Chinese traditional medicine (GuiZhi-ShaoYao-ZhiMu decoction) as an add-on medication to methotrexate for rheumatoid arthritis: a meta-analysis of randomized clinical trials

Chenxi Feng*, Rongrong Chen*, Keer Wang*, Chengping Wen and Zhenghao Xu

Abstract

Background: GuiZhi-ShaoYao-ZhiMu decoction (GSZD), a traditional Chinese herbal medication, has been frequently used as an add-on medication to methotrexate (MTX) for rheumatoid arthritis (RA) treatment in China. This meta-analysis evaluated the efficacy and safety of adding GSZD to MTX for RA treatment.

Methods: We performed a systematic search of *PubMed, Web of Science, EMBASE*, and the *Cochrane Library* (all databases) for English-language studies and *WanFang, VIP*, and *CNKI* for Chinese-language studies up to 28 July 2020. Data from selected studies, mainly the response rates and rate of adverse events (AEs), were extracted independently by two authors, and a random-effects model (Mantel–Haenszel method) was used for the meta-analysis.

Results: A total of 14 randomized controlled trials and 1224 patients were included (623 patients in the GSZD + MTX group and 601 patients in the MTX group). For efficacy, the meta-analysis found that combining GSZD with MTX increased the effective rate [relative risk (RR) = 1.24, 95% confidence interval (CI): 1.18–1.30, based on 1069 patients], defined as >30% efficacy, American College of Rheumatology 20, or a decrease of disease activity score 28 >0.6. Adding GSZD reduced the swollen and tender joint counts, the duration of morning stiffness, the levels of C-reactive protein and rheumatoid factor, and erythrocyte sedimentation rate. The adjuvant therapeutic effect of GSZD was independent of the dose of MTX or the combined utilization of other drugs in both groups. For safety, adding GSZD was associated with a lower rate of total AEs (RR = 0.46, 95% CI: 0.26–0.83, based on 615 patients) and gastrointestinal tract AEs (RR = 0.46, 95% CI: 0.24–0.88, based on 537 patients).

Conclusion: Combining GSZD with MTX may be a more efficacious and safer strategy for treating RA compared with MTX alone. Further large studies are warranted to investigate the long-term efficacy and safety of adding GSZD to MTX for RA treatment.

Keywords: meta-analysis, methotrexate, rheumatoid arthritis, traditional Chinese medication

Correspondence to:
Zhenghao Xu
School of Basic Medical Science, Zhejiang Chinese Medical University, Binwen Road 548, Hangzhou, Zhejiang, 310053, China
xuzhenghao@zcmu.edu.cn

Chenxi Feng
The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Rongrong Chen
Keer Wang
Chengping Wen
School of Basic Medical Science, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

*The first three authors contributed equally.

Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease characterized by systemic and synovial inflammation.[1] RA affects 0.5–1.0% of the general population, especially women and the elderly.[2] If not well controlled, RA may result in permanent joint damage and disability. The use of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and biologic agents may attenuate symptoms and prevent joint deformation.[3] However, current pharmacologic

therapies do not produce an adequate response in many patients and may also have long-term side effects.[1] For example, only 30% of patients have low disease activity with the DMARD methotrexate (MTX) alone, which is an anchor drug for initial RA treatment but may also lead to many adverse effects.[4,5] Combining MTX with other drugs, such as NSAIDs, steroids, or other DMARDs, could be used when RA cannot be well-controlled by MTX. However, the use of NSAIDs may be restricted because of the risk of gastrointestinal and cardiovascular toxicity during treatment;[6,7] steroids and other DMARDs may also lead to side effects;[8] and biologics may be too expensive.[9] More importantly, using these combination therapies still does not produce an adequate response in many patients.[10] Thus, new pharmacological strategies for RA treatment are still warranted.

GuiZhi-ShaoYao-ZhiMu decoction (GSZD), a traditional Chinese medicine (TCM) herbal formula, has been used for RA treatment in China since the Han Dynasty. GSZD is composed of *Cinnamomum cassia* (L.) J.Presl (Gui Zhi, 12 g), *Paeonia albiflora* Pall. (Shao Yao, 9 g), *Ephedra sinica* Stapf. (Ma Huang, 12 g), *Anemarrhena asphodeloides* Bunge (Zhi Mu, 12 g), *Radix Glycyrrhizae Preparata* (Zhi Gan Cao, 6 g), *Saposhnikovia divaricata* (Turcz.) Schischk. (Fang Feng, 12 g), *Aconitum carmichaeli* var. *carmichaeli* (Fu Zi, 10 g), *Zingiber officinale* Roscoe (Sheng Jiang, 15 g), and *Atractylodes macrocephala* Koidz. (Bai Zhu, 15 g).[11] A previous general meta-analysis showed that GSZD may have equal or superior effectiveness and safety for treating RA compared with DMARDs.[12] Recently, several randomized controlled trials (RCTs) indicated that combining GSZD with MTX may achieve better effectiveness than MTX in patients with RA. However, the evidence for GSZD as an add-on medication to MTX in RA remains inadequate. Therefore, we conducted a meta-analysis to assess the efficacy and safety of combining GSZD with MTX for use in patients with RA.

Methods
Our study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13]

Protocol and registration
Our protocol has been submitted to PROSPERO, registered on 28 April 2020, and updated on 27 October 2020 (Protocol registration number: CRD42020151593). Ethical approval was not required as the current study was based on published data.

Data sources and literature search
We performed a systematic search of *PubMed, Web of Science, EMBASE*, and the *Cochrane Library* (all the databases in the Cochrane library) for English-language studies up to 28 July 2020 without limiting the beginning date. We also performed a systematic search of *WanFang DATA* (http://www.wanfangdata.com.cn/), *VIP* (http://www.cqvip.com/), and the *Chinese National Knowledge Infrastructure* (*CNKI*) (http://www.cnki.net/) for Chinese-language studies. Details of our search strategy are shown in Supplemental material Tables 1–4 online for English-language studies and Supplemental Table 5 for Chinese-language studies. Additional studies were identified from published reviews and the reference lists of selected papers.

Eligibility criteria
Inclusion criteria: (1) the study must be a RCT; (2) patients must be diagnosed as having RA according to American College of Rheumatology (ACR) diagnostic criteria; (3) patients must have received intervention treatment with GSZD and MTX; (4) the study must include an ACR 20 or ACR 50 response rate, modified response rate based on ACR response criteria (such as 30% efficacy),[14–16] or a decrease of disease activity score 28 (ΔDAS28)[17] as the main outcome indicator.

Exclusion criteria: (1) the dose of MTX does not meet the ACR guidelines (such as 5 mg/day or 10 mg/day); (2) except for concurrent use of drugs, no other therapeutic factors, such as acupuncture, were used.

Study selection
Study selection was conducted based on the PRISMA flow diagram. The results of the literature search were imported into the software Endnote X9. Two reviewers (C.F. and R.C.) independently assessed the potentially eligible studies for inclusion. First, the titles and abstracts were screened to exclude the duplicated and other irrelevant studies according to the inclusion/exclusion criteria. Then, we re-screened the

full-text of each potentially relevant article that was not excluded. Any discordances were resolved by a third investigator (Z. X.).

Data collection

Two reviewers (C.F. and R.C.) independently reviewed studies to extract potentially eligible studies and data. We mainly collected the response rates, RA related clinical symptoms and laboratory indexes, and adverse events (AEs) or side effects. When the results were inconsistent, the third investigator was responsible for reconciling (Z.X.).

Risk-of-bias assessments

To assess the risk of bias of included trials, we used the Cochrane risk of bias tool. Six domains of bias were assessed: (1) selection bias (randomization and allocation concealment); (2) performance bias (blinding of participants and investigators); (3) detection bias (blinding of outcome adjudicators); (4) attrition bias (differential loss to follow-up); (5) reporting bias (selective outcome reporting); and (6) other sources of bias. The risk of bias assessment was conducted by two independent reviewers, and discrepancies were resolved by the third investigator (Z.X.).

Statistical analysis

All analyses were performed using Review Manager, version 5.3 (Nordic Cochrane Centre). Standardized mean differences were estimated with 95% confidence intervals (CIs) for continuous outcomes, including tender joint counts (TJCs), swollen joint counts (SJCs), duration of morning stiffness (DMS), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). Relative risks (RRs) were estimated for dichotomous outcomes, including the response rates and rate of AEs. Statistical heterogeneity was assessed by Cochran's Q statistic and the I^2 statistic. As the studies included in the analysis are not functionally identical and we wanted to compute the common effect size to generalize to other populations, a random-effects model (Mantel–Haenszel method) was employed for the meta-analysis. Subgroup meta-analyses were based on the dose of MTX and the additional drugs concurrently used in both groups. Begg's funnel plots were generated for assessing

publication bias when possible. In addition, to evaluate the strength and stability of the meta-analysis, sensitivity analysis was conducted by omitting the individual studies one by one. The sensitivity analysis was carried out for response rates, clinical symptoms and laboratory indexes, and the rate of AEs. A two-tailed $p < 0.05$ was considered statistically significant.

Results

RCT selection

The study selection process is depicted in Figure 1. A total of 419 articles were extracted from the literature search for the initial assessment. In total, 212 articles were removed after reading the abstracts and 193 articles were removed after full-text assessment. Of note, three RCTs were excluded because they used GSZD monotherapy.[18–20] Two RCTs were removed because of the excessive dose of MTX (5 mg/day for 12 weeks in Liu and Shi[21] and 10 mg/day for 8 weeks in Liu *et al.*[22]). Finally, a total of 14 articles were included in the current meta-analysis.

Characteristics and quality of the studies

All 14 RCTs used GSZD in the form of water decoction.[23–36] The details of the included studies are summarized in Table 1. Of note, four RCTs (Zhou *et al.*,[23] Yuan,[24] Zhang *et al.*,[25] and Xi and Zhang[26]) did not additionally use any other drugs in both groups, For RCTs (Xiao,[27] Ji,[28] Cui,[29] Li *et al.*[30]) used NSAIDs in both groups, two RCTs (Yu and Zhang,[31] Li *et al.*[32]) used other DMARD (sulfasalazine) in both groups, three RCTs (Huang *et al.*,[33] Liang and Yang,[34] Dong[35]) used other DMARDs (sulfasalazine or leflunomide) plus NSAIDs (celecoxib or diclofenac sodium) in both groups and the other one RCT (Wu[36]) used other DMARD (sulfasalazine) and glucocorticoid (methylprednisolone) in both groups.

The risk of bias assessment for the included studies is shown in Figure 2. A random sequence was adequately generated in 11 RCTs (78.6%), and the risk of selection bias was judged to be low. The risk of bias for allocation concealment was unclear because most of the studies did not report clear information about the methods used to conceal the allocation. Performance biases were judged to be high or unclear because blinding of
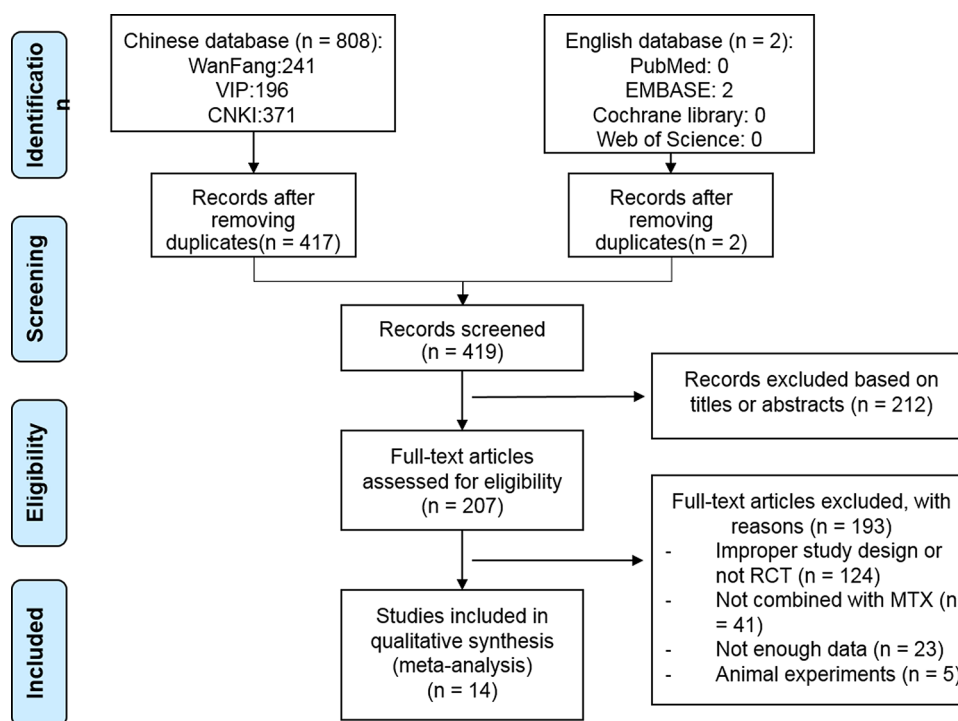
Figure 1. Flow diagram of the study selection process.
MTX, methotrexate; RCT, randomized controlled trial.
ACR, American College of Rheumatology; CI, confidence interval; DAS28, Disease activity score 28; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; MTX, methotrexate; M–H, Mantel–Haenszel.

participants and personnel was not performed in any RCTs due to the obvious difference between the GSZD and MTX. Moreover, blinding of outcome assessor was unclear in each RCT. The incomplete outcome data element had a low risk of bias for 13 RCTs (92.9%). There was also a low risk of selective outcome reporting for 12 RCTs (85.7%). Other sources of bias were unclear.

Also, the funnel plots for risk ratio of efficacy rate is asymmetric, which indicates that some publication bias for the RCTs, reporting biases or other interference factors may exist, such as poor methodological quality.[37]

Efficacy

Among the included trials,[23–36] (1) 13 RCTs (total of 1069 patients) reported the effective rate,[23–25,27–36] defined as >30% efficacy, ACR20, or ΔDAS28 >0.6; (2) 11 RCTs (total of 1022 patients) reported partial remission rate,[23–26,28,30–34,36] defined as >50% efficacy, ACR50 or ACR70,

or ΔDAS28 >1.2; (3) five RCTs (total of 471 patients) reported the remission rate,[23,26,29,31,35] defined as >85% efficacy or ACR90. The meta-analysis indicated that adding GSZD was associated with a higher effective rate (RR = 1.24, 95% CI: 1.18–1.30; Figure 3), partial remission rate (RR = 1.47, 95% CI: 1.24–1.75; Figure 3) and remission rate (RR = 1.51, 95% CI: 1.16–1.95; Figure 3). Of note, the results are similar when excluding each one of these included studies (Supplemental Table 6). The heterogeneity for the effective rate and remission rate is low (I^2 <50%), while it is high for partial remission rate (I^2 = 54%).

In addition, subgroup meta-analysis based on the dose of MTX showed that MTX 7.5 mg/week plus GSZD had a similar effect as MTX 10 mg/week plus GSZD (Supplemental Figure 1). Subgroup meta-analysis according to the additional drugs concurrently used in both groups, including no other drugs, NSAIDs, other DMARDs, and glucocorticoid, showed that the effective rate of the MTX plus GSZD group was still higher than that

Table 1. Characteristics of the randomized clinical trials of GuiZhi-ShaoYao-ZhiMu decoction for rheumatoid arthritis: GSZD+MTX *versus* MTX.

Study	Number of patients[a]	Female %	Age (years, mean ± SD or range)	RA duration (years)	MTX (mg/week)	GSZD (dose/day)	Other drugs	Study duration (weeks)	Effective rate[b]	Efficacy	Clinical manifestations, laboratory test indicators	AEs
Zhou et al.[23]	A: 36 B: 33	A: 63.89 B: 66.67	A: 21–66 B: 23–64	A: 2.46 B: 2.52	7.5	+1	None	6	A: 88.89% B: 63.64%	30% efficacy, 60% efficacy, 90% efficacy	No	No
Yuan[24]	A: 44 B: 44	A: 40.91 B: 36.36	A: 20–68 B: 20–70	NR	7.5	+1	None	8	A: 95.45% B: 75.00%	ΔDAS28 > 0.6, ΔDAS28 > 1.2	No	Yes
Zhang et al.[25]	A: 45 B: 45	A: 51.11 B: 53.33	A: 37–79 B: 38–78	A: 6.11 B: 5.96	10	+1	None	11	A: 91.11% B: 73.33%	35% efficacy, 75% efficacy	CRP, ESR, RF, DMS	No
Xi and Zhang[26]	A: 80 B: 75	A: 37.5 B: 44.00	A: 44–85 B: 45–85	A: 12.4 B: 12.2	15	+1	None	24	A: 96.25% B: 84.00%	60% efficacy, 90% efficacy	DMS, SJC, TJC	Yes
Xiao[27]	A: 18 B: 18	A: 55.56 B: 61.11	A: 41 ± 5.1 B: 42 ± 4.6	A: 4.5 B: 4.6	7.5	+1	Dic	12	A: 94.44% B: 66.67%	ACR20, ACR30	ESR	No
Ji[28]	A: 83 B: 83	A: 44.58 B: 38.55	A: 37–66 B: 36–68	A: 3.8 B: 3.6	7.5	+1	IBU	8	A: 96.38% B: 80.72%	ACR20, ACR50	CRP, ESR, RF	No
Cui[29]	A: 53 B: 53	A: 60.38 B: 64.15	A: 36–78 B: 35–78	A: 3.61 B: 3.61	10	+1	IBU	8	A: 94.34% B: 81.13%	35% efficacy, 85% efficacy	CRP, ESR, RF	No
Li et al.[30]	A: 40 B: 39	A: 78.05 B: 73.17	A: 45–70 B: 43–69	A: 6.64 B: 6.18	7.5	+1	CLX	12	A: 95.00% B: 61.54%	30% efficacy, 70% efficacy	CRP, ESR, RF	No

(Continued)

Table 1. (Continued)

Study	Number of patients[a]	Female %	Age (years, mean ± SD or range)	RA duration (years)	MTX (mg/week)	GSZD (dose/day)	Other drugs	Study duration (weeks)	Effective rate[b]	Efficacy	Clinical manifestations, laboratory test indicators	AEs
Yu and Zhang[31]	A: 40 B: 41	A: 67.50 B: 60.98	A: 18–65 B: 20–69	A: 6.8 B: 5.4	10	+1	SSZ	12	A: 90.00% B: 70.73%	ACR20, ACR50, ACR90,	CRP, ESR, DMS, SJC, TJC	Yes
Li et al.[32]	A: 45 B: 45	A: 48.89 B: 46.67	A: 21–75 B: 21–76	NR	7.5	+1	SSZ	24	A: 95.56% B: 77.78%	ΔDAS28 > 0.6, ΔDAS28 > 1.2	CRP, ESR, DMS	Yes
Huang et al.[33]	A: 36 B: 27	A: 77.78 B: 85.19	A: 21–65 B: 22–64	A: 2.75 B: 2.65	10	+1	SSZ, CLX	12	A: 91.67% B: 66.67%	ACR20, ACR50, ACR80	CRP, ESR, RF, DMS, SJC,	Yes
Liang and Yang[34]	A: 40 B: 38	A: 55.00 B: 57.89	A: 39–79 B: 40–80	A: 2.3 B: 2.1	10	+1	LEF, Dic	8	A: 95.00% B: 78.95%	30% efficacy, 70% efficacy, 95% efficacy	CRP, ESR, RF, DMS, SJC	Yes
Dong[35]	A: 30 B: 30	A: 43.33 B: 46.67	A: 52–79 B: 35–78	A: 6.10 B: 5.93	10	+1	SSZ, CLX	12	A: 96.67% B: 80.00%	35% efficacy, 95% efficacy	CRP, ESR, RF, DMS, SJC,	Yes
Wu[36]	A: 33 B: 30	A: 63.64 B: 66.67	A: 28–64 B: 31–67	A: 5.7 B: 5.5	10	+1	LEF, MePr	24	A: 100% B: 83.33%	ACR20, ACR50, ACR70,	CRP, ESR, RF, DMS, SJC, TJC,	No

[a]A = GSZD group; B = control group.
[b]Effective rate is defined as ACR20, 30% or 35% efficacy, ΔDAS28 >0.6.
ACR, American College of Rheumatology; AE, adverse event; CLX, celecoxib; CRP, C-reactive protein; ΔDAS28, a decrease of DAS28; DAS28, disease activity score 28; Dic, diclofenac sodium; DMS, duration of morning stiffness; ESR, erythrocyte sedimentation rate; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; IBU, ibuprofen; LEF, leflunomide; MePr, methylprednisolone; MTX, methotrexate; NR, not reported; RF, rheumatoid factor; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count.
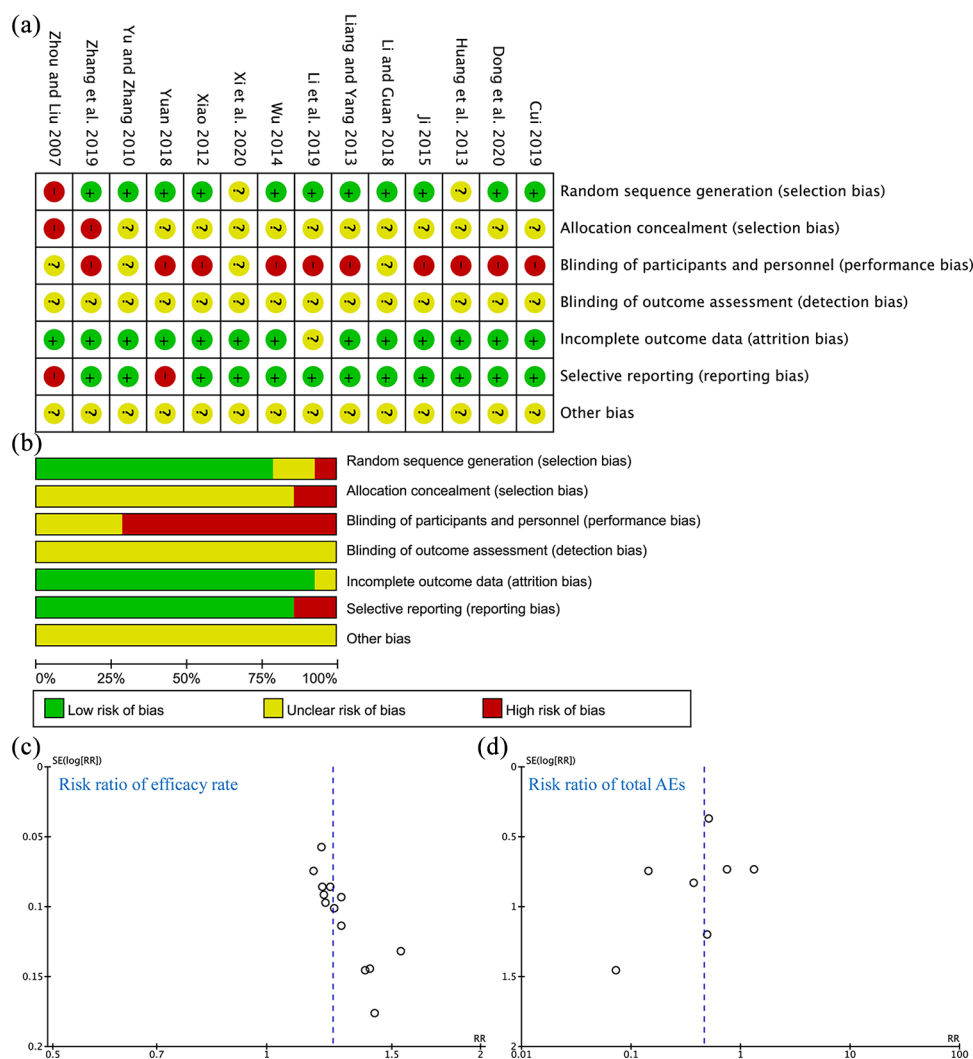
Figure 2. Risk of bias of included RCTs. (a) Summary of risk of bias. (b) Risk of bias graph for each item presented as a percentage across all included studies. (c) Funnel plot for the risk ratio of efficacy rate. (d) Funnel plot for the risk ratio of total AEs.

AE, adverse event; RCT, randomized controlled trial.

ACR, American College of Rheumatology; CI, confidence interval; DAS28, Disease activity score 28; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; MTX, methotrexate; M–H, Mantel–Haenszel.

of the MTX group in all of these conditions (Supplemental Figure 2).

After analyzing symptoms of RA, as shown in Figure 4, we also found that adding GSZD was associated with a higher rate of TJC (standardized mean difference=−0.93, 95% CI: −1.28 to −0.57), SJC (standardized mean difference=−0.81, 95% CI: −1.05 to −0.57), DMS (standardized mean difference=−1.58, 95% CI: −2.38 to −0.78), ESR (standardized mean difference=−1.52, 95% CI: −2.10 to −0.93), CRP (standardized mean difference=−1.08, 95% CI: −1.48 to −0.68), and RF (standardized mean difference=−1.36, 95% CI: −2.14 to −0.58).

Safety

Seven trials reported AEs.[21,24,26,31–34] Out of the 615 patients, 68 experienced at least one AE, 20 out of 315 patients in the experimental group and 48 out of 300 in the control group. As shown in Figure 5, adding GSZD was associated with a lower rate of total AEs (RR=0.46, 95% CI:
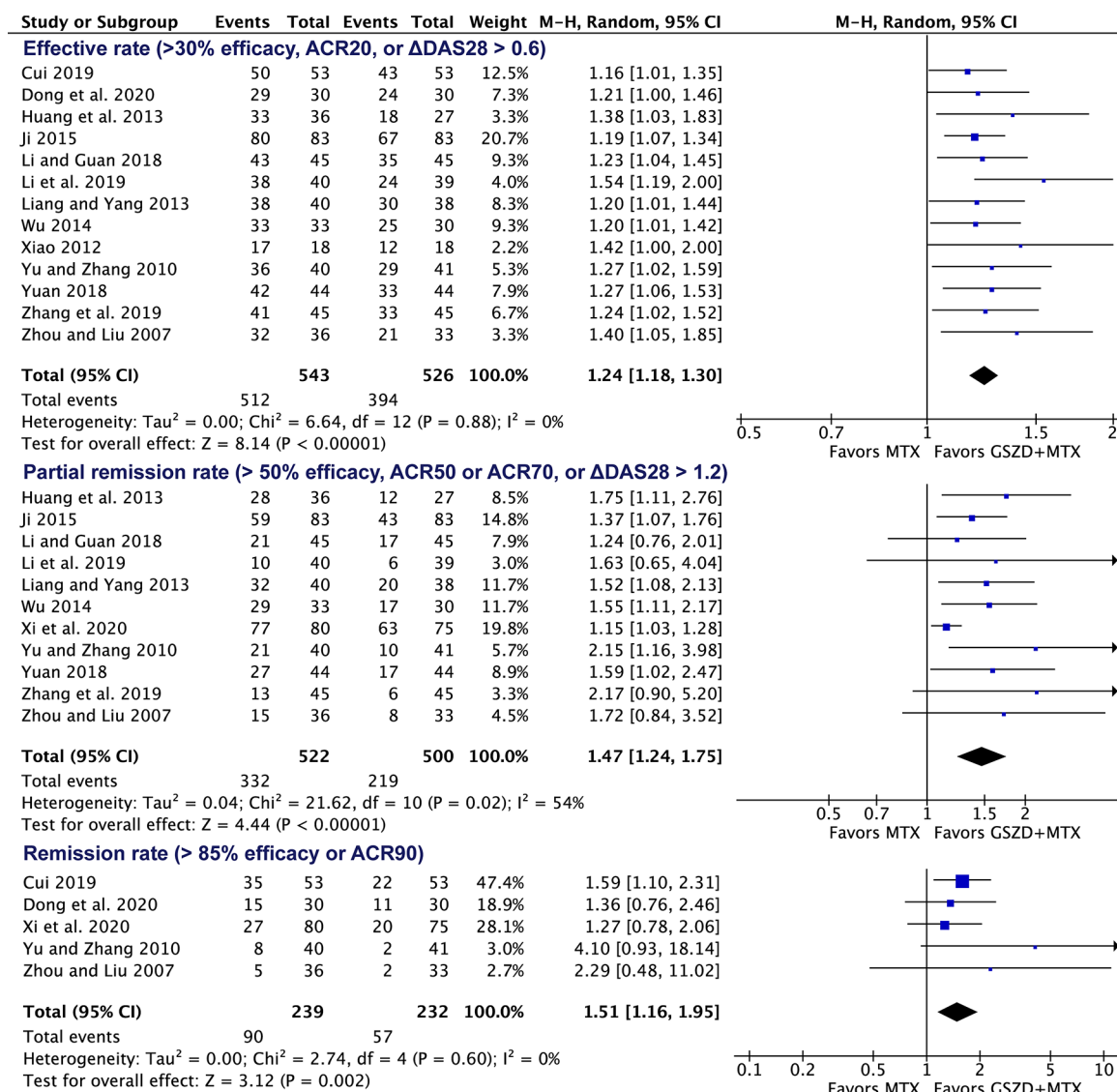
Figure 3. Forest plot indicating the increased response rates following MTX plus GSZD treatment of RA.
ACR, American College of Rheumatology; CI, confidence interval; DAS28, Disease activity score 28; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; MTX, methotrexate; M–H, Mantel–Haenszel.

0.26–0.83). No withdrawal events due to AEs were found in either group. All AEs occurring in the seven trials are listed in Supplemental Table 7.

As shown in Figure 6, adding GSZD was associated with a lower rate of gastrointestinal tract AEs (RR = 0.46, 95% CI: 0.24–0.88), but it had no significant effect on the rate of liver AEs (RR = 0.31, 95% CI: 0.05–1.90), AEs of the nervous system (RR = 0.97, 95% CI: 0.24–3.85), or other AEs (RR = 0.65, 95% CI: 0.15–2.83). The most common AEs in the MTX plus GSZD group were vertigo (2.3%) and nausea (1.3%),

which is comparable to the MTX group (nausea: RR = 0.41, 95% CI: 0.18–0.95) and (vertigo: RR = 0.93, 95% CI 0.22–3.97). Of note, the results for the rate of gastrointestinal tract AEs may also become comparable between two groups when excluding the study of Xi and Zhang[26] or Yu and Zhang[31] (Supplemental Table 6).

Discussion

Methotrexate (MTX) is a first-line synthetic DMARD used in the pharmacological management of RA.[38] Due to limited efficacy and intolerance of

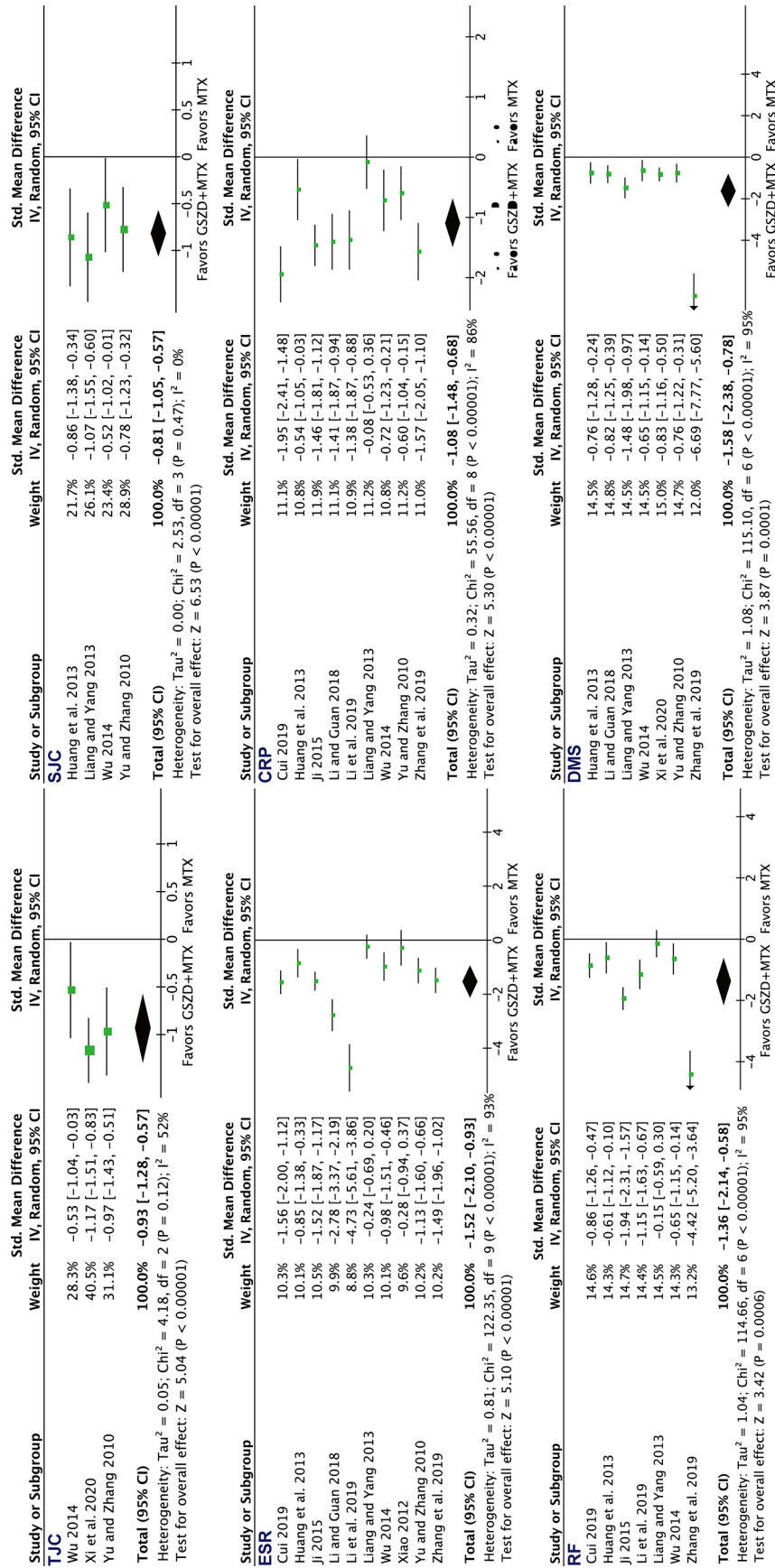**Figure 4.** Forest plot indicating the enhanced efficacy on clinical symptoms and laboratory indexes following MTX plus GSZD treatment of RA.
CI, confidence interval; CRP, C-reactive protein; DMS, duration of morning stiffness; ESR, erythrocyte sedimentation rate; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; IV, inverse variance; MTX, methotrexate; RF, rheumatoid factor; SJC, swollen joint count; Std., standardized; TJC, tender joint count.
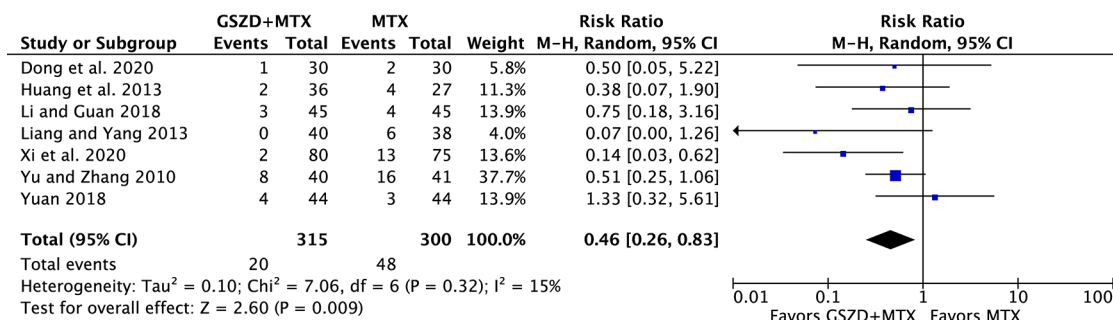
Study or Subgroup	GSZD+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
Dong et al. 2020	1	30	2	30	5.8%	0.50 [0.05, 5.22]
Huang et al. 2013	2	36	4	27	11.3%	0.38 [0.07, 1.90]
Li and Guan 2018	3	45	4	45	13.9%	0.75 [0.18, 3.16]
Liang and Yang 2013	0	40	6	38	4.0%	0.07 [0.00, 1.26]
Xi et al. 2020	2	80	13	75	13.6%	0.14 [0.03, 0.62]
Yu and Zhang 2010	8	40	16	41	37.7%	0.51 [0.25, 1.06]
Yuan 2018	4	44	3	44	13.9%	1.33 [0.32, 5.61]
Total (95% CI)		315		300	100.0%	0.46 [0.26, 0.83]
Total events	20		48			

Heterogeneity: Tau² = 0.10; Chi² = 7.06, df = 6 (P = 0.32); I² = 15%
Test for overall effect: Z = 2.60 (P = 0.009)

Figure 5. Forest plot indicating decreased rate of total adverse events (AEs) following MTX plus GSZD treatment of rheumatoid arthritis. GSZD add-on group had fewer AEs than the MTX group. Events means AEs. CI, confidence interval; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; M–H, Mantel–Haenszel; MTX, methotrexate.

Study or Subgroup	Weight	Risk Ratio M–H, Random, 95% CI
Gastrointestinal AEs		
Dong et al. 2020	7.5%	0.50 [0.05, 5.22]
Huang et al. 2013	4.2%	0.25 [0.01, 5.96]
Li and Guan 2018	13.7%	0.67 [0.12, 3.80]
Xi et al. 2020	18.5%	0.24 [0.05, 1.06]
Yu and Zhang 2010	44.8%	0.47 [0.18, 1.22]
Yuan 2018	11.3%	1.00 [0.15, 6.79]
Total (95% CI)	100.0%	0.46 [0.24, 0.88]
Total events		

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

Nervous system AEs		
Huang et al. 2013	33.0%	0.25 [0.01, 5.96]
Yu and Zhang 2010	67.0%	0.34 [0.04, 3.15]
Total (95% CI)	100.0%	0.31 [0.05, 1.90]
Total events		

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.21)

Liver AEs		
Li and Guan 2018	25.1%	1.00 [0.06, 15.50]
Xi et al. 2020	22.4%	0.12 [0.01, 2.16]
Yu and Zhang 2010	18.8%	3.07 [0.13, 73.28]
Yuan 2018	33.6%	2.00 [0.19, 21.26]
Total (95% CI)	100.0%	0.97 [0.24, 3.85]
Total events		

Heterogeneity: Tau² = 0.02; Chi² = 3.04, df = 3 (P = 0.39); I² = 1%
Test for overall effect: Z = 0.05 (P = 0.96)

Other AEs		
Huang et al. 2013	60.8%	0.75 [0.11, 4.99]
Yu and Zhang 2010	39.2%	0.51 [0.05, 5.43]
Total (95% CI)	100.0%	0.65 [0.15, 2.83]
Total events		

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
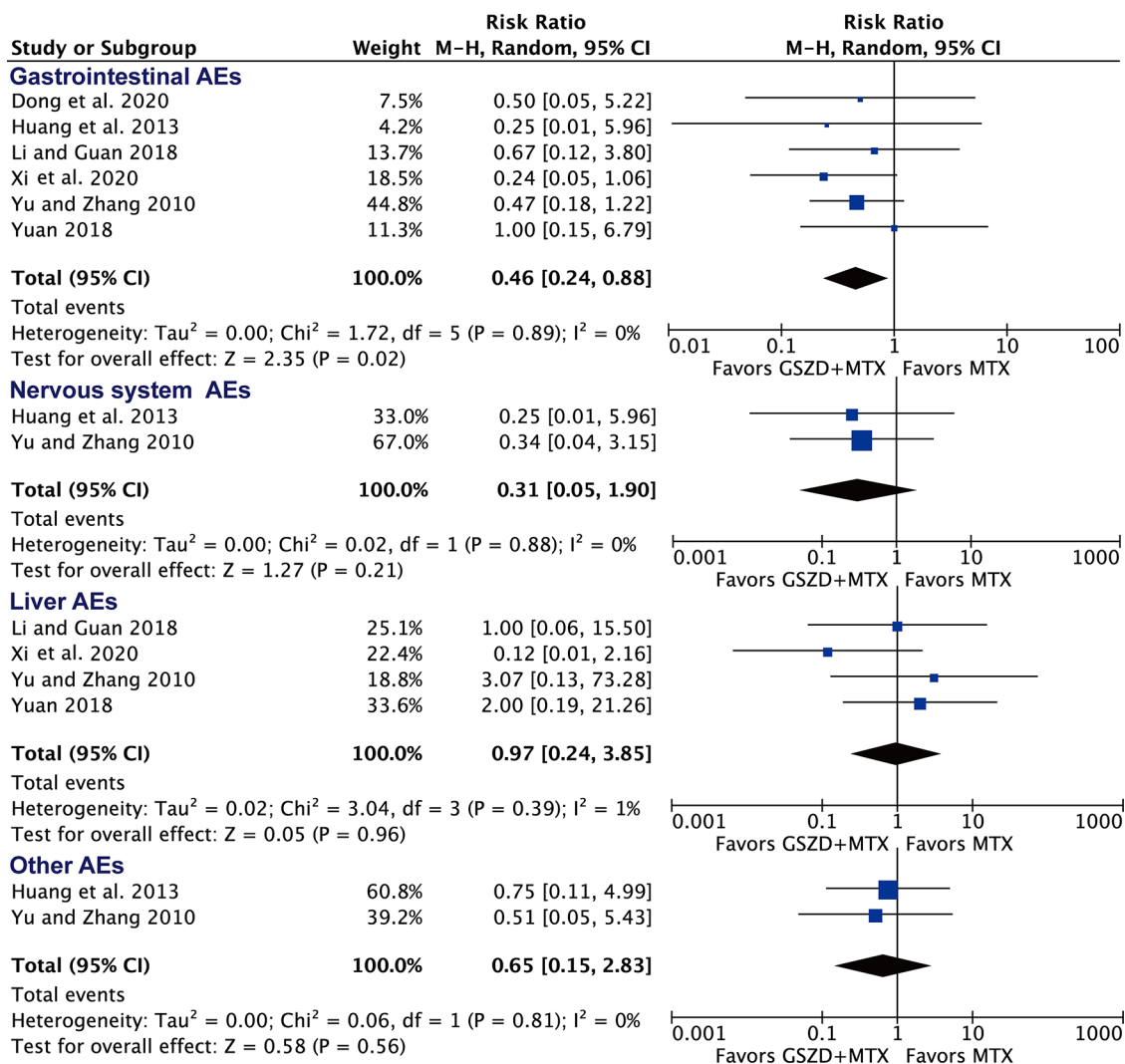Test for overall effect: Z = 0.58 (P = 0.56)

Figure 6. Forest plot for the rate of specific adverse events (AEs) following MTX plus GSZD treatment of rheumatoid arthritis. GSZD add-on group was comparable to or had fewer AEs than MTX group. Events means AEs.
CI, confidence interval; GSZD, GuiZhi-ShaoYao-ZhiMu decoction; M–H: Mantel–Haenszel; MTX, methotrexate.

MTX in many patients, MTX plus GSZD has become a first-line integrated Chinese and western medical therapy strategy for RA in China in recent decades, which may enhance the response rates and reduce the rate of AEs. Using a meta-analysis strategy, we found the following: (1) for efficacy, the combination of GSZD and MTX had a higher effective rate compared with MTX alone (or in a condition of combined utilization of other drugs in both groups); (2) adding GSZD was also associated with lower levels of SJC, TJC, DMS, and ERS, as well as the levels of CRP and RF; and (3) for safety, adding GSZD was associated with a lower rate of the total AEs and the rate of gastrointestinal AEs. Therefore, taken together, our analysis indicated that MTX plus GSZD may be more efficacious and safer than MTX alone for the treatment of RA. Thus, our analysis suggests that MTX combined with GSZD may be a promising therapeutic strategy for the treatment of RA.

A previous meta-analysis showed that GSZD may have equal or superior effectiveness and safety for treating RA compared with western RA drugs, where studies using different western RA drugs were generally pooled together and only two included studies focused on the combination of GSZD and MTX.[12] Here we did a more specific meta-analysis on the efficacy and safety of adding GSZD to MTX. Moreover, we collected and included more RCTs, including seven new RCTs that were reported after 2018.[24–26,29,30,32,35] Thus, our study provided an update and potentially more reliable evidence supporting the use of MTX plus GSZD for the treatment of RA. Based on 14 RCTs and a total of 1224 patients, our meta-analysis found that adding GSZD was associated with higher response rates, lower rates of SJC, TJC, DMS, and ERS, and lower levels of CRP and RF. The adjuvant therapeutic effect of GSZD was independent of the dose of MTX or the combined utilization of other drugs (such as NSAIDs in both groups). Thus, our results suggested that the combination of GSZD and MTX may be more efficacious than MTX alone for RA patients. Further studies are still warranted to confirm the effect of the combination of GSZD and MTX for RA treatment.

Common AEs were observed in patients treated with MTX involving toxicities in several organs.[39] According to a recent systematic review on the side effects of MTX therapy for RA, gastrointestinal AEs were the most frequent AEs associated with MTX.[40] In particular, about 11% of RA patients discontinued MTX therapy mainly because of gastrointestinal AEs.[41] Our analysis found that adding GSZD was associated with a lower rate of total AEs and the rate of gastrointestinal AEs but did not significantly affect the rate of other AEs. The most common AEs in both MTX plus GSZD and MTX groups were nausea (2.3% for MTX plus GSZD *versus* 5.6% for MTX) and vertigo (1.3% for MTX plus GSZD *versus* 2.0% for MTX). Recently, a retrospective cohort study also indicated that adding GSZD was associated with a lower risk of ischemic stroke among patients with RA.[42] Thus, these results suggest that the combination of GSZD and MTX may be safer than MTX alone for RA patients, especially for patients with MTX related gastrointestinal AEs. Further studies are needed to confirm whether adding GSZD was associated with a lower rate of total AEs.

Similar to most TCM formulas, the mechanism of GSZD is complex and unclear. According to previous network pharmacology studies,[10,17] GSZD may target hundreds of RA related proteins and may partially reverse the inflammation–immune system imbalance, which therefore is likely to satisfy the therapeutic outcomes for RA. In a recent animal study, GSZD inhibited many serum proinflammatory cytokine levels, including TNF-α, IL-1β, IL-6, and IL-17a, in collagen-induced arthritis (CIA) rats.[43] Though the therapeutic effect of MTX on RA remains unclear, it is well-known that MTX mainly works by inhibiting dihydrofolate reductase,[44] which does not seem to be the potential target of GSZD. Thus, these results suggest that the combination of GSZD and MTX may have a complementary effect for RA therapy.

Several limitations in our meta-analysis should be noted as follows: (1) the quality of some trials was poor, such as having an unclear bias for allocation concealment, unclear blinding of outcome assessor, and high risk of performance biases; (2) all included trials were conducted in the Chinese population, which implies a high risk of selection bias; (3) according to the funnel plot, publication bias may exist; (4) although all studies used the basic GSZD formulation, the use of other herbs or drugs may have influenced our analysis. Thus, the clinical interpretation of these findings is limited by these high or unclear risks of bias. Further

large and multi-center clinical studies are still warranted.

Conclusion

This meta-analysis preliminarily indicated that the combination of GSZD and MTX is a more effective and safer strategy compared with MTX alone for RA treatment. Of note, as the specific risk of bias and heterogeneity exist, further large and multi-center clinical studies are still needed to investigate the long-term efficacy and safety of the combination of GSZD and MTX for RA treatment.

Author contributions

Z.X. designed the study. C.F and R.C. performed the systematic search. C.F and R.C. reviewed studies to extract potentially eligible studies and the data. K.W. helped to check the extracted data for analysis. C.F., K.W., and Z.X. analyzed the data. C.F. and Z.X. wrote the manuscript in consultation with C.W.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Consent statement and ethical approval

Consent statement and ethical approval are not required as the current study was based on published data.

ORCID iD

Zhenghao Xu (iD) https://orcid.org/0000-0003-0033-525X

Supplemental material

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