9 %) 68.90 %	OR 3.69 (2.68–5.07)	233 more per 1000 (from 191 more to 267 more) 196 more per 1000 (from 163 more to 223 more)	⊕⊕⊕O MODERATE

Notes:
1. Randomization was mentioned in all included trials, with only 50 percent specifying the random allocation method. Allocation concealment and blinding were not documented.
2. Heterogeneity was high (I^2 >75 %), with no studies with negative published results.
3. Randomization was mentioned in all included trials, and only 1 test specified the random allocation method. Allocation concealment and blinding were not documented.

dosage of drugs and slow disease progression, while achieving effective treatment.

In Traditional Chinese Medicine, the differential diagnosis involves a multifaceted approach that considers the five organs as a whole. Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is classified under "Fei Wei" (lung wilting), with its overall pathogenesis being a mix of deficiency and excess, characterised by pulmonary vessel obstruction. Clinically, treatment often employs principles such as boosting qi and nourishing yin, tonifying the lungs and kidneys, ventilating the lungs and detoxifying, promoting blood circulation to remove stasis, and invigorating qi and blood. The choice of medicinal herbs is tailored to the subtle pathological differences among individuals. Table 2 summarises the specific effects, dosages, and administration methods of TCM. Due to the variability in herbal prescriptions, subgroup analyses of different formulas were not conducted in this meta-analysis. For a more detailed analysis of the TCM treatments, Table 3 lists the frequency of use of various herbs in the prescriptions. Huangqi (Astragalus membranaceus), danggui (Angelica sinensis), chuanxiong (Ligusticum chuanxiong), and danshen (Salvia miltiorrhiza) were frequently used. TCM significantly inhibits pulmonary fibrosis. Huangqi has antioxidant, anti-inflammatory, and anti-fibrotic properties, which, in pulmonary fibrosis models, significantly reduce α-SMA protein levels and collagen deposition, thereby slowing disease progression. Cryptotanshinone, a compound from danshen, mitigates lung interstitial transformation, reduces inflammatory cell infiltration and extracellular matrix deposition, and inhibits the transcription factor STAT3, thereby improving the progression of pulmonary fibrosis. Therefore, integrating TCM with conventional Western medicine treatments for RA-ILD may lead to improved therapeutic outcomes.

The data reported in the 18 included studies were meticulously evaluated using the Cochrane risk-of-bias tool, evidence-based assessment, and a modified Jadad score. Although the level of evidence obtained is relatively low, the results of this meta-analysis are considered valid. A comprehensive search strategy was used to include all relevant published studies. This analysis aimed to synthesise the diverse reported data as thoroughly as possible, leading to acceptable meta-analysis results. Trial sequential analysis was performed to confirm the robustness and reliability of the findings.

5. Limitations and future prospects

As indicated by the results of the Cochrane Manual and GRADE evidence assessment ratings, the methodological quality of the trials included in this study was generally low. Future research designs should place greater emphasis on the description of research methods for randomised and employ more rigorous blinding techniques wherever possible to enhance the reliability of the evidence. The small sample sizes of these trials represent a significant limitation, potentially affecting the generalisability of the results. Increasing the sample size in future studies could enhance credibility, suggesting that future trial designs should include as many eligible participants as possible.

It is also noteworthy that the majority of studies employed inconsistent assessment criteria, which poses a potential threat to the validity of the results. The diagnosis of RA-ILD requires collaboration among multiple disciplines, which complicates both diagnosis and treatment. This underscores the need for future research using the most authoritative and definitive diagnostic criteria. Despite a comprehensive data search, all the included studies were conducted in China, raising potential concerns regarding publication bias. Fortunately, the Egger test did not indicate a statistical bias.

In China, a combination of TCM and Western Medicine is considered, and the results of this meta-analysis align with expectations. We hope that this treatment strategy will be recognised and adopted by clinical researchers in different regions to address the current challenges in the treatment of RA-ILD. Thus, dialectical treatment approaches in TCM may not be readily accepted by clinicians in various regions. However, through interdisciplinary collaboration, there may be the potential for developing more effective TCM-derived extracts that are easier to use and demonstrate clinical efficacy.

6. Conclusion

Compared with the use of immunosuppressants or corticosteroids, the combination of Traditional Chinese Medicine (TCM) and Western Medicine (WM) may present superior clinical efficacy in the treatment of rheumatoid arthritis-associated interstitial lung disease (RA-ILD). However, the overall quality of the studies included in this meta-analysis was relatively low, necessitating a cautious interpretation of the findings. It is anticipated that this meta-analysis will stimulate the execution of more rigorously designed randomised controlled trials in the future, thereby enhancing the robustness and reliability of the evaluations.

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

Peipei Lu: Writing – original draft, Data curation. **Li Li:** Writing – review & editing, Data curation. **Bin Liu:** Writing – review & editing, Supervision. **Zhiwen Cao:** Methodology, Formal analysis. **Qi Geng:** Visualization, Validation. **Xinyu Ji:** Visualization, Validation. **Yan Zhang:** Validation, Software. **Lijuan Tang:** Supervision, Project administration. **Zhongde Zhang:** Project administration. **Cheng Lu:** Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38771.

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