

The effects of acupuncture and related techniques on patients with rheumatoid arthritis: A systematic review and meta-analysis

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Abstract

Background: One new type of acupuncture and related techniques (ACNRT) is increasingly used by rheumatoid arthritis (RA) patients to control their disease and improve their quality of life. However, the efficacy of using ACNRT in combination with western medicine (WM) for this purpose remains unknown.

Methods: Randomized controlled trials of ACNRT and WM treatments for RA from January 1, 2000, to January 31, 2021, were searched for in the databases PubMed, Embase, Medline, and the Cochrane Central Register of Controlled Trials, as well as in three Chinese databases: China National Knowledge Infrastructure, Wanfang Data, and Airiti Library. The primary outcomes consisted of inflammatory markers including C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor. The secondary outcomes were clinical characteristics including pain visual analog scale (VAS) score, Disease Activity Score (DAS-28), swollen joints count (SJC), tender joints count (TJC), morning stiffness, and the results of a health assessment questionnaire. The three types of ACNRT used in the focal trials were acupuncture, moxibustion, and electro-acupuncture. Two qualified researchers extracted data from these trials' results and independently assessed their risk of bias. Statistical analyses were performed using Comprehensive Meta-Analysis V3 software.

Results: A total of 12 RCTs with 874 patients met the inclusion criteria. As compared with the patients who received WM treatment alone, those who were given integrated ACNRT/WM treatment showed greater reductions in CRP (weighted mean difference [WMD]: -6.299; 95% CI: -9.082 to -3.517), ESR (WMD: -6.563; 95% CI: -8.604 to -4.522), VAS (WMD: -1.089; 95% CI: -1.575 to -0.602), DAS-28 (WMD: -0.633; 95% CI: -1.006 to -0.259), SJC (WMD: -1.921; 95% CI: -3.635 to -0.207), and TJC (WMD: -1.491; 95% CI: -2.941 to -0.042).

Conclusion: This meta-analysis of RA provides reliable evidence in favor of ACNRT plus WM. However, longer term, high-quality, repeatable, multicenter randomized controlled trials with larger sample sizes are needed.

Keywords: Acupuncture; Electro-acupuncture; Meta-analysis, Moxibustion; Rheumatoid arthritis; Systematic review

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease characterized by synovial membrane inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic features¹ and affects approximately 1% of the world's population.² Western medicine (WM) treatments

for RA mainly include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GCs), and biological agents. Although these treatments reduce inflammation and joint destruction, their use is limited by their high costs and severe side effects such as life-threatening infections and increased risk of malignancies.³⁻⁵ These drawbacks often prompt patients to turn to complementary therapies, in the hope that such therapies will alleviate both their symptoms and the side effects of their WM treatments.⁶ One such complementary therapy is acupuncture, which typically includes manual stimulation with needles. However, its commonly used variations include moxibustion—in which the moxa herb, *Artemisia vulgaris* (mugwort), is burned at the handle end of the needle⁷—and electro-acupuncture (EA). These acupuncture and related techniques (ACNRTs) are part of traditional Chinese medicine (TCM), the source of many of the forms of complementary and alternative medicine that are most frequently used by RA patients.^{8,9} In light of this popularity, it is reasonable to expect that a combination of ACNRT and conventional WM might help to control such patients' disease and improve their quality of life.

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Several previous meta-analyses have explored the effects of TCM on RA. A Cochrane review in 2005 included two randomized controlled trials (RCTs) that had examined the effects of acupuncture on disease activity in 84 patients with RA.⁸ The results showed that the acupuncture treatment they received was not significantly superior to the control intervention, as measured by pain, general health, and disease activity, among other factors. Lee et al⁶ conducted a meta-analysis of eight RCTs in 2008 and reported that neither penetrating nor nonpenetrating sham-controlled RCTs showed any specific effects of acupuncture on pain control in RA patients. The meta-analysis by Choi et al¹⁰ of 14 RCTs found no conclusive evidence for the superior effectiveness of moxibustion over drug therapy for rheumatic conditions. Li et al¹¹ conducted a meta-analysis of five RCTs and reported favorable effects of acupuncture plus WM on symptoms. The meta-analysis by Xing et al¹² of 20 RCTs conducted up to January 2020 found that integration of TCM with WM could yield effective and safe treatment of RA. However, the efficacy of ACNRT combined with WM has not previously been the subject of meta-analysis, despite evidence having become available. Therefore, to arrive at a more precise estimation of the effect of integrated ACNRT/WM on RA, we performed the present updated meta-analysis of all eligible studies.

2. METHODS

2.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses and PROSPERO

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,¹³ and its protocol has been registered in PROSPERO (registration number: CRD42021230077).

2.2. Data sources and search strategy

We searched four English databases, PubMed, Embase, Medline, and the Cochrane Central Register of Controlled Trials and three Chinese ones—China National Knowledge Infrastructure, Wanfang Data, and Airiti Library—from January 1, 2000, to January 31, 2021.

Our search strategy comprised the following English keywords and their Chinese equivalents: [“rheumatoid arthritis” OR “RA” OR “arthritis rheumatoid”] AND [“acupuncture” OR “moxibustion” OR “warming needle” OR “warm acupuncture” OR “electroacupuncture” OR “electro-acupuncture”]. Database searches were conducted according to guidance from the *Cochrane Collaborative Network System Evaluator’s Manual*, Version 5.0. Two researchers (H.L.L. and C.M.C.) separately selected literature from among the search results by reading titles and abstracts. The studies initially deemed relevant by either of them were imported into Endnote X9 to aid in the removal of duplicative material.

2.3. Inclusion criteria

We included RCTs and excluded comparative experimental trials, single-armed follow-up studies, case series, and case reports.

2.4. Participants

The target population comprised patients with RA treated with WM, including DMARDs, NSAIDs, GC, and/or analgesic drugs, irrespective of their country of residence, age, race, or sex.

2.5. Interventions

In the experimental group, RA patients were treated with needle acupuncture, with or without EA or moxibustion. In the control group, RA patients received WM plus either control (sham acupuncture) or no TCM treatment.

2.6. Types of outcome measures

- (1) Primary outcome. Inflammatory markers: C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF).
- (2) Secondary outcomes. Clinical characteristics: pain visual analog scale (VAS) score, Disease Activity Score (DAS-28), swollen joints count (SJC), tender joints count (TJC), morning stiffness (MS), and health-assessment questionnaire (HAQ) results.

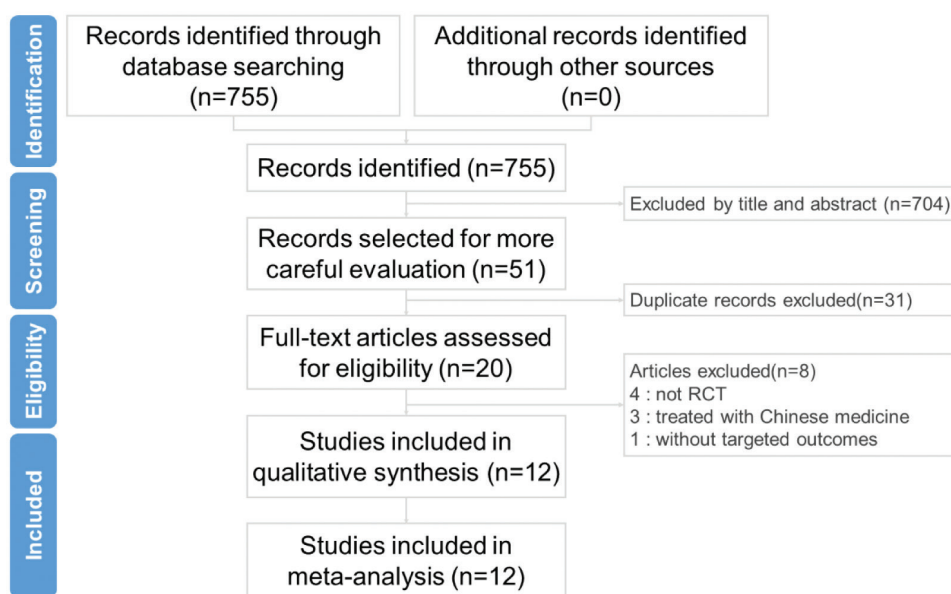


Fig. 1 Preferred reporting items for systemic reviews and meta-analysis (PRISMA) flow diagram for searching and identification of included studies.

Table 1**Basic characteristics and methodologies of the retrieved studies of rheumatoid arthritis**

Author/year	study design	Double blind	Diagnosis	Intervention arms		Sample number (male/female)	Average age year, mean (SD)	Duration of RA, mean (SD)	Outcome measurement
Liu et al, 2003 ¹⁵	RCT	No	RA (ACR criteria)	EA	WM	49 (23/26)	36.7 (-)	0.71 (-), mo	CRP, RF, ASO, walking distance.
Ai et al, 2005 ¹⁶	RCT	No	RA (ACR criteria)	EA	WM	49(24/25)	36.6 (-)	0.72 (-), mo	CRP, ESR, RF, clinical effect
Tam et al, 2007 ¹⁸	RCT	Yes	Active RA	AC	WM	74 (13/61)	39.5 (9.7)	2.5 (1.6), y	CRP, ESR, RF, clinical effect
Tam et al, 2007 ¹⁸	RCT	Yes	Active RA	AC	WM	72 (10/62)	41.2 (8.2)	2.4 (2.3), y	CRP, ESR, RF, clinical effect
Xiang and Lee 2007 ¹⁷	RCT	No	Active RA	AC	MB	12 (-/-)	58.1 (12.0)	10.8 (6.2), y	CRP, ESR, VAS, DAS28, HAQ, SJC, TJC, PGA, PhGA
Zanette et al, 2008 ¹⁹	RCT	No	RA (ACR criteria)	AC	WM	12 (-/-)	57.6 (8.3)	8.1 (6.9), y	CRP, ESR, VAS, DAS28, HAQ, SJ, TJC, PGA, PhGA
Zhou et al, 2016 ²⁰	RCT		RA (ACR criteria)	PLAC	EA	12 (-/-)	56.4 (8.5)	8.4 (5.6), y	CRP, ESR, VAS, DAS28, HAQ, SJ, TJC, PGA, PhGA
Zhu et al, 2018 ²¹	RCT	No	Active RA	AC	WM	21 (7/14)	50.2 (8.9)	4.9 (2.7), y	CRP, ESR, RF, Clinical effect
Seca et al, 2019 ²²	RCT	Yes	Active RA with CM pivot syndrome or turning point syndrome	AC	WM	21 (6/15)	51.7 (8.7)	4.8 (2.3), y	CRP, ESR, VAS, DAS28, HAQ, ACR20, MS, SJC, TJC, PhGA
Zeng et al, 2019 ²³	RCT	Yes	Active RA	PLAC	EA	20 (3/17)	53.1 (12.44)	12.33 (5.93), y	CRP, ESR, VAS, DAS28, HAQ, TJC, SJ, PGA, PhGA, TCM symptom scoring
Zeng et al, 2019 ²³	RCT	Yes	Active RA	AC	WM	20 (0/20)	46.5 (9.9)	11.97 (7.48), y	CRP, ESR, VAS, HAQ, TJC, SJ, PGA, PhGA, TCM symptom scoring
Zeng et al, 2019 ²³	RCT	Yes	Active RA	AC	WM	34 (5/29)	57.33 (11.17)	9.69 (7.4), y	CRP, ESR, DAS28, RF, PLT, FBG and D-dimer, symptom grade quantitative score, blood stasis syndrome symptom score
Jia et al, 2020 ²⁴	RCT	No	RA patients with CM cold dampness obstruction patterns	AC	MB	28 (21/7)	53 (13)	12.8 (8.1), y	CRP, ESR, VAS, DAS28, HAQ, SJC, TJC, AS, hands grasp strength, arm strength, pressure algometry, HRQoL, SF36
Gao et al, 2020 ²⁵	RCT	No	RA patients with CM exterior cold dampness obstruction patterns	AC	MB	35 (31/4)	57.31 (11.3)	12.15 (8.82), y	CRP, ESR, VAS, DAS28, HAQ, SJC, TJC, AS, hands grasp strength, arm strength, pressure algometry, HRQoL, SF36
Xie et al, 2020 ²⁶	RCT	No	RA patients with CM kidney deficiency and cold coagulation	AC	MB	20 (5/15)	56.46 (16.43)	14.67 (10.38), y	CRP, ESR, DAS28, VAS, SJ, TJC, MS, PICP, N-MID, β -CTX, IL-17, B-ALP, TRACP-5b
						20 (6/14)	46 (-)	5.7 (1.4), mo	CRP, ESR, DAS28, VAS, SJ, TJC, MS, PICP, N-MID, β -CTX, IL-17, B-ALP, TRACP-5b
						20 (5/15)	55 (-)	6.0 (1.8), mo	CRP, ESR, DAS28, VAS, SJ, TJC, MS, PICP, N-MID, β -CTX, IL-17, B-ALP, TRACP-5b
						59 (20/39)	49.88 (6.36)	7.1 (1.9), y	CRP, ESR, RF, VAS, DAS28, HAQ, SJC, TJC, MS, CCP-Ab, MCV-Ab, TNF- α , IL-1 β , IL-6, IL-17
						59 (22/37)	49.39 (6.64)	6.99 (1.83), y	VAS, CD4, CD8, CD4/CD8 level, TCM symptom scoring
						40 (16/24)	46.6 (6.9)	4.3 (0.6), y	VAS, CD4, CD8, CD4/CD8 level, TCM symptom scoring
						40 (17/23)	45.3 (7.1)	4.5 (0.5), y	CRP, ESR, DAS28, DAI, symptomatic grading and quantifying score, clinical efficacy.
						30 (8/22)	51.8 (13.2)	11.5 (7.6), y	CRP, ESR, DAS28, DAI, symptomatic grading and quantifying score, clinical efficacy.
						30 (7/23)	52.1 (13.3)	12.3 (7.3), y	CRP, ESR, DAS28, DAI, symptomatic grading and quantifying score, clinical efficacy.

AC = acupuncture; ASO = antistreptolysin O; CRP = C reactive protein; DAI = disease activity index; DAS-28 = disease activity score by 28 joints; EA = electro-acupuncture; ESR = erythrocyte sedimentation rate; FBG = fibrinogen; HAQ = health assessment questionnaire; MB = moxibustion; MS = morning stiffness; PGA = patient's global assessment; PhGA = physician's global assessment; PLAC = placebo-acupuncture; PLT = platelet; RCTs = randomized clinical trials; RF = rheumatoid factor; SJC = swollen joints count; TCM = traditional Chinese medicine; TJC = tender joints count; VAS = visual analog scale; WM = western medicine.

Table 2**Summary of the intervention details of acupuncture and related techniques in the retrieved trials**

Author/year	Intervention arms	Intervention details	Intervention location	Treatment times (min)	Intervention time
Liu et al, 2003 ¹⁵	EA WM	(a) EA: inserted the acupuncture needles for acupuncture points and stimulated by an electrical current (Continuous wave 60 HZ) generated by the generator (Model G6805-2) + (b) (b) WM: intravenous drip of cefotaxime sodium and oral dexamethasone	Group A points: zhijian point DU14, SJ5, GB34, BL60, ST31, GB33 and group B points: zhijian point LI11, DU3, LI10, ST35, GB39 alternatively.	30 min	2 times everyday total period of 20 d
Ai et al, 2005 ¹⁶	EA WM	(c) EA: inserted the acupuncture needles for acupuncture points to appropriate depth and stimulated by an electrical current (continuous wave 60 HZ) generated by the generator (Model G6805-1) + (d) (d) WM: meloxicam (QD 75 mg/time), sulfasalazine (0.5 g/time BID first week, then 0.75 g/time TID) and MTX (10 mg/time QW)	Basic acupoints: LI11, LI4 and GB34. Additional acupoints: BL11, BL18, BL23, ST36, LR3, LI15, SJ14, SI9, SJ4, LI5, SI5, ST41, GB40, LR4 and EX-UE9.	25 min	1 time per day, 5 times per wk total period of 1 month
Tam et al, 2007 ¹⁸	AC WM	(e) AC: The acupuncturist inserted the acupuncture needles (0.25 × 40 mm) for acupuncture points LI11, TE5, ST36, GB36, GB39 to a depth of 20 mm. For acupuncture point LI4, the acupuncturist inserted 0.25 × 25 mm acupuncture needles to a depth of 10 mm. Intermittent specific manual twirling till de qi + (f) (f) WM: patients taking DMARDs were eligible if they were on a stable dose for at least 3 mo before screening. Patients on stable doses of one NSAID or up to 10 mg daily prednisone were also included. Analgesia, including NSAID, steroids, and DMARDs were continued. All patients were instructed not to make any changes in their background therapies during the study	LI11, TE5, LI4, ST36, GB34, GB39	40 min	20 sessions over a period of 10 wk.
Tam et al, 2007 ¹⁸	EA WM	(g) Electroacupuncture with needles stimulated by an electrical current (dense wave at 4 HZ and disperse wave at 20 HZ) generated by the generator (Model G6805-2) and intermittent nonspecific manual twirling + (f)	LI11, TE5, LI4, ST36, GB34, GB39	40 min	20 sessions over a period of 10 wk.
Xiang and Lee 2007 ¹⁷	AC MB WM	(h) AC: patient sitting, sterile needle pricked swollen joint for four points around the swollen center till a drop of blood. + (i) + (j) (i) MB: The patient took a prone position. After sterilization, we put acu-point BL20 and BL23 with herbal powder compressed Cookie, then do moxibustion on it. (j) WM: meloxicam (15 mg/time, QD), MTX (10 mg/time, QW)	AC: four points of swollen joint around the swollen center. MB: BL20 and BL23		AC: Once a week. MB: Once a day, 6 times a week total period of 5 wk
Zanette et al, 2008 ¹⁹	AC WM	(k) AC: sterile needles with diameter of 0.25 × 40 mm were inserted and stimulated with production of the “De Qi” sensation + (m)	Supine: EX 1, PC6, IG4, EX 28, CV 12, CV 6, ST 36, SP 6, and LV 3 Ventral position: UB 20, UB 22, UB 23, GV 4, GV 14, UB 11, and UB60	20 min in supine. 20 min in ventral.	The patients received a total of ten sessions of AC or control AC, twice a week for 5 consecutive wk.
	PLAC WM	(l) PLAC: superficial acupuncture at nonacupuncture points, with minimal needle stimulation. Using fewer needles and shorter insertion duration. Needles of 15 × 0.25 mm size were inserted up to 2 mm, at nonacupuncture points. +(m). (m) WM: pharmacological treatment had to be stable for at least 1 mo before the study, including analgesics, NSAIDs, glucocorticoids (should be equal or less than 15 mg/d of prednisone or equivalent) and DMARDs	Nonacupuncture points.	10 min in supine. 10 min in ventral.	
Zhou et al, 2016 ²⁰	EA WM	(n) EA: sterile needles with diameter of 0.25 × 40 mm were inserted and stimulated with production of the “teh Qi” sensation and needles on GB39, ST36, BL18, BL23 stimulated by an electrical current (dense wave at 4 HZ and disperse wave at 20 HZ) generated by the generator (Model G6805-2) +(o). (o) WM: MTX (7.5 mg/time, QW), leflunomide (10 mg/time, QD)	Bilateral BL18, BL23, GB39, ST36, LR3, LI4,	30 min	3 times a week total period of 12 wk

(Continued)

Table 2 (Continued)

Author/year	Intervention arms	Intervention details	Intervention location	Treatment times (min)	Intervention time
Zhu et al, 2018 ²¹	AC	WM (p) AC: sterile needles with diameter of 0.30 × 25 mm, 0.3 mm ~ 40 mm were inserted and stimulated with production of “DeQi” sensation, combined reinforcing-reduction was achieved by lifting- inserting one time. + (q). WM (q) WM: ibuprofen sustained—release tablets (0.3 g/time, BID); MTX (10 mg/time, QW); folic acid tablets (5 mg/time, QW)	BL 18, BL 20. BL 23, LI 4, LI 11, ST 36, combined with local ashi points	30 min	once every day for continuous 6 d a week, the treatment for 30 d as one course, a total of 3 courses were required
Seca et al, 2019 ²²	AC	WM (r) AC: the acupoints and the nonacupoints were stimulated using sterile subcutaneous needles (0.30 × 8 mm) (BD Micro-Fine!) 29 using the Leopard Spot technique (bloodletting or fang xue acupuncture), a way of dispelling “blood” (xue) stasis described in the third century. The therapists were trained to execute the Leopard Spot technique by pricking quickly the points (five times per point, three to five blood drops per point) with the color indicated by the randomization computer program + (s). (s)WM: All patients were under stable doses of biomedical com Bination therapies, including NSAIDs, DMARD, biologics, and analgesic drugs, and were instructed not to change their usual therapies during the study.	SJ5, GB39, HT3, and KI7		Three treatment sessions in the first week. After the first week, they were treated twice per week over a period of 3 wk, with a minimum interval of 72 h in between treatments
	PLAC	WM (t) PLAC: The patients allocated to the PLAC group were treated with the exact same number, depth, and stimulation of needles, but not according to the CM diagnosis. + (s).	Points allocated in areas close to the real acupoints but at nonacupoints.		
Zeng et al, 2019 ²³	AC	WM (u) AC: a 0.3 × 50 mm acupuncture needle was inserted perpendicular to the skin to a depth of 1.5–2.5 cm in the BL 23, BL 20, BL 18, and ST 36. Combined reinforcing-reduction was achieved by lifting- inserting after De Qi (arrival of Qi). The acupuncture needles were inserted from shallow to deep and left to right with hardly any left turning and later pulled out gently with right turning. The frequency of stimulation was 20–30 times per minute, and needles were retained for 30 min after insertion was complete. For the DU 4 and DU 14, 0.30 mm acupuncture needles were inserted into the skin to a depth of 1.5–2.5 cm with an approximately 75 upward inclinations, and the needles were retained for 30 min after insertion was complete. For points along the target joint, a similar insertion procedure was followed as for the necessary basic acupoints, except that the stimulation frequency was 30–40 times per minute. At the beginning of the retaining period, the needles were energizing. + (v) WM (v) WM: MTX: 7.5 mg/wk, LEF: 20 mg/d	Basic acupoints: DU 14, BL 23 DU 4, BL 20, BL 18, ST 36. Additional acupoints: used for different lesions were LI 15, SJ 14, SJ 5, LI 11, LI 4, LI5, SJ 4, EX-UE 9, GB 30, EX-LE 4, ST 35, BL 40, GB 34, SP 9, ST 41, BL 60, GB 40, EX-LE 10	30 min	Once every other day and 10 treatments made up one course over a total period of 8 wk.
Zeng et al, 2019 ²³	EA	WM EA treatments were per formed with the G91-A electropuncture instrument (Kangling, Yangzhou, China) and the dilatational wave was allowed to persist for 30 min. +(u) +(v) WM (v)	The choice of acupoints for electroacupuncture therapy was flexible; 1–2 points for the necessary basic acupoints and 1 point for the local target joint according to the patient’s condition.	30 min	Once every other day and 10 treatments made up one course over a total period of 8 wk.
Jia et al, 2020 ²⁴	AC MB	WM (w) AC: sterile needles with diameter of 0.3×40 mm were inserted and stimulated with production of the “teh Qi” sensation. (x) MB: Put a 2cm length moxibustion on the needles and ignite it. Every acupoint for three times continuously. + (y) WM (y) WM: methotrexate (10 mg/time, QD) combined with celecoxib (0.2 g/time, BID)	Major acupoints: ST36, LI11, SP6, RN6, RN4, GB34. Adjunct acupoints: Those around joint lesions were selected. SJ14, GB21, PC3, LU5, SJ5, LI10, LI4, EX-UE9,		Once every day for continuous 5 d a week. The treatment for 4 wk as one course. Total 3 courses.

(Continued)

Table 2 (Continued)

Author/year	Intervention arms	Intervention details	Intervention location	Treatment times (min)	Intervention time
Gao et al, 2020 ²⁵	AC MB WM	(z) AC: sterile needles with diameter of 0.3 × 25 mm were inserted and stimulated with production of the “de Qi” sensation. (1) MB: put a 2 cm length moxibustion on the needles and ignite it. +(2) WM (2) WM: ibuprofen sustained—release tablets (0.3 g/time, BID); MTX (initial dose: 7.5 mg once weekly, increased by 5 mg every 2 to 4 wk. Maximum: 15 mg/dose)	BL23, BL18, GB33, SP9, LI5, KI6		Once every other day a total period of 4 wk.
Xie et al, 2020 ²⁶	AC MB EA WM	(3) AC: patient took a supine position. After routine disinfection, we used filiform needles (Suzhou Medical Supplies Co., Ltd., China) of 0.25 mm in diameter and 40 mm in length to needle the acupoints perpendicularly. After needling qi was obtained, Then, we perpendicularly needled the adjunct acupoints and performed reducing manipulations. The patient turned into a prone position after the needles were withdrawn. We sterilized his skin around the selected back acupoints, then inserted needles obliquely towards the spine, and twirled the needles with the even reinforcing-reducing manipulation. +(4), (5), (6). (4) EA: we KWD-808 Yingdi pulse acupuncture therapeutic apparatus (Shanghai Zhangdong Medical Technology Co., Ltd., China). Continuous wave was used with frequency of 50 Hz. (5) MB: the patient took a prone position. After sterilization, we first wiped the moxibustion area with fresh ginger sap, then spread fresh ginger mash with a thickness of about 0.5 cm and a width of about 3 cm from top to bottom, and finally spread moxa evenly on the ginger mash with an appropriate thickness. Ignited all the flosses and replaced them with new ones for 2 times after burning out, then removed the ashes and ginger mash to clean the back. WM (6) WM: methotrexate tablets and nimesulide dispersible tablets after meals. Methotrexate tablet [2.5 mg/tablet,] was taken orally at 10.0-12.5mg/time, Once a week. Nimesulide dispersible tablet (0.1 mg/tablet, was taken orally at 0.1 mg/time, twice a day. Additional omeprazole enteric-coated capsules (10 mg/capsule, could be taken according to his individual conditions if some patient had gastrointestinal discomfort. This capsule was taken orally before meals at 100 mg/time, twice a day.	Major acupoints: LI 11, LI 4, TE 5, ST 36, GB 34, GB 39, BL 18, BL 20, GV 8 and BL 23. Adjunct acupoints: Those around joint lesions were selected. TE 14, LI 15, LU 5, PC 3, TE 4, SI 5, LI 5, EX-UE 9, EX-LE 4, LR 8, GB 33, KI 3, ST 41, BL 60, GB 40, EX-LE 10. EA points: LI 4, LI 11, GB 34 and ST 36. MB: the rectangular area was from GV 14 to GV 4, taking 1.5 cm away from the spine midline as its two sides.	60 min	12 wk. EA: once every other day. MB: twice a week

AC = acupuncture; CRP = C reactive protein; DAS-28 = disease activity score by 28 joints; DMARDs = disease modifying antirheumatic drugs; EA = electro-acupuncture; ESR = erythrocyte sedimentation rate; HAQ = health assessment questionnaire; MB = moxibustion; MS = morning stiffness; NSAID = nonsteroidal anti-inflammatory drug; PLAC = placebo-acupuncture; RCTs = randomized clinical trials; RF = rheumatoid factor; SJC = swollen joints count; TCM = traditional Chinese medicine; TJC = tender joints count; VAS = visual analog scale; WM = western medicine.

2.7. Exclusion criteria

We excluded interventions with Chinese herbal medicines, laser acupuncture, auricular acupuncture, acupressure, point application, and single-moxibustion. The bibliographies of the included trials and related review articles were manually reviewed for relevant references.

2.8. Study selection

After removing duplicate studies, two researchers (H.L.L. and C.M.C.) independently screened the titles and abstracts of the identified studies for preliminary inclusion. Then, they reviewed the full texts of the selected studies for final inclusion. Any disagreement was resolved via discussion with one other researcher (Y.Y.K.).

2.9. Data extraction

Two qualified researchers (P.C.H. and J.C.W.) extracted data from the final group of studies independently, using pre-defined data collection forms (Excel 2007; Microsoft, Redmond, WA). Any inconsistent views were resolved through discussion with a third researcher (Y.Y.K.). The extracted items included the name of the lead author, publication year, diagnosis, intervention arms, enrolled sample size, the participants' ages, the duration of their RA, outcome measurements, ACNRT intervention details, and WM details.

2.10. Risk-of-bias assessment

The methodological quality of the enrolled studies was evaluated by researchers (P.C.H. and J.C.W.) independently using the

Cochrane RoB 2.0 tool,¹⁴ which has five assessment domains for risk of bias; together, these domains would lead to overall bias. Discrepancies between the reviewers were resolved through discussions arbitrated by the researcher (Y.Y.K.).

2.11. Data analysis

Statistical analysis was conducted using Comprehensive Meta Analysis V3 software (Biostat Inc., Englewood, NJ). Continuous outcomes were presented as weighted mean difference (WMD) or standardized mean difference (SMD), with 95% CIs. Data that could not be applied to meta-analysis have been summarized in the text below. Subgroup analyses were conducted to assess whether treatment effects differed across subgroups. A random-effects model was employed. Statistical significance was defined as p values < 0.05 , except when determining publication bias, in which context it was defined as $p < 0.10$. Analysis was performed by intention-to-treat, if possible. For continuous variables, we used simple sensitivity analysis. Because more than 10 studies were included in the meta-analysis, publication bias was investigated using funnel plots.

3. RESULTS

3.1. Study description

Our database searches retrieved 755 documents. After eliminating those that violated the inclusion criteria or were duplicative, 20 articles remained and were subjected to meticulous full-text evaluation for eligibility. At this stage, eight further studies were excluded because they were not RCTs, had not targeted outcomes, and/or had utilized Chinese herbal medicine rather than ACNRT. Therefore, 12 RCT studies¹⁵⁻²⁶ were included in our meta-analysis. A flow diagram of how we searched for and identified the included studies is presented as Fig. 1.

3.2. Study characteristics

All the included RCTs¹⁵⁻²⁶ were published between January 2003 and December 2020. Our final quantitative analysis showed that they included 874 participants. The basic characteristics and methodologies of the retrieved studies are listed in Table 1, and details of their ACNRT interventions and outcomes are summarized in Table 2.

3.3. Risk-of-bias assessment

The risk-of-bias assessment of the retrieved studies is summarized in Fig. 2A and presented in graph form in Fig. 2B. The studies' quality was variable, and their risk of bias "due to deviations from intended interventions" was especially high. The most likely reason for this is that none of the retrieved studies had a patient-blinded study design.

3.4. Efficacy of ACNRTs for RA treatment

Meta-analysis was performed on the studies' final evaluations of the following outcomes: CRP (11 studies), ESR (10 studies), VAS (7 studies), DAS-28 (7 studies), SJC (6 studies), TJC (6 studies), RF (5 studies), and HAQ (5 studies). Subgroup analysis was performed according to intervention type.

3.5. Primary outcomes

As shown in Fig. 3, the results obtained from 11 of the 12 trials indicated significantly better CRP outcomes for their ACNRT-plus-WM groups than for their WM-only groups (WMD: -6.299 ; 95% CI: -9.082 to -3.517 , $p = 0.00$, $I^2 = 82\%$). In subgroup analysis, significant benefits remained for acupuncture (five RCTs; WMD: -7.481 , 95% CI: -12.097 to -2.865), EA (five RCTs; WMD: -5.225 , 95% CI: -9.177 to -1.274), and EA plus

moxibustion (one RCT; WMD: -10.050 , 95% CI: -18.393 to -1.707), but not for acupuncture plus on moxibustion.

The results from 10 trials (Fig. 4) indicated that the ACNRT-plus-WM groups had much better ESR outcomes than the WM-only groups did (WMD: -6.563 ; 95% CI: -8.604 to -4.522 , $p = 0.73$, $I^2 = 0\%$). Subgroup analysis revealed that significant benefits remained for acupuncture (five RCTs; WMD: -5.697 , 95% CI: -8.584 to -2.811), acupuncture plus moxibustion (two RCTs; WMD: -6.844 , 95% CI: -11.397 to -2.309), and EA (four RCTs; WMD: -8.088 , 95% CI: -11.656 to -4.520), but not for EA plus moxibustion.

The results obtained from five studies indicated no significant improvement in RF, either overall or within any subgroup (Fig. 5).

3.6. Secondary outcomes

In terms of VAS (Supplementary Fig. 1, <http://links.lww.com/JCMA/A115>), seven studies reported significantly better outcomes for their ACNRT-plus-WM groups than for their WM-only groups (WMD: -1.089 ; 95% CI: -1.575 to -0.602 , $p = 0.21$, $I^2 = 27\%$). In subgroup analysis, the significant benefits remained, whether for acupuncture (four RCTs; WMD: -1.388 , 95% CI: -2.321 to -0.455), acupuncture plus moxibustion (two RCTs; WMD: -0.791 , 95% CI: -1.331 to -0.250), or EA (three RCTs; WMD: -1.307 , 95% CI: -2.011 to -0.603).

The results obtained from seven studies indicated significantly better DAS-28 outcomes for ACNRT-plus-WM groups than for WM-only groups (WMD: -0.633 ; 95% CI: -1.006 to -0.259 , $p = 0.20$, $I^2 = 28\%$) (Supplementary Fig. 2, <http://links.lww.com/JCMA/A115>). However, subgroup analysis revealed that significant DAS-28 benefits were only associated with EA (three RCTs; WMD: -0.815 , 95% CI: -1.502 to -0.127).

Six trials' results regarding SJC (Fig. 6) indicated significantly better outcomes for the ACNRT-plus-WM groups, as compared to the WM-only groups (WMD: -1.921 ; 95% CI: -3.635 to -0.207 , $p = 0.00$, $I^2 = 86\%$). But in subgroup analysis, significant benefits were again only associated with EA (three RCTs; WMD: -3.096 , 95% CI: -3.635 to -0.207).

The results of six trials that included TJC again favored the ACNRT-plus-WM groups over their WM-only counterparts (WMD: -1.491 ; 95% CI: -2.941 to -0.042 , $p = 0.00$, $I^2 = 69\%$) (Fig. 7), but once more, the significance was driven by EA alone (three RCTs; WMD: -2.866 , 95% CI: -4.460 to -1.271).

None of the five trials that used HAQ as an outcome measure reported overall significant improvement in it (Supplementary Fig. 3, <http://links.lww.com/JCMA/A115>). However, subgroup analysis revealed that EA's impact on HAQ was positive and significant (two RCTs; SMD: -1.725 , 95% CI: -3.345 to -0.106).

Last, the three trials that looked at MS as an outcome indicated significantly more improvement in the ACNRT-plus-WM groups than in the WM-only ones (WMD: -0.235 ; 95% CI: -0.434 to -0.036 , $p = 0.16$, $I^2 = 42\%$) (Supplementary Fig. 4, <http://links.lww.com/JCMA/A115>). Subgroup analysis found that such significance remained only for acupuncture plus moxibustion (one RCT; WMD: -0.374 , 95% CI: -0.512 to -0.236).

3.7. Other outcome measurements

Liu et al,¹⁵ based on their comparison of an EA-plus-WM group against a WM-only group, reported that while both groups had significantly lower levels of antistreptolysin O after the intervention than before it, the drop was more significant for the former group ($p < 0.005$) than for the latter ($p < 0.05$).

Similarly, Zhu²¹ reported that both an AC-plus-WM group and a WM-only group had significantly lower levels of platelets, fibrinogen, and D-dimer after their respective treatments, but the drop was more significant for the former ($p < 0.05$).

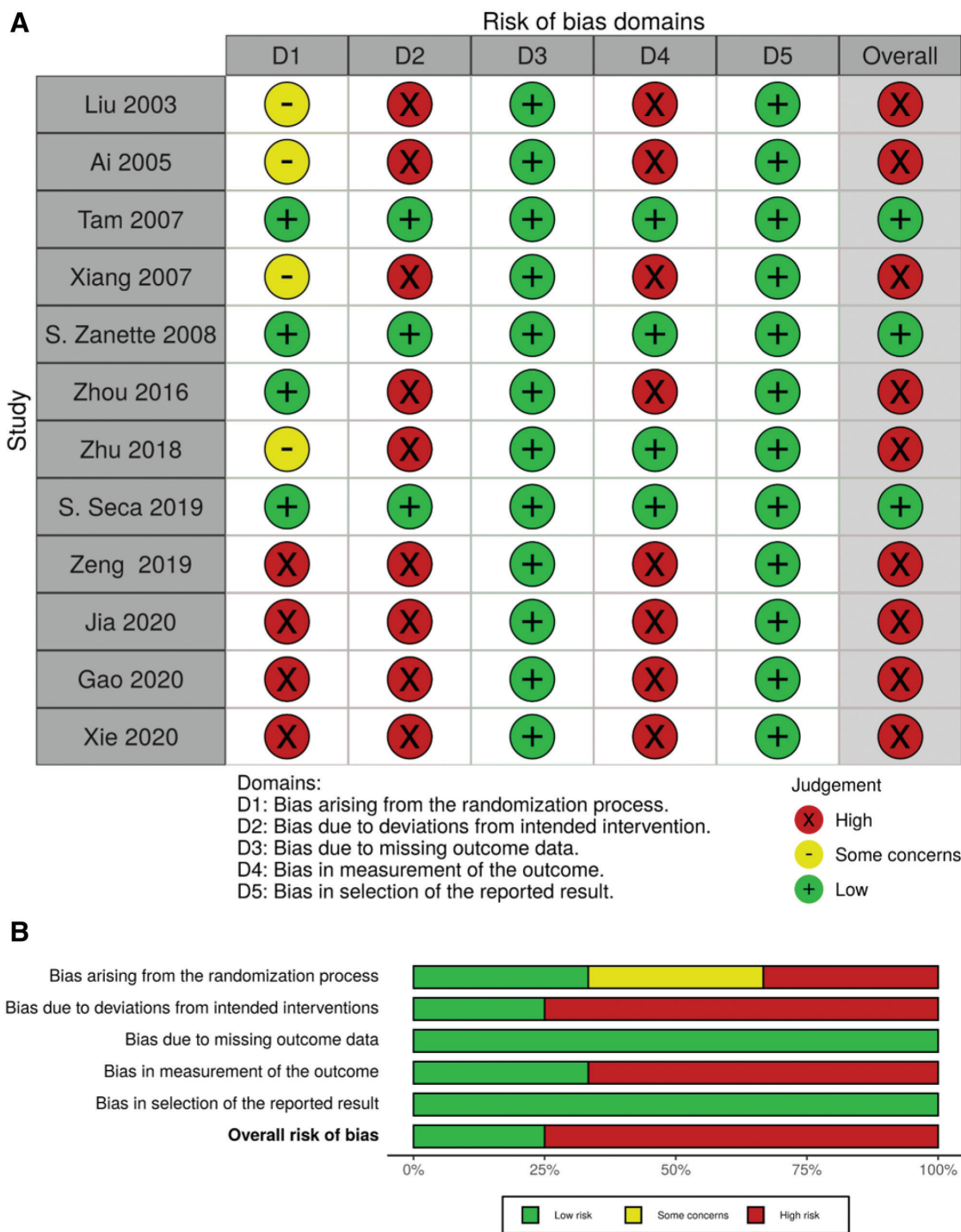


Fig. 2 Risk-of-bias summary (A) and risk-of-bias summary graph (B) about risk-of-bias item for each included trial (RoB 2.0).

Seca et al,²² comparing verum acupuncture-plus-WM group against a placebo-acupuncture-plus-WM group, reported that the former experienced significantly improved pressure algometry ($Z = \text{Zhu } 5.086, p < 0.001$), hand-grip strength ($Z = \text{Zhu } 5.086, p < 0.001$), and arm strength ($Z = \text{Zhu } 5.086, p < 0.001$) and that their quality of life (SF-36) improved significantly in seven of eight survey domains. Placebo-acupuncture, on the other hand, was not associated with any significant changes.

Zeng et al²³ reported that the concentrations of serum PICP, N-MID, and B-ALP were increased after treatment with methotrexate plus leflunomide plus EA, while the concentrations of serum β -CTx and TRACP-5b decreased. The differences in these indexes were significantly greater for their EA-plus-WM group than for their WM-only (control) group. The concentration of serum IL-17 in the EA group was also dramatically reduced after treatment, as compared with the control.

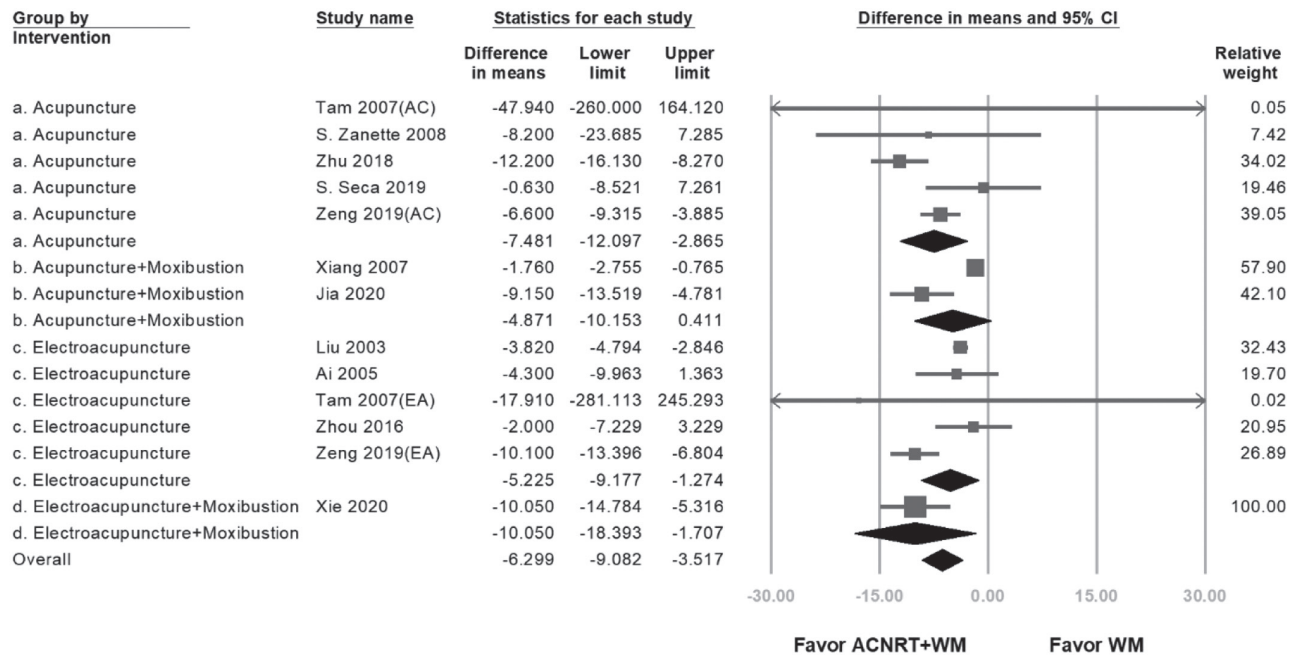


Fig. 3 Improvement in C reactive protein (CRP) levels associated with acupuncture and related techniques vs western medicine in the sampled rheumatoid arthritis patients.

Jia et al²⁴ compared an acupuncture-plus-moxibustion-plus-WM group against a WM-only group and reported that both had significantly lower posttreatment levels of IL-1 β , IL-6, IL-17, and TNF- α , but that the significance was greater for the former than for the latter ($p < 0.05$).

3.8. Adverse events

Tam et al¹⁸ reported three episodes of minor adverse events, each affecting a different patient. These included a tingling sensation

after acupuncture, herpes zoster, and dyspepsia. The latter two events were thought to be unrelated to the treatments.

Zhou et al²⁰ reported that in their EA-plus-WM group, one patient presented with abnormal sensations in the throat; another, with loss of appetite and bloating; and six, with subcutaneous hematoma. The incidence of adverse drug reactions in the same group was 6.06%. In the WM group, one patient presented with severe liver dysfunction, meeting the exclusion criteria, and thus quit the study; two patients presented with

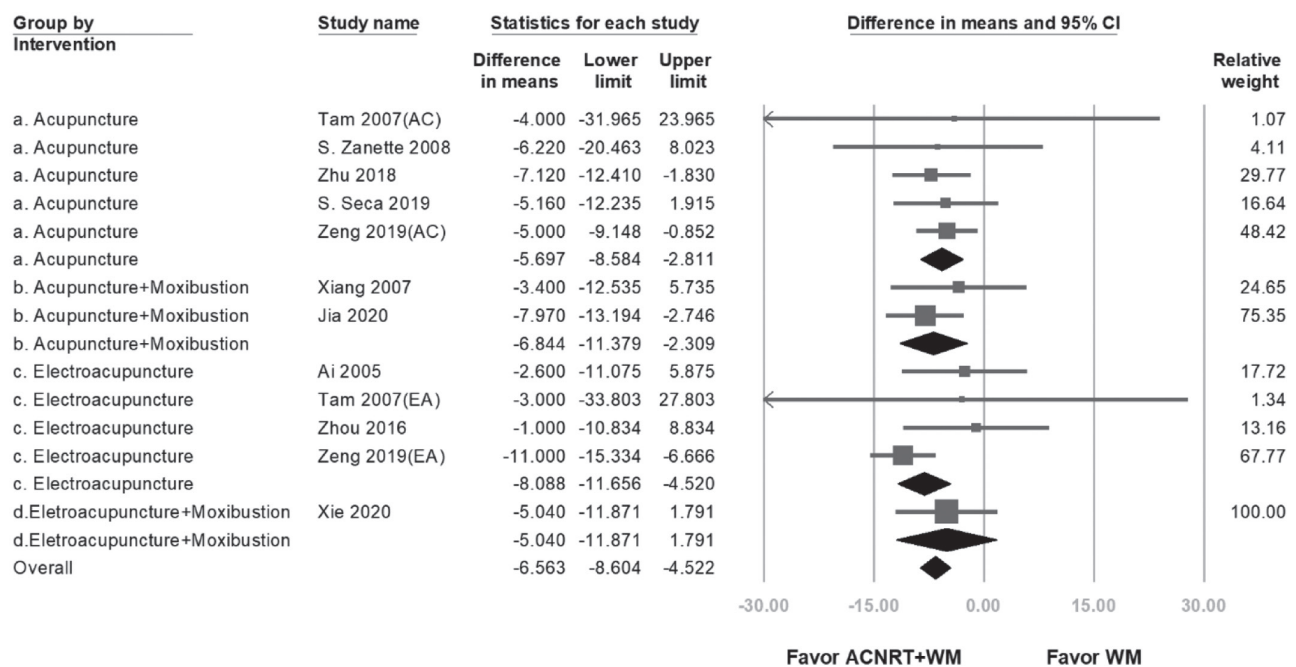


Fig. 4 Improvement in erythrocyte sedimentation rate (ESR) associated with acupuncture and related techniques vs western medicine in the sampled rheumatoid arthritis patients.

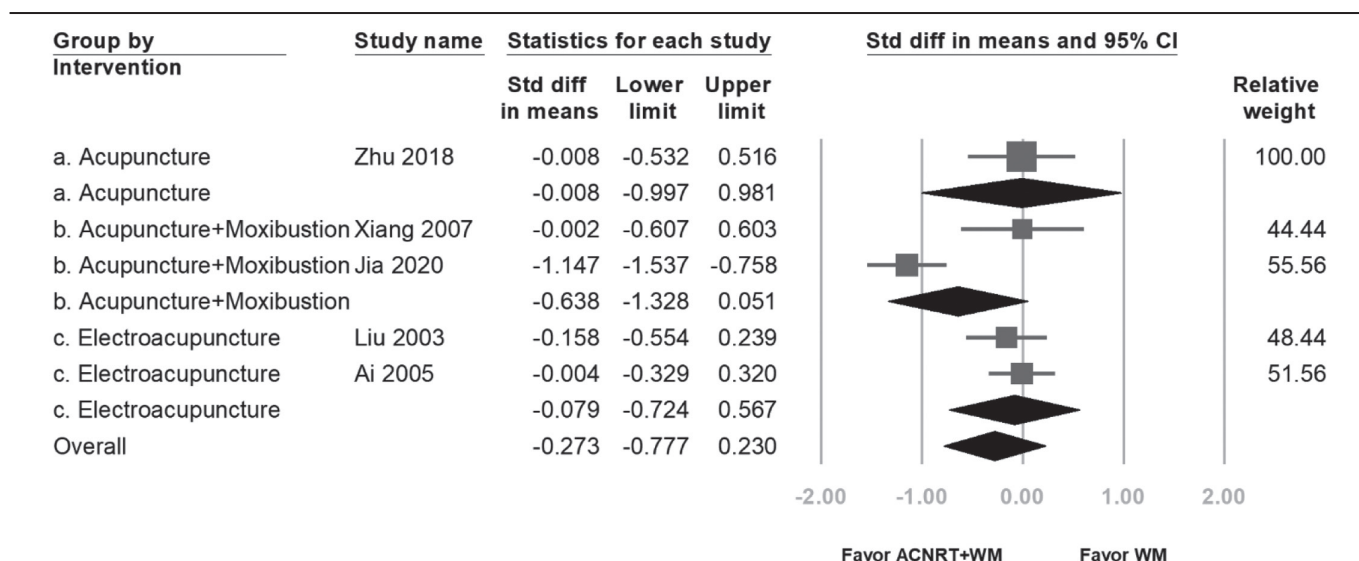


Fig. 5 Improvement in the rheumatoid factor (RF) associated with acupuncture and related techniques vs western medicine in the sampled rheumatoid arthritis patients.

dyspepsia; and one, with mild leukopenia. This group’s incidence of adverse drug reactions was double that of its EA-plus-WM counterpart.

Kao et al²⁵ reported that both their acupuncture-plus-moxibustion group and their WM group included two patients who presented with nausea, vomiting, and dyspepsia. However, all four of them had their symptoms relieved after treatment.

Xie et al²⁶ reported that four patients presented with mild liver dysfunction, including one in their EA-plus-moxibustion-plus-WM group and three in their WM-only group. Their conditions improved after taking silymarin tablets, and all remained in the study. Three other patients experienced leukopenia, including one in the EA-plus-moxibustion-plus-WM group and two in the WM group. After taking leucogen tablets, their leukocyte counts returned to normal, and they continued treatment.

3.9. Publication bias

An Egger’s test revealed no significant publication bias ($p = 0.306$). The funnel plot of the relevant mean differences is shown in Fig. 8.

4. DISCUSSION

Covering 12 RCTs published between January 2003 and December 2020, this article is believed to be the first meta-analysis of whether ACNRT integrated with WM improves RA patients’ inflammatory markers and clinical characteristics more than WM alone does. As this was confirmed, we suggest that ACNRT combined with WM is a useful modality for improving RA patients’ conditions.

RF, CRP, and ESR are among the serial biomarkers and acute-phase reactants in the 2010 ACR/EULAR RA classification

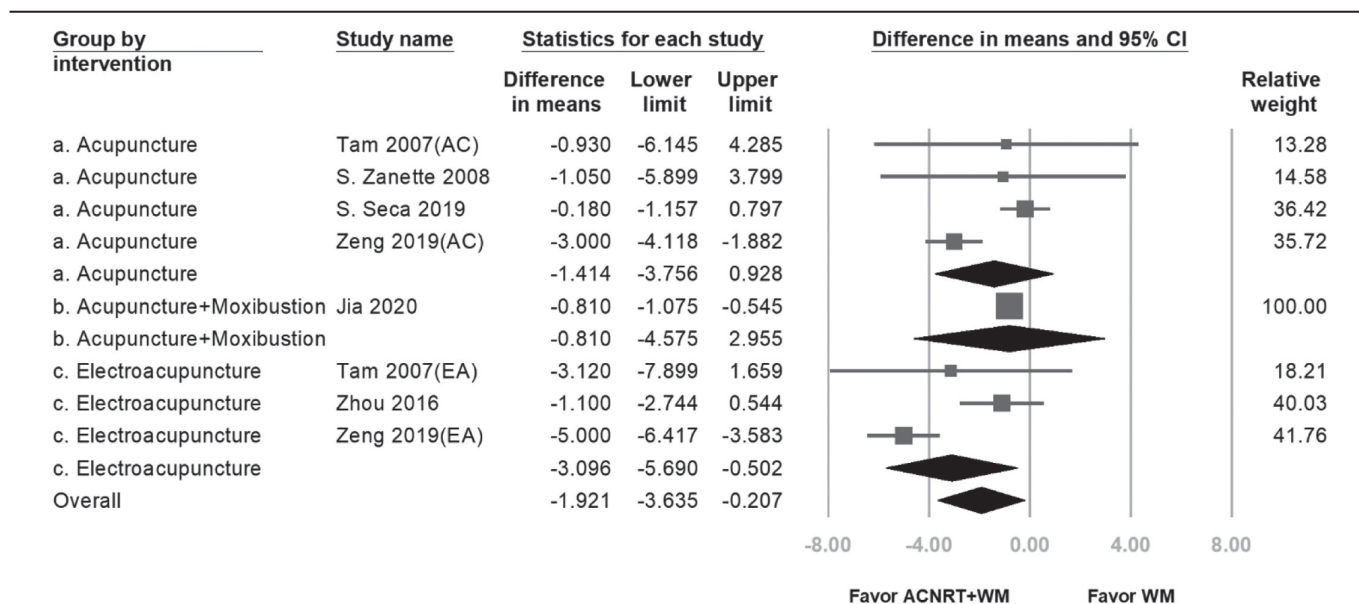


Fig. 6 Improvement in swollen joints count (SJC) associated with acupuncture and related techniques vs western medicine in the sampled rheumatoid arthritis patients.

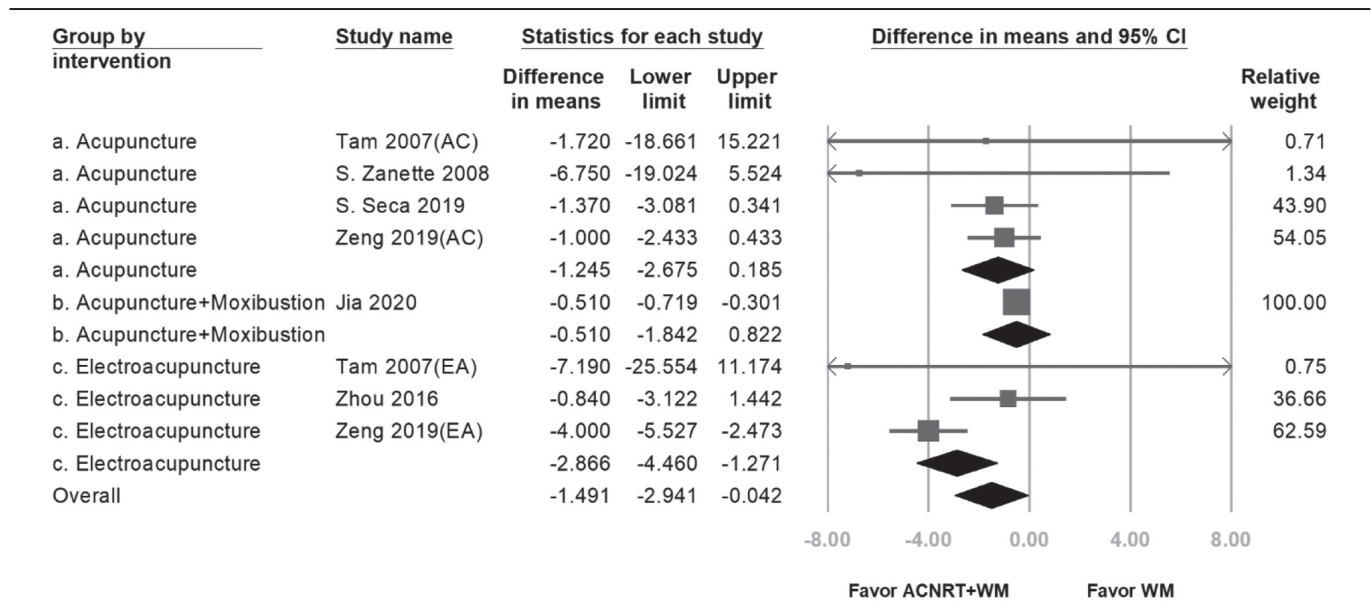


Fig. 7 Improvement in tender joints count (TJC) associated with acupuncture and related techniques vs western medicine in the sampled rheumatoid arthritis patients.

criteria. Acute-phase reactants ESR and CRP are important when assessing the degree of activity of chronic inflammatory lesions, because increases in the levels of these clinical inflammatory markers indicate high disease activity,²⁷ and the combination of these three indicators can be taken to confirm a diagnosis of RA.²⁸

DAS-28 has been used very extensively both in daily practice and RA clinical trials and has demonstrated its usefulness in monitoring this disease's evolution.²⁹ It provides a composite score derived from four measures including TJC, SJC, ESR, and a global assessment of health. In the current study, integrated ACNRT/WM treatment improved CRP and ESR more than WM did but had no such superior effect on RF.

Acupuncture therapy for RA is one of the specialties of Chinese medicine. It is believed that electrical impulses and moxibustion's

heat effect strengthen stimulation at acupoints. Several possibly important mechanisms for this have been reported, including anti-inflammatory effects, antioxidative effects, and regulation of immune-system function.³⁰ Some prior findings might provide explanations for the therapeutic effects of ACNRT treatment on RA. He et al,³¹ for example, pointed out that EA treatment resulted in enhanced immunostaining for vasoactive intestinal peptide (VIP), a potent anti-inflammatory neuropeptide, in the synovial tissue. Other studies found that ACNRT had antioxidative effects, such as inducing increased activity by superoxide dismutase and catalase in the serum of RA patients, alleviating oxidative stress and inflammation, and improving antioxidant and energy-metabolic status.³²⁻³⁴ Moreover, ACNRT has been found to regulate immune function as IgG, IgA, and IgM decrease.³⁵⁻³⁸

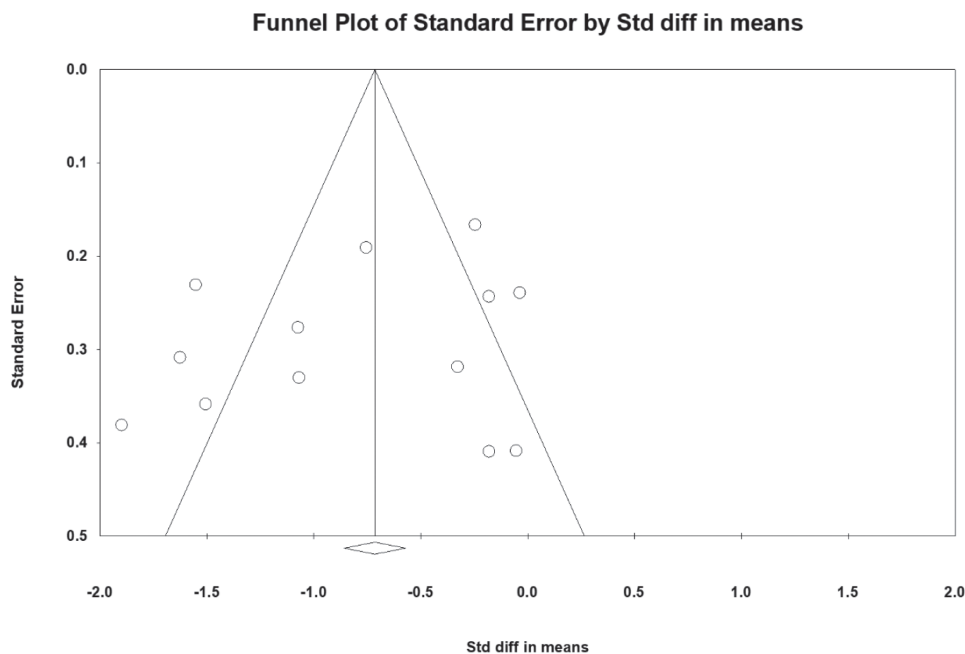


Fig. 8 Funnel plot for mean difference in publication bias.

Interpretation of the results of clinical trials requires assessment not only of the statistical significance of treatment differences but also of their clinical importance. The minimal clinically important improvement (MCII)/minimal clinically important changes/minimal clinically important difference (MCID) are those improvements (or deteriorations) recognized as meaningful. Few studies have attempted to define clinically important changes in RA activity measures, and among them, there has been little consensus. According to Wolfe et al,³⁹ MCID for improvement and worsening of pain in RA is about 0.5–1.1 units, and according to our analysis of VAS's WMD, this standard was met. Ward et al⁴⁰ reported that MCII for RA were -0.375 for HAQ, -1.2 for DAS-28-ESR, and -1.0 for DAS28-CRP, and our analysis suggests that this standard was met in the case of CRP and ESR values. Therefore, we can conclude that ACNRT combined with WM is therapeutic for RA at the MCII level.

Our subgroup analysis results imply that EA may serve as an adjunct, by reducing TJC, SJC, and HAQ more than acupuncture does, either alone or in combination with moxibustion. However, our results do not suggest that acupuncture plus moxibustion has any advantages over acupuncture alone. Some previous studies may provide explanations for the therapeutic effects of EA. Tian et al,⁴¹ for example, reported that EA might work best in situations that involve significant muscle spasms, while Ulett et al⁴² indicated that the analgesic effect of EA was greater than that of manual acupuncture.

There are some limitations to this study. First, when performing meta-analysis, the outcome variable is continuous, and standard meta-analytic approaches assume that the primary studies report the sample mean and standard deviation of the outcome. However, when the outcome is skewed, authors sometimes summarize the data by reporting the sample median and the first and third quartiles and do not report the mean or standard deviation. In such cases, we used the quantile estimation method⁴³ to derive the mean and standard deviation from the median and first and third quartiles. This method has a considerably larger average relative error for estimating sample standard deviation than for estimating the sample mean. Hence, outcomes might demonstrate high heterogeneity, as indeed could be observed here in the cases of CRP, SJC, TJC, and HAQ. Second, most of the sampled studies contained little or no description of their processes of randomization, allocation concealment, or blinding. And third, small sample sizes, loose experimental designs, different treatment durations, inconsistent interventions, and different sites of intervention would have affected the sampled studies' outcomes to varying degrees and led to a certain heterogeneity in their results.

In conclusion, from the foregoing review and meta-analysis, we can conclude that ACNRT combined with WM is beneficial to the clinical conditions of RA and can reduce laboratory markers and improve clinical symptoms to a meaningful (MCII) degree. Such a combination also appears to be both more effective and safer than WM monotherapy. On that basis, we recommend that ACNRT integrated with WM be applied in the clinical treatment of RA. However, these conclusions are limited by methodological considerations. Thus, longer term, high-quality, repeatable, multicenter RCTs with larger sample sizes should be conducted to confirm them.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://links.lww.com/JCMA/A115>.

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