# Effectiveness and safety of 99Tc-methylene diphosphonate as a disease-modifying anti-rheumatic drug (DMARD) in combination with conventional synthetic (cs) DMARDs in the treatment of rheumatoid arthritis: A systematic review and meta-analysis of 34 randomized controlled trials

Guoqian Deng [a,1], Xinyi Chen [a,1], Le Shao [b,**], Qibiao Wu [c,d,***], Shenzhi Wang [b,*]

[a] Hunan University of Chinese Medicine, Changsha, Hunan, China
[b] The First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, China
[c] State Key Laboratory of Quality Research in Chinese Medicines and Faculty of Chinese Medicine, Macau University of Science and Technology, Taipa, Macau, China
[d] Zhuhai MUST Science and Technology Research Institute, Zhuhai, Guangdong, China

## ARTICLE INFO

## ABSTRACT

*Background:* Technetium [99Tc] methylene diphosphonate injection (99Tc-MDP) is widely used for the treatment of rheumatoid arthritis (RA), but there is still insufficient evidence for its application. Through the utilization of meta-analysis and systematic reviews, this study aimed to evaluate the effectiveness and safety of 99 TC-MDP in combination with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for RA.
*Methods:* This study was registered on PROSPERO in advance (CRD42021220780). A systematic search was conducted in PubMed, Embase, the Cochrane Library, and multiple international public databases from their inception to April 2023 to identify clinical randomized controlled trials exploring the use of 99Tc-MDP combined with csDMARDs in the treatment of RA. Each outcome was subjected to meta-analysis, and the quality of evidence was assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The American College of Rheumatology's 50 %/70 % response criteria scores (ACR50/70) scores were utilized as the primary effectiveness outcomes, and risks were measured by assessing the rates of AEs. Moreover, secondary efficacy outcomes were evaluated, including the Disease

Activity Score 28 (DAS28) and bone mineral density (BMD) as joint function indicators and the erythrocyte sedimentation rate (ESR) and interleukin-17 (IL-17) as inflammatory indicators.

*Results:* In this meta-analysis, a total of 34 studies (2296 patients) were included out of 1149 retrieved studies. The summarized results showed that the treatment group treated with the combination of 99Tc-MDP and csDMARDs had significantly higher ACR50 (RR = 1.32, 95 % CI: 1.13–1.55, P = 0.0004) and ACR70 (RR = 1.40, 95 % CI: 1.07–1.82, P = 0.01) scores than the control group receiving csDMARDs alone. In addition, the overall incidence of AEs was lower with the combination of 99Tc-MDP and csDMARDs than with csDMARDs alone (RR = 0.75, 95 % CI: 0.60–0.93, P = 0.009), but the possibility of phlebitis was higher in the treatment group (RR = 4.15, 95 % CI: 1.04–16.50, P = 0.04). In addition, the combination of 99Tc-MDP and csDMARDs had advantages over csDMARDs alone in improving DAS28 (WMD = 1.56, 95 % CI: 0.86–2.25, P < 0.0001), BMD (SMD = 1.12, 95 % CI 0.46–1.78, P = 0.0008), ESR (SMD = 0.71, 95 % CI 0.45–0.97, P < 0.00001), and IL-17 (WMD = 5.82, 95 % CI 3.86–7.77, P < 0.00001). However, the above results might have been influenced by the 99Tc-MDP dosage, csDMARD category, and treatment duration. Combining methotrexate and leflunomide, administering continuous treatment for 24 weeks, or using 3 sets of 99Tc-MDP doses (16.5 mg) may be the optimal 99Tc-MDP treatment plan for RA.

*Conclusion:* Compared with csDMARD therapy alone, the combination therapy with 99Tc-MDP is more effective for RA patients and is associated with a lower overall incidence of adverse events, although the possibility of phlebitis was higher. However, due to the inherent limitations of the included RCTs, high-quality clinical trials are still needed to further assess the effectiveness and safety of this combination therapy.

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease characterized by synovitis, and it has been reported to affect physical function and quality of life due to joint swelling and pain and eventually leading to joint destruction and loss of function [1]. Currently, conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) are the first-line drugs for the treatment of RA, including methotrexate (MTX), leflunomide (LEF), salazosulfapyridine (SASP), hydroxychloroquine (HCQ), iguratimod (IGU), and *Tripterygium* glycosides (TG) [2]. For RA patients who have not reached their treatment target with csDMARDs, a combination therapy of biological (b) DMARDs or biosimilars and targeted synthetic (ts) DMARDs could be considered [3]. However, there are safety issues and economic affordability issues for patients using these drugs [4]. Therefore, selecting an appropriate alternative method is crucial for patients with RA.

Technetium [99Tc] methylene diphosphonate injection (99Tc-MDP, trade name: Yunke, patent No. ZL94113006.1) is a new drug independently developed in China. Its main component is a chelate compound formed by reducing technetium [99Tc] with stannous chloride and methylene diphosphonate salt [5]. According to statistics from the China Rheumatology Data Center, the utilization rate of 99Tc-MDP in Chinese RA patients was 7.7 % in 2017 [6]. 99Tc-MDP induced the proliferation and differentiation of osteoblasts (OBs) and inhibited the activation of osteoclasts (OCs), thus playing a bone-protective role [7].

Recently, a double-blind multicentre clinical study confirmed that 99Tc-MDP combined with methotrexate has a certain therapeutic effect on patients with moderate-to-severe RA, but there are limitations regarding the included population and sample size [8]. The consensus of experts in 99Tc-MDP therapy for RA also pointed out that more evidence-based medicine was needed to determine the optimal dose and course of treatment for RA [6]. A meta-analysis suggested that 99Tc-MDP combined with slow-acting anti-rheumatic drugs had superior efficacy in the treatment of RA, but this study was limited in sample size and quality of evidence [9].

In this article, a systematic review and meta-analysis were conducted to evaluate the impact of 99Tc-MDP combined with csDMARDs compared to the use of csDMARDs alone on the efficacy and joint activity of RA patients and to evaluate the changes in RA inflammatory indicators and bone density caused by 99Tc-MDP. In addition, we evaluated the impact of the incidence of adverse events (AEs) to assess safety.

## 2. Methods

### 2.1. Search strategy

PubMed, The Cochrane Central Register of Controlled Trials, Wanfang Database, China National Knowledge Network (CNKI), China Biomedical Literature Database (CBM), VIP Database, and Chinese Clinical Trial Registry were searched up to April 2023. The search terms were as follows: ("rheumatoid arthritis" OR "RA" OR "Arthritis, Rheumatoid") AND ("Technetium-99 conjugated with methylene diphosphonate" OR "99 TC-MDP" OR "99Tc-methylene diphosphonate" OR "yunke") AND ("randomized controlled trial") (as shown in Supplementary Table 1). No restriction was placed on publication language. We manually searched for the references of the identified articles to identify possible relevant studies.

## 2.2. Screening criteria

### 2.2.1. Inclusion criteria

(a) Participants: The patients included in the study were diagnosed with RA, according to the diagnostic criteria for "RA" in the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League against Rheumatism (EULAR) Criteria [10,11], and all patients had comparable and balanced baseline characteristics.

(b) Interventions and Comparison: The intervention was 99Tc-MDP and DMARD therapy in the treatment group and DMARDs without 99Tc-MDP in the control group.

(c) Outcomes: The ACR 50/70 scores were utilized as the primary effectiveness outcomes, with AE occurrence rates used to measure risks. Moreover, secondary efficacy outcomes were evaluated, including disease Activity Score 28 (DAS28) and bone mineral density (BMD) as joint function indicators and erythrocyte sedimentation rate (ESR) and interleukin-17 (IL-17) as inflammatory indicators.

(d) Study Design: Only randomized controlled trials (RCTs) with parallel designs were included, and all studies used the correct randomized methods.

### 2.2.2. Exclusion criteria

A study was manually removed from the analysis if any of the following parameters were met: (a) articles that did not meet the inclusion criteria; (b) all other types of studies, including reviews, experimental studies, case reports, retrospective analyses, and before-after studies in the same patient; (c) studies whose original research design was not rigorous and whose study data were irrelevant; (d) republished literature, and (e) articles that were not available.

### 2.2.3. Data extraction

The preliminary retrieved studies on the treatment of RA via 99Tc-MDP were screened by two reviewers (Deng and Chen) working
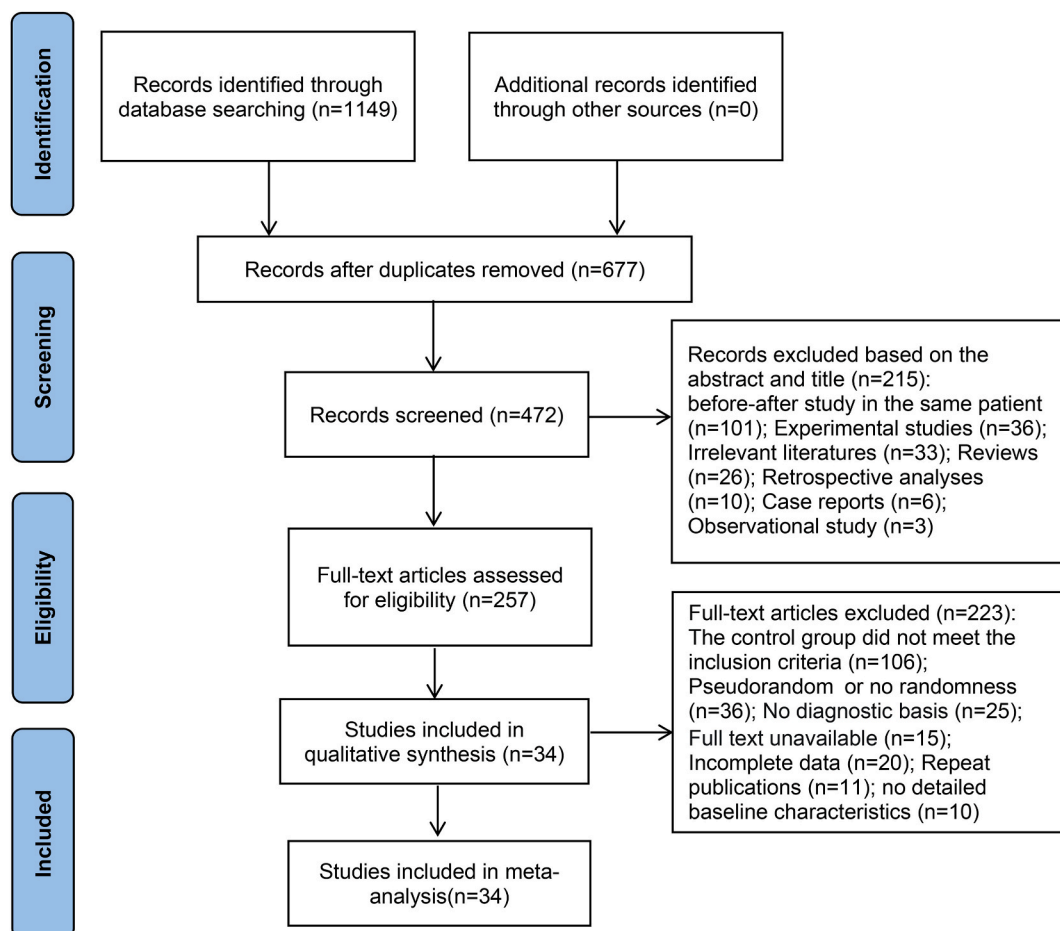


**Fig. 1.** The flow chart of the study selection process.

independently in parallel. If there was any disagreement, a third senior researcher (Shao) was consulted for evaluation. Relevant information was extracted from the selected studies, and the extracted data included the dose of 99Tc-MDP, treatment duration, relevant outcomes, and safety outcomes.

### 2.3. Quality risk assessment of the included studies

Two evaluators (Deng and Chen) used the Revised Cochrane Risk-of-Bias Tool for RCTs (RoB 2) to assess the methodological quality of each included study. For quality assessment, the risk of each form of bias was rated as "low risk", "some concern" and "high risk" according to the evaluation criteria.

The overall quality of the outcomes was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guideline development tool by two independent reviewers (Deng and Chen), and a third senior research analyst (Shao) was consulted to finalize the results.

#### 2.3.1. Statistical processing

RevMan 5.4 software and Stata 12.0 were used for the data analysis of the included studies. For the meta-analysis of the dichotomous outcomes, the risk ratio (RR) with a 95 % confidence interval (95 % CI) was used. For continuous outcomes with consistent units, the weighted mean difference (WMD) within a 95 % confidence interval was adopted, whereas a standardized mean difference (SMD) was utilized in the opposite scenario. Data heterogeneity was assessed by using the chi-square test combined with $I^2$ to determine the pooled effect model. An $I^2 < 50$ % indicated low heterogeneity, and the fixed-effects model was used; otherwise, a random-effects model was applied.

To further explore the source of heterogeneity, we successively used meta-regression and subgroup analysis to detect the influence of different factors on different efficacy outcomes, such as 99Tc-MDP dosage, csDMARD category, and treatment duration (the definitions of the above variables are shown in Supplemental Table 2). In addition, if more than 10 studies were included in a particular meta-analysis, a sensitivity analysis was conducted by removing individual studies to assess the stability of the results via Stata 12.0, and funnel plots and Egger's test were adopted to assess publication bias.

## 3. Results

### 3.1. Retrieval results and characteristics of the included studies

The initial search identified 1149 studies. As shown in Fig. 1, thirty-four studies with 2296 patients were ultimately identified based
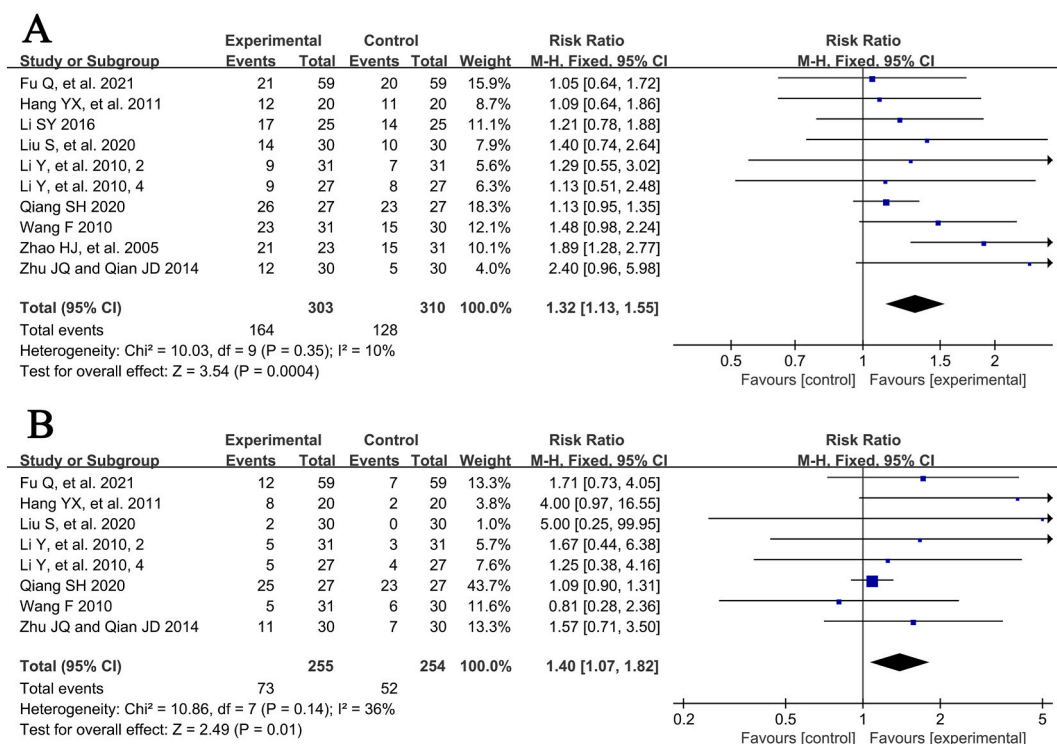


**Fig. 2.** Meta-analysis of primary outcomes and safety outcomes. (A) ACR50; (B) ACR70.

on the inclusion and exclusion criteria. Moreover, all of the studies were RCTs with two parallel arms, and the sample sizes ranged from 40 to 118 patients.

The treatment group was treated with 99Tc-MDP combined with csDMARDs, while the control group was treated with csDMARDs alone. Ten studies used MTX as the combined csDMARD [8,12–20], 12 used MTX combined with LEF [21–32], and 5 studies used MTX and SASP [33–37]. Only 1 study used MTX combined with HCQ as the combined csDMARDs [38], 1 used MTX and TG [39], and 1 used MTX and IGU [40]. Therefore, 2 studies used LEF as the csDMARD for combination treatment [41,42], 1 used TG [43], and 1 used LEF and IGU [44]. The main characteristics of the included RCTs are shown in Supplementary Table 3, while the dosage and usage of 99Tc-MDP are listed in Supplementary Table 4.

### 3.2. Evaluation of methodological quality

As displayed in Supplementary Figs. 1–2, the methodological quality assessment revealed that the risks of bias in most of the included studies was not high. All studies noted the use of randomization. Seven studies [13,15,23,24,27,30,32] used a random number table, one study [8] used SAS software for randomization, and the remaining studies did not specify the randomization method. One study [8] used a unique code number for allocation concealment, one study [40] used random envelope allocation, and the remaining studies did not disclose the allocation concealment plan.

One study [8] was considered to have overall low risk due to the use of double-blind multicentre methods. One study [22] was double-blind, while four studies [28,35,39,40] were single-blind, but none reported specific blinding procedures; thus, these five studies were considered to have potential biases in the intervention measures. Moreover, three studies [8,32,33] reported dropouts or patients lost to follow-ups, and all studies reported using full data.



**Fig. 3.** Meta-analysis of safety outcomes. (A) AEs; (B) probability of phlebitis.

## A

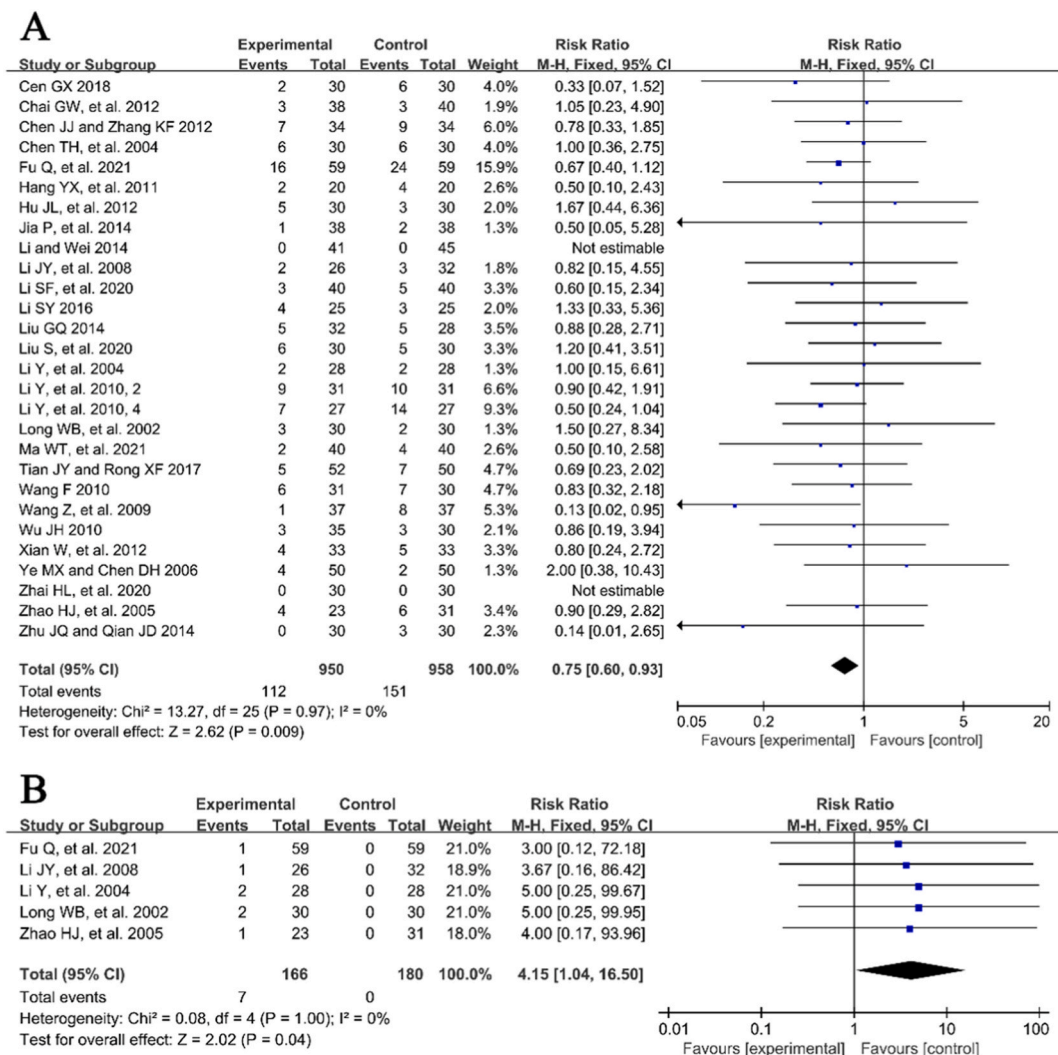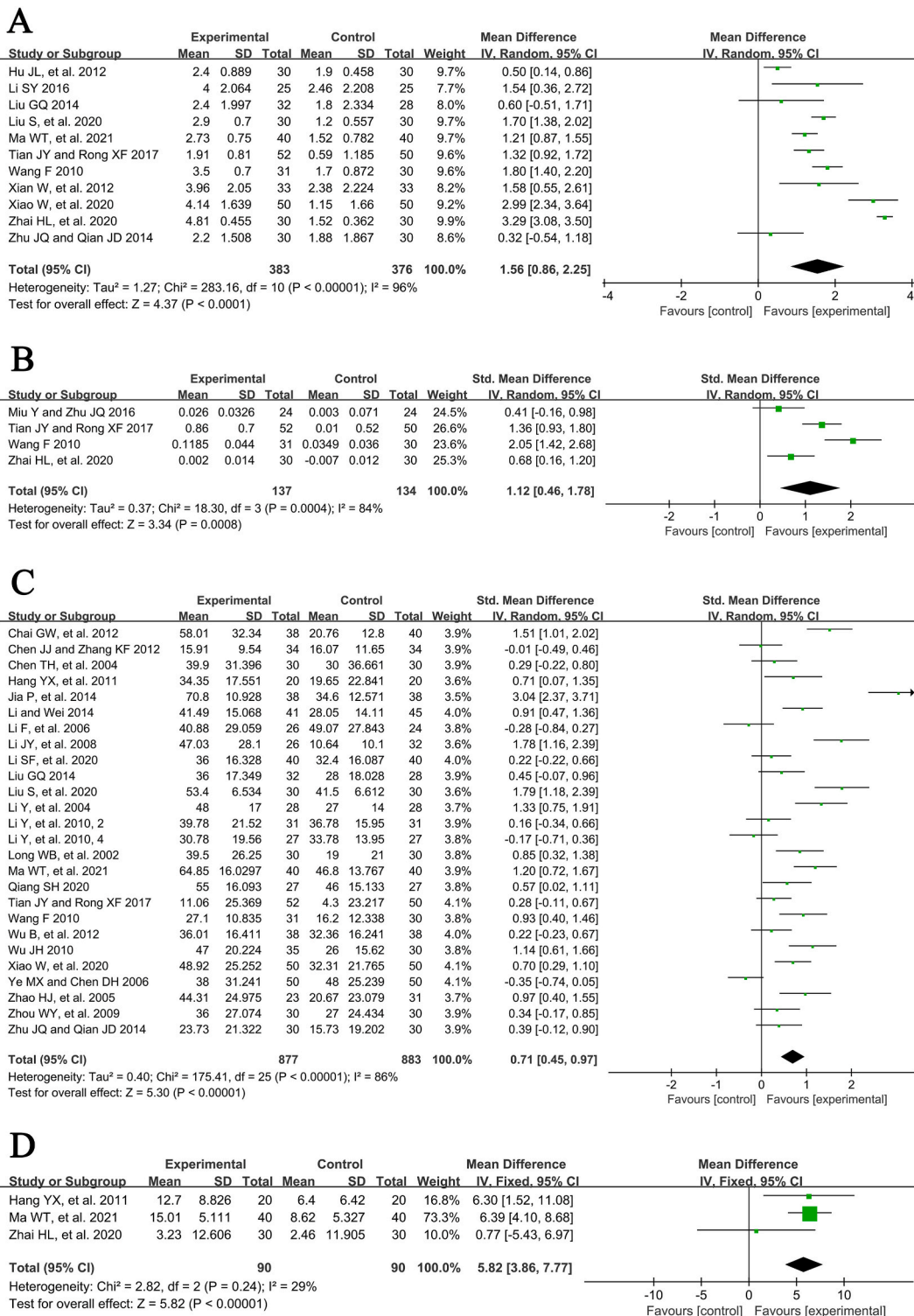| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hu JL, et al. 2012 | 2.4 | 0.889 | 30 | 1.9 | 0.458 | 30 | 9.7% | 0.50 [0.14, 0.86] |
| Li SY 2016 | 4 | 2.064 | 25 | 2.46 | 2.208 | 25 | 7.7% | 1.54 [0.36, 2.72] |
| Liu GQ 2014 | 2.4 | 1.997 | 32 | 1.8 | 2.334 | 28 | 8.0% | 0.60 [-0.51, 1.71] |
| Liu S, et al. 2020 | 2.9 | 0.7 | 30 | 1.2 | 0.557 | 30 | 9.7% | 1.70 [1.38, 2.02] |
| Ma WT, et al. 2021 | 2.73 | 0.75 | 40 | 1.52 | 0.782 | 40 | 9.7% | 1.21 [0.87, 1.55] |
| Tian JY and Rong XF 2017 | 1.91 | 0.81 | 52 | 0.59 | 1.185 | 50 | 9.6% | 1.32 [0.92, 1.72] |
| Wang F 2010 | 3.5 | 0.7 | 31 | 1.7 | 0.872 | 30 | 9.6% | 1.80 [1.40, 2.20] |
| Xian W, et al. 2012 | 3.96 | 2.05 | 33 | 2.38 | 2.224 | 33 | 8.2% | 1.58 [0.55, 2.61] |
| Xiao W, et al. 2020 | 4.14 | 1.639 | 50 | 1.15 | 1.66 | 50 | 9.2% | 2.99 [2.34, 3.64] |
| Zhai HL, et al. 2020 | 4.81 | 0.455 | 30 | 1.52 | 0.362 | 30 | 9.9% | 3.29 [3.08, 3.50] |
| Zhu JQ and Qian JD 2014 | 2.2 | 1.508 | 30 | 1.88 | 1.867 | 30 | 8.6% | 0.32 [-0.54, 1.18] |
| **Total (95% CI)** | | | 383 | | | 376 | 100.0% | 1.56 [0.86, 2.25] |

Heterogeneity: Tau² = 1.27; Chi² = 283.16, df = 10 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.37 (P < 0.0001)

## B

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Miu Y and Zhu JQ 2016 | 0.026 | 0.0326 | 24 | 0.003 | 0.071 | 24 | 24.5% | 0.41 [-0.16, 0.98] |
| Tian JY and Rong XF 2017 | 0.86 | 0.7 | 52 | 0.01 | 0.52 | 50 | 26.6% | 1.36 [0.93, 1.80] |
| Wang F 2010 | 0.1185 | 0.044 | 31 | 0.0349 | 0.036 | 30 | 23.6% | 2.05 [1.42, 2.68] |
| Zhai HL, et al. 2020 | 0.002 | 0.014 | 30 | -0.007 | 0.012 | 30 | 25.3% | 0.68 [0.16, 1.20] |
| **Total (95% CI)** | | | 137 | | | 134 | 100.0% | 1.12 [0.46, 1.78] |

Heterogeneity: Tau² = 0.37; Chi² = 18.30, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 3.34 (P = 0.0008)

## C

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chai GW, et al. 2012 | 58.01 | 32.34 | 38 | 20.76 | 12.8 | 40 | 3.9% | 1.51 [1.01, 2.02] |
| Chen JJ and Zhang KF 2012 | 15.91 | 9.54 | 34 | 16.07 | 11.65 | 34 | 3.9% | -0.01 [-0.49, 0.46] |
| Chen TH, et al. 2004 | 39.9 | 31.396 | 30 | 30 | 36.661 | 30 | 3.9% | 0.29 [-0.22, 0.80] |
| Hang YX, et al. 2011 | 34.35 | 17.551 | 20 | 19.65 | 22.841 | 20 | 3.6% | 0.71 [0.07, 1.35] |
| Jia P, et al. 2014 | 70.8 | 10.928 | 38 | 34.6 | 12.571 | 38 | 3.5% | 3.04 [2.37, 3.71] |
| Li and Wei 2014 | 41.49 | 15.068 | 41 | 28.05 | 14.11 | 45 | 3.8% | 0.91 [0.47, 1.36] |
| Li F, et al. 2006 | 40.88 | 29.059 | 26 | 49.07 | 27.843 | 24 | 3.8% | -0.28 [-0.84, 0.27] |
| Li JY, et al. 2008 | 47.03 | 28.1 | 26 | 10.64 | 10.1 | 32 | 3.6% | 1.78 [1.16, 2.39] |
| Li SF, et al. 2020 | 36 | 16.328 | 40 | 32.4 | 16.087 | 40 | 3.9% | 0.22 [-0.22, 0.66] |
| Liu GQ 2014 | 36 | 17.349 | 32 | 28 | 18.028 | 28 | 3.9% | 0.45 [-0.07, 0.96] |
| Liu S, et al. 2020 | 53.4 | 6.534 | 30 | 41.5 | 6.612 | 30 | 3.6% | 1.79 [1.18, 2.39] |
| Li Y, et al. 2004 | 48 | 17 | 28 | 27 | 14 | 28 | 3.7% | 1.33 [0.75, 1.91] |
| Li Y, et al. 2010, 2 | 39.78 | 21.52 | 31 | 36.78 | 15.95 | 31 | 3.9% | 0.16 [-0.34, 0.66] |
| Li Y, et al. 2010, 4 | 30.78 | 19.56 | 27 | 33.78 | 13.95 | 27 | 3.8% | -0.17 [-0.71, 0.36] |
| Long WB, et al. 2002 | 39.5 | 26.25 | 30 | 19 | 21 | 30 | 3.8% | 0.85 [0.32, 1.38] |
| Ma WT, et al. 2021 | 64.85 | 16.0297 | 40 | 46.8 | 13.767 | 40 | 3.9% | 1.20 [0.72, 1.67] |
| Qiang SH 2020 | 55 | 16.093 | 27 | 46 | 15.133 | 27 | 3.8% | 0.57 [0.02, 1.11] |
| Tian JY and Rong XF 2017 | 11.06 | 25.369 | 52 | 4.3 | 23.217 | 50 | 4.1% | 0.28 [-0.11, 0.67] |
| Wang F 2010 | 27.1 | 10.835 | 31 | 16.2 | 12.338 | 30 | 3.8% | 0.93 [0.40, 1.46] |
| Wu B, et al. 2012 | 36.01 | 16.411 | 38 | 32.36 | 16.241 | 38 | 4.0% | 0.22 [-0.23, 0.67] |
| Wu JH 2010 | 47 | 20.224 | 35 | 26 | 15.62 | 30 | 3.8% | 1.14 [0.61, 1.66] |
| Xiao W, et al. 2020 | 48.92 | 25.252 | 50 | 32.31 | 21.765 | 50 | 4.1% | 0.70 [0.29, 1.10] |
| Ye MX and Chen DH 2006 | 38 | 31.241 | 50 | 48 | 25.239 | 50 | 4.1% | -0.35 [-0.74, 0.05] |
| Zhao HJ, et al. 2005 | 44.31 | 24.975 | 23 | 20.67 | 23.079 | 31 | 3.7% | 0.97 [0.40, 1.55] |
| Zhou WY, et al. 2009 | 36 | 27.074 | 30 | 27 | 24.434 | 30 | 3.9% | 0.34 [-0.17, 0.85] |
| Zhu JQ and Qian JD 2014 | 23.73 | 21.322 | 30 | 15.73 | 19.202 | 30 | 3.9% | 0.39 [-0.12, 0.90] |
| **Total (95% CI)** | | | 877 | | | 883 | 100.0% | 0.71 [0.45, 0.97] |

Heterogeneity: Tau² = 0.40; Chi² = 175.41, df = 25 (P < 0.00001); I² = 86%
Test for overall effect: Z = 5.30 (P < 0.00001)

## D

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hang YX, et al. 2011 | 12.7 | 8.826 | 20 | 6.4 | 6.42 | 20 | 16.8% | 6.30 [1.52, 11.08] |
| Ma WT, et al. 2021 | 15.01 | 5.111 | 40 | 8.62 | 5.327 | 40 | 73.3% | 6.39 [4.10, 8.68] |
| Zhai HL, et al. 2020 | 3.23 | 12.606 | 30 | 2.46 | 11.905 | 30 | 10.0% | 0.77 [-5.43, 6.97] |
| **Total (95% CI)** | | | 90 | | | 90 | 100.0% | 5.82 [3.86, 7.77] |

Heterogeneity: Chi² = 2.82, df = 2 (P = 0.24); I² = 29%
Test for overall effect: Z = 5.82 (P < 0.00001)

**Fig. 4.** Meta-analysis of the secondary efficacy outcomes. (A) DAS28; (B) VAS; (C) ESR; (D) IL-17.

## 4. Outcomes

### 4.1. Primary efficacy outcomes

#### 4.1.1. ACR50

Ten RCTs [8,13,15,19,28,33,38,40,42,43] compared ACR50 scores between the csDMARD-alone group and the 99Tc-MDP combination group. There was a significant improvement in the ACR50 score in the 99Tc-MDP combination group compared with the csDMARD-alone group [RR = 1.32, 95 % CI: 1.13–1.55, P = 0.0004, Fig. 2A], with low heterogeneity ($I^2$ = 10 %, P = 0.35).

#### 4.1.2. ACR70

Eight RCTs [8,15,19,28,38,40,42,43] compared ACR70 scores between the csDMARD-alone group and the 99Tc-MDP combination group. There was a significant improvement in the ACR70 score in the 99Tc-MDP combination group compared with the csDMARD-alone group [RR = 1.40, 95 % CI: 1.07–1.82, P = 0.01, Fig. 2B], also with low heterogeneity among the eight studies ($I^2$ = 36 %, P = 0.14).

#### 4.1.3. Safety outcome

Twenty-eight RCTs [8,12–15,17–19,21–26,28,29,31–42] assessed the safety of 99Tc-MDP by comparing the AEs occurring in the 99Tc-MDP combination group with those in the group using csDMARDs alone. The overall frequency of adverse reactions in the experimental group was 112/950, while the frequency in the control group was 151/958. The incidence of adverse events in treating RA with csDMARDs combined with 99Tc-MDP is lower than when using csDMARDs alone [RR = 0.75, 95 % CI: 0.60–0.93, P = 0.009; $I^2$ = 0, P = 0.97, Fig. 3A]. The details of all reported adverse reactions in the study are provided in the additional file.

The frequently occurring AEs were gastrointestinal discomfort [RR = 0.65, 95 % CI: 0.42–1.02, P = 0.06; $I^2$ = 0, P = 0.96], leukopenia [RR = 0.63, 95 % CI: 0.34–1.17, P = 0.14; $I^2$ = 0, P = 0.93], liver dysfunction [RR = 0.86, 95 % CI: 0.50–1.49, P = 0.59; $I^2$ = 0, P = 0.80], rash [RR = 1.35, 95 % CI: 0.54–3.40, P = 0.52; $I^2$ = 0, P = 0.63], low fever [RR = 0.57, 95 % CI: 0.01–24.31, P = 0.77; $I^2$ = 68, P = 0.08], and dizziness [RR = 1.07, 95 % CI: 0.27–4.22, P = 0.92; $I^2$ = 0, P = 0.73]. The combined rate of these AEs showed no significant differences between the control and treatment groups. However, five studies [8,31,33,35,39] indicated that treatment with 99Tc-MDP could lead to phlebitis, which was not observed in the control groups, and the between-group differences were statistically significant [RR = 4.15, 95 % CI: 1.04–16.50, P = 0.04; Fig. 3B]. The majority of adverse effects were mild; in contrast, serious AEs, such as life-threatening events, were not found in the included RCTs.

## 5. Secondary efficacy outcomes

### 5.1. Joint signs

#### 5.1.1. DAS28

Eleven RCTs [12,13,18,22,26,28,29,32,38,40,44] compared the DAS28 in the csDMARD-alone group and in the 99Tc-MDP combination group. The results from the random-effects model showed that 99Tc-MDP combined with csDMARDs had a significantly decreased the DAS28 compared with csDMARDs alone [WMD = 1.56, 95 % CI: 0.86–2.25, P < 0.0001, Fig. 4A].

#### 5.1.2. BMD

Three studies [18,27,28] measured BMD in a total of 271 patients, including 137 patients in the experimental group and 134 patients in the control group. 99Tc-MDP combined with csDMARDs resulted in a significant reduction in BMD compared with csDMARDs alone [SMD = 1.12, 95 % CI: 0.46–1.78, P = 0.0008; $I^2$ = 84 %, P = 0.0004, Fig. 4B].

**Table 1**
Subgroup analyses of secondary efficacy outcomes.

| Variable | DAS28 | | | | ESR | | | |
|---|---|---|---|---|---|---|---|---|
| | Number | WMD (95 % CI) | $I^2$ | P value for heterogeneity | Number | SMD (95 % CI) | $I^2$ | P value for heterogeneity |
| The dose of 99Tc-mTDP | | | | | | | | |
| One set | 1 | 1.54 (0.36, 2.72) | – | – | 4 | 0.04 (−0.29, 0.37) | 50.8 | 0.107 |
| Two sets | 3 | 1.74 (0.50, 2.97) | 91.7 | 0.00 | 6 | 0.62 (0.13, 1.12) | 82.2 | 0.000 |
| Three sets | 5 | 1.38 (1.10, 1.66) | 41.8 | 0.14 | 9 | 1.09 (0.57, 1.62) | 89.9 | 0.000 |
| Four sets | 1 | 0.50 (0.14, 0.86) | – | – | 2 | 0.42 (−0.06, 0.89) | 37.0 | 0.208 |
| Forty sets | 1 | 3.29 (3.08, 3.50) | – | – | 3 | 1.11 (0.79, 1.42) | 0.0 | 0.471 |
| csDMARDs category | | | | | | | | |
| MTX | 2 | 1.90 (−0.84,4.63) | 99 | 0.00 | 6 | 0.35 (0.01, 0.69) | 63.0 | 0.019 |
| MTX + LEF | 6 | 1.40 (1.19,1.60) | 32.9 | 0.19 | 8 | 1.16 (0.57, 1.76) | 90.9 | 0.000 |
| MTX + SASP | 1 | 0.32 (−0.54, 1.18) | – | – | 5 | 0.67 (−0.01, 1.35) | 88.7 | 0.000 |
| Treatment duration | | | | | | | | |
| <12 weeks | 2 | 2.13 (0.50, 3.77) | 94.6 | 0.00 | 9 | 0.65 (0.22, 1.08) | 86.2 | 0.000 |
| 12~24 weeks | 7 | 1.31 (0.14, 2.47) | 97.6 | 0.00 | 14 | 0.70 (0.31, 1.09) | 87.3 | 0.000 |
| 24+ weeks | 2 | 1.74 (1.49, 1.99) | 0 | 0.70 | 3 | 1.02 (0.21, 1.83) | 84.8 | 0.001 |

### 5.2. Inflammatory indicators

#### 5.2.1. ESR

Twenty-six RCTs [14,15,19–22,24–26,28,30–44] compared the ESR in the csDMARD-only and 99Tc-MDP combination groups, consisting of 883 patients and 877 patients, respectively. 99Tc-MDP combined with csDMARDs resulted in a significant reduction in the ESR compared with csDMARDs alone [SMD = 0.71, 95 % CI: 0.45–0.97, P < 0.00001; I$^2$ = 86 %, P < 0.00001, Fig. 4C].

#### 5.2.2. IL-17

Three RCTs [18,19,22] compared IL-17 in the csDMARD alone group and the 99Tc-MDP combination group. 99Tc-MDP combined with csDMARDs treatment was associated with a significant reduction in IL-17 compared with csDMARDs alone [WMD = 5.82, 95 % CI: 3.86–7.77, P < 0.00001; Fig. 4D], with low heterogeneity between the two studies (I$^2$ = 29 %, P = 0.244).

### 5.3. Subgroup analyses and meta-regression

For the substantial heterogeneity in DAS28 (I$^2$ = 96 %, P < 0.00001), we further explored the potential sources through subgroup analysis (Table 1). The results showed that the dose of 99Tc-MDP [only used three sets of 99Tc-MDP [22,26,29] (WMD = 1.38, 95 % CI: 1.10 to 1.66, P < 0.00001)], csDMARD category [only combined with MTX and LEF [13,22,26,28,29,32] (WMD = 1.40, 95 % CI: 1.19 to 1.60, P < 0.00001)], and treatment duration [only treat with 24 weeks [28,40] (WMD = 1.74, 95 % CI: 1.49 to 1.99, P < 0.00001)] may significantly influence heterogeneity. Through subgroup analysis, we found that the dose of 99Tc-MDP [only used forty sets of 99Tc-MDP [35,37,39] (SMD = 1.11, 95 % CI: 0.79 to 1.42, P < 0.00001)] was the main source of heterogeneity in the ESR (Table 1).

Furthermore, after conducting a meta-regression analysis on the DAS28 and ESR, the results showed that the dose of 99Tc-MDP, the csDMARD category, and the treatment duration had a minor impact on the high heterogeneity (Table 2). However, due to the significant impact of the aforementioned covariates on the treatment, there may be a risk of overfitting [45].

### 5.4. Publication bias and sensitivity analysis

Funnel plots of studies included in the ACR50 and AE analyses displayed good symmetry (Fig. 5A and B), but the DAS28 and ESR were not asymmetrical. The application of Peter's test to the funnel plots showed low publication bias for ACR50 and AEs, also low in DAS28 for Egger's test (Table 3). However, there was a publication bias in the results of ESR (Table 3). After data from virtual studies were incorporated using the trim-and-fill method, the results for the ESR (Q = 314.34, P < 0.0001) were also robust.

A sensitivity analysis was performed by sequentially excluding one study at a time to observe the combined effect size, and the results showed that the aforementioned outcome indicators were relatively stable (Fig. 6A–D).

### 5.5. GRADE assessment

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) standards were used to evaluate the quality of all of the outcome indicators (Supplemental Table 5). Most of the included studies were of "some concern", but had negligible impact on the results and therefore were not downgraded. The inconsistency of some indicators was considered serious, as the combined results of the meta-analysis combined had an I$^2$ greater than 50. This study's inclusion criteria, interventions, control measures, and expected outcomes in the study were consistent; thus, all indirectness from the studies was categorized as "not serious". One study had a 95 % CI that was too wide, resulting in the imprecision of the ACR70 score being classified as "serious". Overall publication bias was low in all studies; therefore, it is believed that the other considerations are not significant.

## 6. Discussion

This study systematically reviewed 34 RCTs on the clinical efficacy of 99Tc-MDP combined with csDMARDs in treating RA, and all included studies utilized csDMARDs. The ACR50/70 score is a composite index of RA disease remission based on ACR criteria with improvement degrees exceeding 50 % or 70 % [46]. BMD is an examination of bone strength that helps observe RA-related bone loss [47]. The results showed that the 99Tc-MDP combination therapy was more effective than csDMARDs alone in improving symptom relief and joint function. Some studies have employed valuable evaluation indicators, but unfortunately, meta-analysis cannot be

**Table 2**
The meta-regression model of efficacy outcomes.

| DAS28 | coefficient | SE (95%CI) | P |
|---|---|---|---|
| The dose of 99Tc-mTDP | −0.1893 | 0.29 (−0.47, 0.85) | 0.533 |
| csDMARDs category | 0.1770 | 0.26 (−0.41, 0.76) | 0.509 |
| Treatment duration | −0.1808 | 0.49 (−1.30, 0.94) | 0.723 |
| ESR | coefficient | SE (95%CI) | P |
| The dose of 99Tc-mTDP | 0.0580 | 0.07 (−0.10, 0.21) | 0.445 |
| csDMARDs category | −0.0271 | 0.06 (−0.16, 0.12) | 0.679 |
| Treatment duration | 0.1407 | 0.23 (−0.34, 0.62) | 0.553 |

**A**

**B**
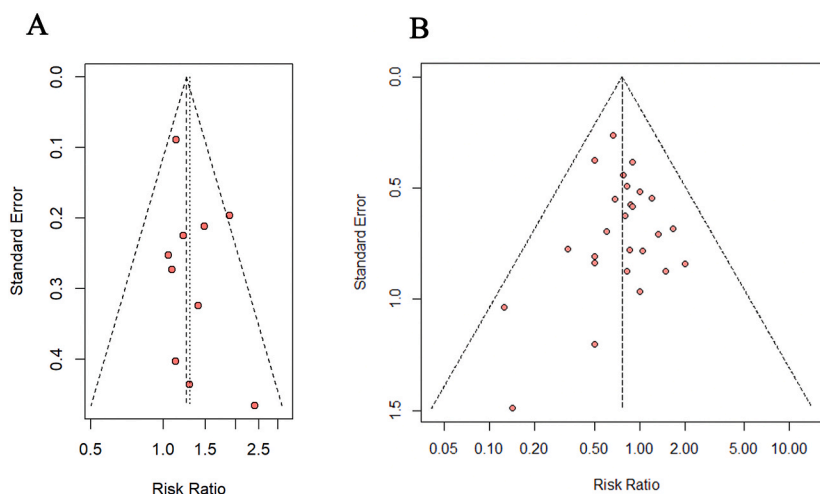


**Fig. 5.** Funnel plot of ACR50 and AEs. (A) ACR50; (B) AEs.

**Table 3**
Publication bias of outcomes.

| Variable | t | P value |
|---|---|---|
| Peter's test of funnel plots | | |
| ACR50 | 0.69 | 0.5125 |
| AEs | 0.33 | 0.7412 |
| Egger' test of funnel plots | | |
| DAS28 | −1.57 | 0.1503 |
| ESR | 3.36 | 0.0026 |

carried out. For example, Fu et al. [8] evaluated changes in bone erosion and joint space narrowing in patients using X-rays of the hands and feet. Zhai, H.L. et al. [18] evaluated systemic bone resorption in patients using type I collagen carboxy terminal peptide β special sequence (β-CTX) levels, which effectively reflects the systemic bone resorption.

99Tc-MDP has a certain protective effect on the skeleton in RA, which may be related to the MDP component it contains [48]. The P–C–P structure of MDP contributes to the localization of 99Tc-MDP, enabling its sustained action on bone joints [49]. 99Tc-MDP induces the differentiation of osteoblasts by significantly increasing the expression of bone morphogenetic protein-2 (BMP-2) and alkaline phosphatase (ALP) in vitro [7]. In addition, 99Tc-MDP regulates the osteoprotegerin/receptor activator of nuclear factor-kappaB and its ligand (OPG/RANK/RANKL) system, and inhibit OCs mediated bone resorption [50,51]. MDP is a new type of bisphosphonate, and bisphosphonates are considered the most classic drugs for combating osteoporosis [52]. However, 99Tc-MDP does not exhibit severe side effects, such as atypical fractures and jaw necrosis, as seen with bisphosphonates [53,54]. A multi-centre non-randomised trial showed that 99Tc-MDP improves lumbar spine BMD and quality of life in postmenopausal differentiated thyroid cancer patients under TSH suppression [54].

The combination of MDP and 99Tc is essential. 99Tc has a strong anti-inflammatory ability and has a direct inhibitory effect on immune regulatory factors. 99Tc-MDP significantly reduced IL-1, IL-6, IL-1β and tumour necrosis factor (TNF)-α in vitro and in vivo experiment [55–57], and downregulated high levels of rheumatoid factors [58]. 99Tc-MDP was shown to downregulate inflammatory cytokines such as interferon (IFN)-γ, IL-35, and soluble TNF receptor 1 (sTNF-R1) in ankylosing spondylitis patients [59]. In addition, 99Tc-MDP directly regulated the number of immune cells, such as Regulatory T cells (Tregs), which are an important component of RA immune tolerance [60]. Su et al. [61] found that 99Tc-MDP could regulate the expression levels of the anti-inflammatory serum transforming growth factor (TGF)-β and proinflammatory cytokines IL-6 and TNF-α in patients with active RA, possibly further contributing to a favorable cytokine microenvironment for peripheral blood γδT cells and CD4$^+$CD25+Foxp3+ Treg cells, which have an amelioraing effect on disease activity.

IL-17 is a potent proinflammatory cytokine that strongly promotes autoimmune diseases [62]. IL-17 mediates the differentiation of OCs by inducing the secretion of TNF-α, IL-1, and IL-6, ultimately leading to an increase in the expression of RANKL in fibroblasts [63]. This meta-analysis outcome showed that a reduction in IL-17 was observed at 99Tc-MDP combined with csDMARDs compared with csDMARDs alone. 99Tc-MDP reduced the levels of IL-17 in the serum and synovial fluid of collagen-induced arthritis (CIA, an animal model of RA) rats, and downregulated the expression of IL-17 and RANKL in the synovial tissue [64]. IL-17 is an important therapeutic target for RA treatment [65], and it may also serve as a mechanistic biomarker for the treatment of RA with 99Tc-MDP. The secretion of IL-17 is dependent on T helper (Th) 17, and the differentiation of Th17 is regulated by the inflammatory factors IL-6, IL-1β, and TGF-β [66]. Therefore, the mechanism of 99Tc-MDP on IL-17 may be related to its regulatory effects on these specific inflammatory factors,
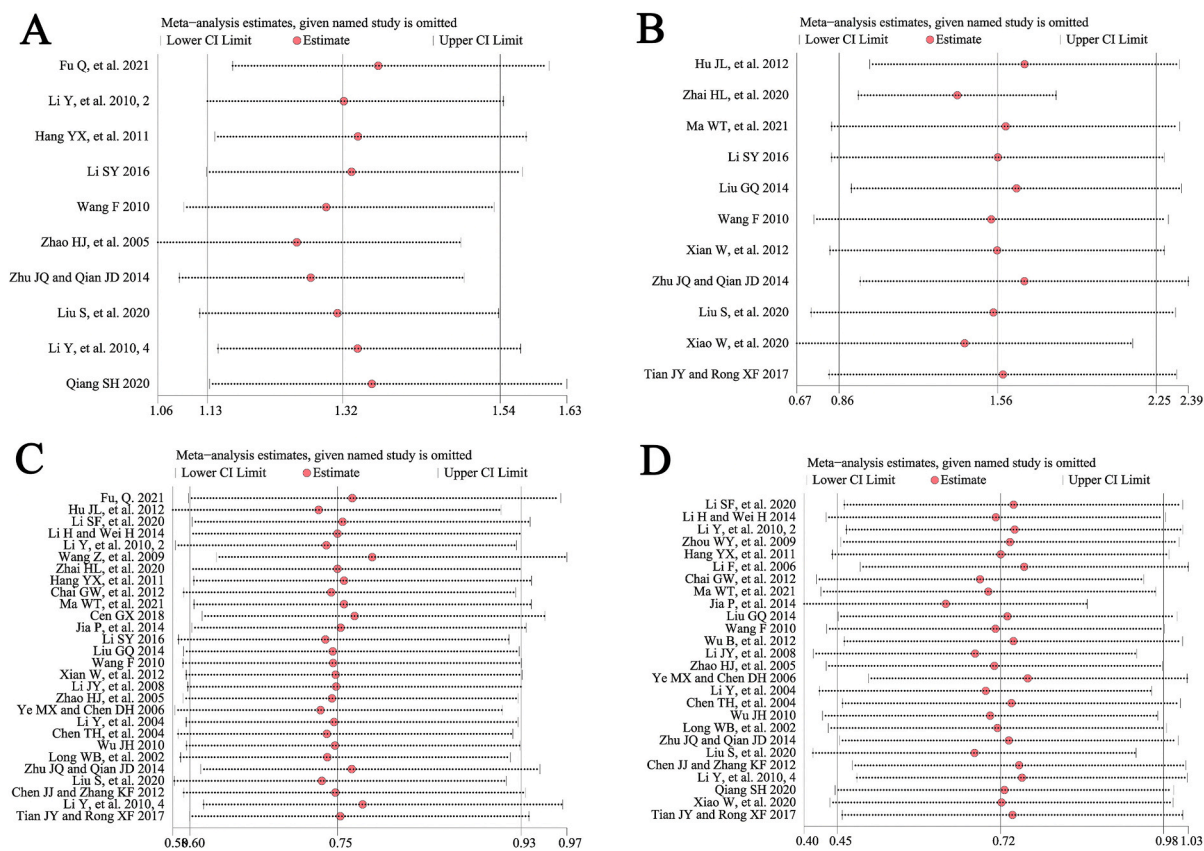
**Fig. 6.** Sensitivity analysis results. (A) ACR50; (B) AEs; (C) DAS28; (D) ESR.

which in turn affect Th17 cell-related responses.

Our results suggest that the incidence of adverse events in treating RA with csDMARDs combined with 99Tc-MDP is lower than when using csDMARDs alone. However, we are unable to deny that this result may be influenced by factors such as sample size, the number of adverse reactions, and the duration of the study. Therefore, further large-scale studies with long-term follow-up are needed to confirm this result. The frequently occurring AEs were gastrointestinal discomfort, leukopenia, liver dysfunction, rash, low fever, and dizziness. The rate of these AEs showed no significant differences between the control and treatment groups. However, the possibility of phlebitis with 99Tc-MDP is high, and this phlebitis may be related to the duration of infusion. Weakly acidic liquids continuously impact the vascular wall, and the longer the duration, the more likely it is that venous inflammation could occur. Most patients experience mild symptoms, which may be relieved through symptomatic treatment. Overall, the safety of combining 99Tc-MDP with csDMARDs for the treatment of RA is considered acceptable.

The dosage form of 99Tc-MDP is as follows: each set contains 5.5 mg (bottle A and bottle B); bottle A is a colourless and clear liquid with 5 ml per bottle, containing 0.05 μg of 99Tc; and bottle B is a white lyophilized powder that is readily soluble in water, and 5 mg of MDP and 0.5 mg of stannous chloride are found in each bottle [67]. While the 99Tc-MDP dose consisted of three sets (16.5 mg), the improvement of the DAS28 was better than that of the control group. When the dose of 99Tc-MDP consisted of 40 sets, the improvement in the ESR was better than that of the control group. The DAS28 has been developed to measure disease activity in RA remission [68], and thus, the three sets of 99Tc-MDP may be the most effective for treatment. When 99Tc-MDP was used in combination with MTX and LEF, the improvements in the DAS28 were greater than those of the MTX and LEF groups. Moreover, during the 24-week treatment course, the 99Tc-MDP combination group showed significantly better improvement in the DAS28 than the csDMARD-only group.

There are limitations of this meta-analysis. For example, the included studies have certain defects in the aspects of randomization, allocation concealment, and blinding. Furthermore, the control group DMARDs were all csDMARDs; therefore, further observations are needed to evaluate the efficacy of combining 99Tc-MDP with biosimilar bDMARDs and tsDMARDs. In addition, RA is a chronic disease that requires long-term follow-up, and its manifestations can differ among different ethnicities [69]; hence, it is necessary to conduct multicentre, large-sample, high-quality RCTs in multiple countries and extend the follow-up period to further evaluate the long-term efficacy of 99Tc-MDP for treating RA.

## 7. Conclusions

The combined use of 99Tc-MDP and csDMARDs in the treatment of RA was shown to be effective in improving joint function, inflammation level, and bone protection and is relatively safe; thus, it may be used as an effective alternative when routine csDMARD treatment becomes ineffective. However, due to the inherent limitations of the included RCTs, high-quality clinical trials are still needed to further assess the effectiveness and safety of this combination therapy.

## Protocol and registration

This systematic review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and elaboration for standardized reporting. The protocol of this study was registered in PROS-PERO with the registration number CRD 42022355700. In the initial plan, only RCTs evaluating combination therapy with 99Tc-MDP and MTX for the treatment of RA were included. However, during the research process, we found a limited number of studies investigating the combination therapy of 99Tc-MDP and MTX. To improve the feasibility of our meta-analysis, we expanded the scope of the search and conducted a subgroup analysis based on different types of csDMARDs.

## Data availability statement

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

## CRediT authorship contribution statement

**Guoqian Deng:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Xinyi Chen:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Le Shao:** Conceptualization, Formal analysis, Funding acquisition, Resources, Software, Supervision, Validation, Writing – review & editing. **Qibiao Wu:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Visualization, Writing – review & editing. **Shenzhi Wang:** Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing.

## 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.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21691.

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