

Wrist-ankle acupuncture has a positive effect on chronic pain: a systematic review and meta-analysis

Meihua Pan¹, Yanyan Lan², Zhifu Wang^{3,*}

Abstract

An increasing number of practitioners are using acupuncture methods such as wrist-ankle acupuncture (WAA) to treat pain. We aimed systematically to evaluate the effects of WAA on cancer pain, primary pain, chronic musculoskeletal pain and pathological neuralgia pain. Nine electronic databases were searched for randomized controlled trials (RCTs) on WAA from inception of the data base to July 31, 2022. RCTs within the inclusion and exclusion criteria were included in the study. Outcomes included pain score, clinical efficacy (overall efficiency), and occurrence of adverse events. The risk of bias was evaluated using the Cochrane Collaboration criteria and meta-analysis was performed using RevMan 5.4.1 software to determine the effect of WAA intervention and statistical significance was set a $P < 0.05$. A total of 19 RCTs were included in the meta-analysis including 1,380 participants, consisting of 673 who had received WAA alone or in combination with other treatments (WAA group, WG) and 707 who did not receive WAA (control group, CG). Subgroup analyses were performed according to different chronic pain types and occurrence of adverse events of WAA versus oral or non-oral drug therapy. The WG had better analgesic effects on various types of chronic pain than CG ($P < 0.00001$) and clinical efficacy ($P < 0.00001$). Additionally, WAA was shown to be safer than oral medication ($P = 0.09$). Therefore, WAA has good analgesic efficacy for several types of common chronic pain alone and in combination with other therapies, and it is safer than oral medication. However, more high-quality randomized controlled trials are needed in the future to support this evidence.

Keywords: Chronic pain, Meta-Analysis, Randomized controlled trial, WAA, Wrist-Ankle Acupuncture

Graphical abstract: <http://links.lww.com/AHM/A48>

Introduction

The International Association for the Study of Pain (IASP) redefined chronic pain as pain that persists or recurs for more than 3 months, including chronic primary pain, cancer-related pain, postoperative/traumatic pain, secondary musculoskeletal pain, neuropathic pain, etc. Many studies have shown that the development of chronic pain involves multiple biological, psychological and social factors^[1-2]. According to

the literature, approximately 20% to 30% of the global population has chronic pain^[3]. Healthcare practitioners treat chronic pain in a variety of ways, including medical interventions, lifestyle change recommendations, and other forms of treatments depending on the type and cause of pain and other patient specific factors to provide patients with an optimized treatment plan^[4]. An important component of multimodal combination therapy for chronic pain is the combination of medications, and the key to pharmacotherapy is finding a balance between effective treatment and acceptable side effects^[5]. Many of the medications used to treat chronic pain are central nervous system depressants that may impair patient's mobility, memory, and motor abilities^[6].

With the development of traditional Chinese medicine, an increasing number of practitioners are using acupuncture such as wrist-ankle acupuncture (WAA) for analgesia^[7]. WAA was developed by Professor Zhang XS in the 1970s^[8], based on the experience of electrical stimulation therapy for the treatment of mainly neurological disorders, and inspired by biological evolution, embryonic development, traditional meridian theory, auricular acupuncture, acupuncture points, and acupuncture methods. The WAA is a special acupuncture therapy developed from practice, which is easy to perform. It has significant analgesic effect, and with only two entry points (wrist and ankle), and the characteristics of selecting points according to the area and treating a wide range of diseases throughout the body^[8]. The analgesic mechanism of WAA is still being explored, with some studies on the following aspects:

Meihua Pan and Yanyan Lan contributed equally to this work.

¹ The Department of Rehabilitation Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, China; ² The Department of Rehabilitation Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, China; ³ Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, China

*Corresponding author. Zhifu Wang, Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou 350122, China, E-mail: 2007015@fjtc.edu.cn.

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meridian mechanism, neurohumoral mechanism, and biological mechanism. However, further in-depth studies are needed on acupuncture-specific points, acupuncture points, and techniques for different diseases^[9]. In recent years, a large number of scholars have used clinical trials to demonstrate the positive effects of WAA alone or in combination with other treatments (such as drugs^[10], conventional acupuncture^[11], plasters^[12], and moxibustion^[13]) for chronic pain, but there are no systematic evaluation studies and related evidence-based clinical practice guidelines for the treatment of chronic pain with WAA.

Therefore, the purpose of this meta-analysis was to systematically evaluate the effects of WAA on cancer pain, primary pain, chronic musculoskeletal pain and pathological neuralgia, which are common types of chronic pain, and to provide scientific reference for the development of intervention strategies for these types of pain.

Materials and methods

The study has been registered on the ROSPERO website (registration number CRD42022357766), see Supplementary File 1, <http://links.lww.com/AHM/A47>, for full details of search strategy.

Literature search

Chinese and English databases were searched, including China National Knowledge Infrastructure (CNKI), Wanfang, VIP, Chinese Biomedical Literature Database (CBM), PubMed, the Cochrane Library, Embase, Web of Science (WOS), and Foreign Medical Information Resource Retrieval Platform (FMRS). Publications available from the inception of databases to July 31, 2022, were reviewed to find the appropriate randomized control trials on the effects of WAA for chronic pain. Subject terms and free word searches were used as search strategy. Chinese search terms (wrist-ankle acupuncture, wrist acupuncture, ankle acupuncture) and English search terms (Wrist-Ankle Acupuncture, WAA, Wanhuaizhen, Wrist Ankle Acupuncture related to WAA) and terms related to chronic pain (chronic pain, cancer pain, migraine, fibromyalgia, arthralgia, neuralgia, chronic low back pain, dysmenorrhea, arthritis, trigeminal neuralgia, chronic central neuropathic pain, chronic peripheral neuropathic pain, chronic postoperative pain, etc.) were used. The detailed search information is shown in the Supplementary File 1, <http://links.lww.com/AHM/A47>.

Inclusion criteria for the study

Research patients

Patients with chronic pain aged ≥ 18 years and with pain duration ≥ 3 months, regardless of chronic pain disease category, cause, and current treatment modality, regardless of race, nationality, etc.

Chronic pain diagnostic criteria were based on the latest definition of chronic pain by the International Association for the Study of Pain (IASP)^[1-2].

Experimental and control groups

The WG consisted of patients treated with WAA alone or combined with other treatments (drugs, conventional acupuncture, poultices and moxibustion, etc), while CG consisted of patients not treated with WAA but in the treatments such as analgesics (no restrictions on the type of medication—NSAIDs, herbs, etc), physical factor therapy, rehabilitation training therapy, conventional acupuncture, plasters, and moxibustion, etc.

Outcomes

One or two of the following outcomes were available: (1) Pain intensity score, such as the Visual Analogue Scale (VAS)^[14] or the Numerical Rating Scale (NRS) for pain^[14]; (2) Occurrence of adverse events; (3) Clinical efficacy (overall effectiveness)^[15].

The Clinical efficacy of the interventions were classified into four levels: (1) complete remission (CR): the pain basically disappeared after treatment, and there was no recurrence during followup; (2) partial remission (PR): after treatment, pain was significantly reduced, and sleep was not affected; (3) mild remission (MR): the pain was relieved after treatment, but sleep was often affected; (4) no remission (NR): no relief of pain. [overall effectiveness = $n(\text{CR} + \text{PR} + \text{MR})$].

Types of study

Only RCTs were considered for the study.

Exclusion criteria

The exclusion criteria included the following: (1) WAA was not used as one of the primary therapies in the study; (2) duplicate publications or plagiarized literature; (3) the literatures lacked original data or had incomplete research data; (4) literature on studies without pain as an outcome indicator; (5) research on animal experiments, reviews, systematic evaluations, thesis, and case reports.

Literature extraction

Extraction and cross-checking was performed independently by two researchers. In case of disagreement, a third party was asked to make a judgment. The basic data extracted mainly included the first author of the literature, year of publication, number of participants in WG and CG, age of participants, the duration of disease, intervention, time of assessment, control measures, and outcomes of effect evaluation. If key information is missing, the authors of the report were contacted to obtain this information.

Risk of bias assessment

Risk of bias was assessed independently using the Cochrane Assessment Tool^[16], which included the following seven domains: “generation of random sequences, allocation concealment, blinding of subjects

and intervention providers, blinding of outcome evaluators, incomplete outcome data, selective outcome reporting, and other sources of bias"; each question could be rated as follows: yes (+), low risk of bias; unclear (?), risk of bias unclear; and no (-), high risk of bias.

Data analysis

Relevant data from the included literature were processed through the RevMan 5.4.1 software. Dichotomous variables were described by relative risk (RR) and continuous variables were described by standardized mean differences (SMD). In each analysis, I^2 was used to measure the statistical heterogeneity between trials. If $P > 0.1$ and $I^2 < 50\%$, a fixed-effects model was used for analysis due to the homogeneity of trials; if $P < 0.1$, $I^2 \geq 50\%$, a random-effects model was used. If $P < 0.1$ and the source of heterogeneity was unknown, a descriptive analysis was used rather than a meta-analysis. If moderate clinical heterogeneity was found, subgroup analyses were performed, using sensitivity analyses to explore the effect of fixed-effects and random-effects model analyses on the results of heterogeneity and the effect of any assumptions^[17].

Results

Results of literature search

A total of 1,500 articles were detected from the nine databases. Thereafter, 493 duplicates were excluded by using Endnote20 software, 807 articles were removed after screening the title and abstract, and 181 articles were excluded after reading the full text, thus 200 articles remained. Additionally, 78 articles did not match the study population, 32 articles were non-randomized controlled trials, 21 articles did not match the intervention and control measures, 40 articles did not match the outcomes, one article did not match the outcomes, five articles lacked data on the outcomes, the full texts of two articles were not available, and two repetitive articles were removed. Finally, 19 studies were included for meta-analysis. The article identification and selection process is shown in Figure 1.

Characteristics of included studies

The general information of the included studies is shown in Table 1. Participants were between the ages of 20 and 65 years, with a female predominance. Of the included studies, two studies^[26,30] reported WAA interventions alone and 15 studies^[10–12,18–19,21–25,27–29,31–32] reported WAA in combination with other treatments. The number of studies reporting chronic cancer, primary pain (primary dysmenorrhea and migraine), musculoskeletal, and neuropathic pain (postherpetic neuralgia and neuropathic pain after endoscopic surgery for lumbar disc herniation) were four^[12,23–24,27], five^[21,25–26,28,30], eight^[10–11,13,18,20,29,31–32], and two^[19,22], respectively. The specific characteristics of the included WAA intervention studies are shown in Table 2.

Risk of bias in individual trials

The risk of bias was moderate (Figure 2). More than half of the studies in this entry of allocation concealment showed a high risk of bias, with 15 studies^[11–13,18–19,23–32] reporting the generation of randomized sequences, yet only one study^[32] reported blinding of outcome evaluators to subjects and intervention providers.

Data analysis

The results of the meta-analysis are summarized in Table 3.

Pain scores

All 19 studies reported pain scores before and after intervention in WG (WAA alone or WAA combined with other treatments) versus CG (other treatments), of which 15 studies^[10–11,13,18–22,25–31] reported pain scores using VAS and four studies^[12,23–24,27] reported pain scores using NRS. Subgroup analysis according to different types of chronic pain showed that WG was more effective than CG in reducing chronic cancer pain, primary pain, chronic musculoskeletal pain, and neuropathic pain. The difference in pain scores between the two groups was statistically significant (SMD = -0.88, 95% CI = -1.15 to -0.60; $I^2 = 83\%$). This included the meta-analysis comparing the WG and CG in four studies^[12,23–24,27] reporting pain scores for cancer pain (SMD = -1.11, 95% CI = -1.71 to -0.51; $I^2 = 80\%$); five studies^[21,25–26,28,30] reporting primary pain (SMD = -0.93, 95% CI = -1.80 to -0.07; $I^2 = 93\%$), eight studies^[10–11,13,18,20,29,31–32] reporting chronic musculoskeletal pain (SMD = -0.70, 95% CI = -0.97 to -0.43; $I^2 = 64\%$); and two studies^[19,22] reporting neuropathic pain (SMD = -0.91, 95% CI = -1.70 to -0.11; $I^2 = 78\%$). The forest plot for subgroup analysis is shown in Figure 3. The funnel plot (Figure 4) indicated that the publication bias was mild, and the sensitivity analysis (SMD = -0.73, 95% CI = -0.84 to -0.62; $P < 0.00001$) revealed that the model was relatively stable.

Clinical efficacy (overall efficiency)

Only 15 studies reported the clinical efficacy of WG versus CG after the intervention, with subgroup analysis based on different types of chronic pain. The results showed that clinical efficacy (overall efficiency) in the WG was better for chronic cancer pain, primary pain, chronic musculoskeletal pain, and neuropathic pain when compared to the CG which was statistically significant ($RR = 1.23$, 95% CI = 1.11 to 1.35; $I^2 = 70\%$), and this included the meta-analysis comparing clinical efficacy between the WG and CG for cancer pain^[12,23–24,27] ($RR = 1.21$, 95% CI = 1.08 to 1.36; $I^2 = 0\%$); and four studies reporting primary pain^[21,25,28,30] ($RR = 1.46$, 95% CI = 1.21 to 1.75; $I^2 = 46\%$). In five studies reporting chronic musculoskeletal pain^[10,13,20,31–32] and two studies reporting neuropathic pain^[19,22], both WG and CG were shown to improve analgesic efficacy after the intervention, and the difference in clinical efficacy (overall

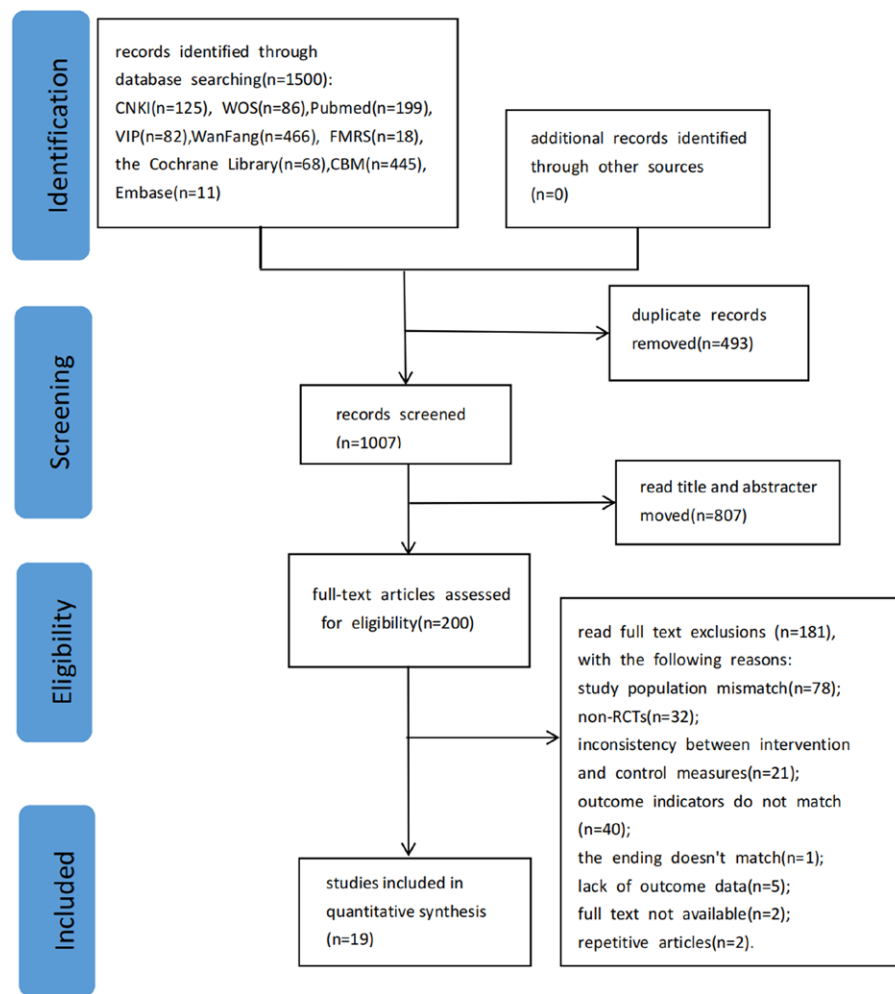


Figure 1. Flow chart diagram of trial identification and selection. RCT: Randomized controlled trial.

efficiency) between the two groups (WG *vs.* CG) for both chronic musculoskeletal pain and neuropathic pain was statistically significant at ($RR = 1.13$, 95% CI = 0.94 to 1.37; $I^2 = 84\%$) and ($RR = 1.10$, 95% CI = 0.98 to 1.23; $I^2 = 0\%$), respectively. The subforest plots are shown in Figure 5.

Occurrence of adverse events

A total of 8 studies^[11–12,18,22–23,25,27,32] reported the occurrence of adverse events, with the main adverse reactions for WAA being subcutaneous bleeding and dizziness, and the main adverse reactions for drug therapy being dizziness, nausea, vomiting, drowsiness, constipation, and urinary retention. Subgroup analysis based on wrist-ankle acupuncture combined with oral medications (eg, Western and Chinese herbs) or wrist-ankle acupuncture combined with non-oral medications (eg, conventional acupuncture, poultices, and moxibustion) showed that WAA was safer than oral medications in the treatment of chronic pain ($RD: -0.13$, 95% CI = -0.28 to 0.02; $P = 0.09$), with significant heterogeneity ($I^2 = 66\%$, $P = 0.02$). In terms of safety issues, WAA was similar to non-oral medications for chronic pain ($I^2 = 0\%$, $P = 0.99$), and the forest plot for subgroup analysis is shown in Figure 6.

Pain score for different outcome measures times

A total of 17 studies were included in this subgroup analysis, including 3, 5, 5, 4, and 2 studies reporting pain scores after 10 days, 2 weeks, 3 weeks, 4 weeks, and 3 months after treatment, respectively. The results showed that after 10 days, 2 weeks, 3 weeks, 4 weeks, and 3 months of treatment, the differences in pain scores between WG group and CG group were statistically significant ($RR = -0.74$, 95% CI = -0.99 to -0.49; $I^2 = 80\%$), with the forest plot for subgroup analysis shown in Figure 7.

Discussion

This meta-analysis is the first systematic evaluation of studies on the use of WAA alone or in combination with other treatments for chronic pain and included 19 randomized controlled studies with a total of 1,380 participants. Fourteen studies reported the generation of randomized sequences and only one study reported blinding evaluators and intervention providers to outcome, however, the evaluators were not blinded to results which may have been due to the particularity of acupoint selection of wrist-ankle acupuncture, the fact that participants can distinguish wrist-ankle acupuncture from other therapies such as drug therapy, and the

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Table 1
General information on included studies

First author (year)	Disease category	Average age (y)	Duration	Sample size (male/female)	Design (wrist-ankle acupuncture group vs. control group)			Outcome
					Interventions	Intervention time and dose	Measurement points	
Ye [11] 2022	Ankylosing Spondylitis	WG: 31.46 ± 8.02 CG: 32.56 ± 8.41	WG: (7.86 ± 4.47) y CG: (7.16 ± 4.27) y	WG: 35 (29/6) CG: 35 (30/5)	Both groups received HE WG: WAA + IN CG: OD	WG: 24 h/time, treatment every other day CG: 15 mg/time, once/d	① before the treatment, 3 and 10 d after the treatment; ⑦⑨ before the treatment and after the last treatment; ⑤ after the last treatment Before the treatment and after the last treatment	①⑤⑦⑨
Cui [13] 2022	Lumbar intervertebral disc herniation	40–80 y	WG: (2.12 ± 0.54) y CG: (2.28 ± 0.60) y	WG: 41 (27/14) CG: 41 (25/16)	WG: WAA + NOD + CG CG: NOD	WG: 1 h/time, once/d, 5 times/w CG: 30 min/time, 2 times/d	②⑥ before the treatment, 7 and 14 d after the treatment; ③④⑤⑥ after the last treatment	②③④⑤⑥⑧
Hu [12] 2021	Refractory bone metastases	WG ₁ : 43.51 ± 17.25 WG ₂ : 42.56 ± 15.89 CG ₁ : 43.19 ± 16.74 CG ₂ : 44.72 ± 15.39	WG ₁ : (9.0 ± 3.4) m WG ₂ : (8.7 ± 3.3) m CG ₁ : (8.5 ± 3.5) m CG ₂ : (8.5 ± 3.7) m	WG ₁ : 30 (17/19) WG ₂ : 31 (19/12) CG ₁ : 29 (16/13) CG ₂ : 32 (18/14)	WG ₁ : WAA + CG ₁ WG ₂ : WAA + CG ₂ CG ₁ : NOD CG ₂ : NOD	WG ₁ : once/d, 1 h/d + CG ₁ WG ₂ : WG ₁ + CG ₂ CG ₁ : 1 patch/part, once/d, 24 h/time CG ₂ : 1 patch/part, once/d, 24 h/time	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑪ before the treatment, 2, 4, and 6 w after the treatment; ⑥ after the last treatment ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑤⑩
Jiang [18] 2021	Knee osteoarthritis	WG: 51.88 ± 5.79 CG: 52.61 ± 5.83	WG: (4.92 ± 3.76) y CG: (4.57 ± 3.69) y	WG: 60 (22/38) CG: 60 (25/35)	WG: WAA + CG CG: NOD	WG: 1 h/time, once/d CG: once/d, 60 min/time, follow up 6 m	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑪ before the treatment, 2, 4, and 6 w after the treatment; ⑥ after the last treatment ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑤⑩
Lv [10] 2021	Stage II and III femoral head necrosis	WG: 44.85 ± 4.25 CG: 45.58 ± 5.21	WG: (7.03 ± 2.34) m CG: (6.90 ± 2.25) m	WG: 40 (29/21) CG: 40 (26/24)	WG: WAA + CG CG: OD + NOD	WG: 12 h/time, once/d CG: 5 tablet/time, 3 times/d; 200 times/d, completed in 3 times	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑥⑲
Huang [19] 2021	Neuropathic pain after endoscopic surgery for extreme lateral lumbar disc herniation	WG: 55.30 ± 12.61 CG: 51.73 ± 14.19	WG: (8.15 ± 4.05) y CG: (8.50 ± 4.50) y	WG: 30 (16/14) CG: 30 (18/12)	WG: WAA + CG CG: OD	WG: 30 min/time, 3 times/w CG: 1 tablet on the first day, 1 tablet in the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑥⑲⑳
Lv [20] 2021	Later period of ankle trauma	WG: 35.90 ± 7.74 CG: 33.27 ± 7.89	WG: (7.67 ± 2.02) m CG: (7.23 ± 2.11) m	WG: 30 (21/9) CG: 30 (23/7)	WG: WAA + CG CG: NOD	WG: WAA + CG CG: NOD	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑥⑲⑳
Yang [21] 2020	Primary dysmenorrhea	WG: 23.0 ± 3.7 CG: 21.0 ± 5.1	WG: (3.0 ± 1.3) y CG: (2.0 ± 1.9) y	WG: 30 CG: 30	WG: WAA + CG CG: NOD (Guanyuan, Zigong, Ciliao, Sanyinjiao)	WG: start treatment 3 d before menstruation, 30 min/time, once/d CG: 20 min/once hole, once/d	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑥
Mei [22] 2020	Postherpetic neuralgia	WG: 61.45 ± 5.85 CG: 61.59 ± 5.93	WG: (2.71 ± 0.64) y CG: (2.79 ± 0.70) y	WG: 33 (18/15) CG: 32 (17/15)	WG: WAA + CG CG: NOD (Jiraji)	WG: pull the needle in the morning of the second day, once/d CG: 30 min/time, once/d, 5 times/w	①⑩ before the treatment and after the last treatment; ⑤⑥ m after the last treatment; ①⑥⑲⑳ before the treatment, 2 and 4 w after the treatment and the morning and 1 tablet on the second day, and then 3 times/d, 1 capsules/time WG: 10–12 h/time, once/d CG: 3 times/d	①⑤⑥⑲⑳

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Table 1
(Continued)

First author (year)	Disease category	Average age (y)	Duration	Sample size (male/female)	Design (wrist-ankle acupuncture group vs. control group)			Outcome
					Interventions	Intervention time and dose	Measurement points	
Fu [23] 2019	Intractable cancer pain	WG: 66 ± 12 CG1: 64 ± 15 CG2: 65 ± 12	WG: (8.2 ± 3.5) m CG1: (9.0 ± 3.3) m CG2: (8.2 ± 3.5) m	WG: 18 (10/8) CG1: 18 (10/8) CG2: 17 (9/8)	WG: WAA + CG1 CG1: OD CG2: NOD + CG1	WG: 1 h/time CG1: oral dose according to pain intensity CG2: 1 h/time	Before the treatment and after the last treatment	①④⑤⑥⑧⑫
Liu [24] 2019	Moderate to severe lung cancer bone metastases Pain	WG: 63.92 ± 8.47 CG: 64.08 ± 8.52	No mention	WG: 43 (28/12) CG: 40 (26/14)	WG: WAA + CG CG: OD	WG: patients with moderate pain, 10 h/time, patients with severe pain 12 h/time, once/d CG: initial dose 10 mg/time, once/12 h, adjust dose based on intensity WG: 2 h/time, once/d; take twice in the morning and after dinner CG: 2 tablet/time,	Before the treatment and after the last treatment	②③④⑥⑫
Gao [25] 2019	Migraine	WG: 36.28 ± 3.32 CG: 35.92 ± 3.73	WG: (5.12 ± 1.74) y CG: (4.96 ± 1.81) y	WG: 20 (12/8) CG: 20 (11/9)	WG: WAA + OD + CG CG: OD	WG: 2 h/time, once/d; take twice in the morning and after dinner CG: 2 tablet/time,	Before the treatment and after the last treatment	①⑤⑫
Ying [26] 2019	Migraine	WG: 39.89 ± 3.45 CG: 39.86 ± 3.43	No mention	WG: 34 (19/15) CG: 34 (18/16)	WG: WAA CG: NOD	WG: 40 min/time, once/d CG: 40 min/time (3 times), once/d	Before the treatment and after the last treatment	①④⑫
Wu [27] 2019	Intractable cancer pain	WG: 56 ± 3 CG: 58 ± 3	WG: (3.5 ± 1.2) y CG: (2.5 ± 1.1) y	WG: 30 (15/15) CG: 30 (16/14)	WG: WAA + CG CG: OD (morphine injection for breakthroughs)	WG: 12 h/time, once/d CG: different drugs and different doses are given according to cancer pain accompanied by pain in other parts; once/d	①the day before treatment, 2, 4, 6, 8, 10 d after the treatment, 3 and 7 d after the last treatment; ⑫the day before treatment, 2, 6, 10 d after the treatment and 7 d after the last treatment	①⑤⑥⑫
Zhou [28] 2018	Primary dysmenorrhea	WG: 22 ± 3 CG: 22 ± 2	WG: (5.43 ± 2.38) y CG: (5.03 ± 2.80) y	WG: 30 CG: 30	WG: WAA + CG CG: NOD	WG: 30 min/time CG: Shenque, Mild 4 zhuang, moderate 6 zhuang. Severe 8 zhuang, once/d, until pain relief	Before the treatment and after the last treatment	①⑥⑫
Zhang [29] 2016	Knee osteoarthritis	WG: 45–65 CG: 50–64	WG: 3 m–6 y CG: 3 m–6 y	WG: 20 (7/13) CG: 20 (6/14)	WG: WAA + CG CG: NOD	WG: 30 min/time, once/d CG: a total of 3 actions, each action 5 times, once/d	Before the treatment and after the last treatment	①⑨
Wang [30] 2013	Primary dysmenorrhea	WG: 21 ± 1 CG1: 21 ± 2 CG2: 21 ± 2	WG: (65.2 ± 28.0) m CG1: (55.8 ± 35.6) m CG2: (63.0 ± 30.1) m	WG: 30 CG1: 30 CG2: 30	WG: WAA CG1: NOD (Sanyinjiao, Guanyuan) CG2: OD	treatment was started 3 d before menstruation, once/d, until pain relief	Before the treatment and after the last treatment	①⑥⑫

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Table 1

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Design (wrist-ankle acupuncture group vs. control group)

First author (year)	Disease category	Average age (y)	Duration	Sample size (male/female)	Interventions	Intervention time and dose	Measurement points	Outcome
He [31] 2009	Lumbar disc herniation	WG: 54.73 ± 6.8 CG: 53.60 ± 7.55	WG: (13.40 ± 5.2) w CG: (13.63 ± 5.0) w	WG: 90 (51/49) CG: 90 (48/42)	WG: WAA + CG CG: NOD (Ashi point on the waist, waist Jiaji point, Dachangshu)	WG: 30 min/time, once/d CG: 30 min/time, adjust every 10 min	Before the treatment and after the last treatment	①②⑩
Chan [32] 2009	Chronic neck pain	WG: 52.4 CG: 53.9	3 m or more	WG: 22 (10/12) CG: 27 (8/19)	WG: WAA + NOD CG: SA + NOD	NE: standardized neck exercises lasting approximately 10 min were performed within 10 min prior to the intervention, 30 min/time, 2 times/w WG: alternate 3/100 HZ for 3s; 30 min/time, 2 times/w CG: no "tingling" sensation during stimulation (e.g., microcurrent electrotherapy and transcutaneous spinal analgesia)	Before the treatment and after the last treatment	②⑤⑦⑫

BA: Body acupuncture; CG: Control group; CWMWT: Conventional Western Medicine Treatment; FHNC: Femoral head necrosis capsule; FT: Functional training; GG: Gabapentin capsules; GP: Gutong paste; GPMT: Ginger-partitioned moxibustion treatment; HE: Health Education; HJAO: Huaji Analgesic Ointment; IN: Intradermal needle; MC: Meloxicam capsules; MST: Muscle strength training; NE: Neck exercise; NOD: Nonoral drugs; OD: Oral drugs; OHT: Oxycodone hydrochloride treatment; OPR: Opioid pain relievers; SA: Sham acupuncture; ST: Strength training; TCMMT: traditional Chinese medicine wax therapy; THD: Tongqiao, Huoxue Decoction; TMT: Thermal moxibustion treatment; WAA: Wrist-ankle acupuncture; WG: Wrist-ankle acupuncture group. ①The Visual Analogue Scale, VAS; ②The Numerical Rating Scale, NRS; ③onset time of analgesia; ④duration of analgesia; ⑤the adverse reaction; ⑥the total effective rate; ⑦the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) scores; ⑧Kamofsky Performance Status score (KPS); ⑨changes in spinal mobility; ⑩the WOMAC score; ⑪Harris hip function score; ⑫recurrence; ⑬the Dermatology Life Quality Index Score (DLQI); ⑭Athens Insomnia Scale (AIS); ⑮the number of bursts of pain; ⑯The Chinese version of the European Cancer Investigation and Treatment Organization Quality of Life Questionnaire (EORTCQLQ-C30); ⑰the number of pains; ⑱symptom score of dysmenorrhea; ⑲constant peak torque; ⑳lumbar vertebral function assessment scale; ㉑the Northwick Park Neck Pain Questionnaire (NPQ); ㉒The Pain Self Efficacy Questionnaire (PSEQ); ㉓the Japanese Orthopedic Association (JOA); ㉔the Oswestry Disability Index (ODI); ㉕the modified MacNab standard; ㉖ankle range of motion; ㉗the American orthopedic foot and ankle society (AOFAS); ㉘Chinese medicine syndrome scores; ㉙serum inflammatory factors. OD: MC, FHNC, GC, Morphine, OHT, THD, ibuprofen. NOD: GP, HJAO, TCMMT, FE, TMT, BA, NE, SA, MST.

Table 2**Specific characteristics of the included wrist-ankle acupuncture studies**

First author (year)	Specification	Acupuncture angle	Acupuncture constituency	Intervention time	Course
Ye ^[11] 2022	0.25 mm × 40 mm	30°	Lumbar pain acupuncture bilateral L5, L6, neck and back acupuncture bilateral U5–U6, joint swelling and pain of the extremities	24 h at a time, treatment every other day	10 d
Cui ^[13] 2022	No mention	No mention	acupuncture points corresponding to the upper or lower limbs according to the division of the tenderness point	1 h at a time, once a day, 5 times a week	2 w
Hu ^[12] 2021	0.25 mm × 25 mm	30°	Ipsilateral U4–U6	1 h at a time, once a day	2 w
Jiang ^[18] 2021	0.25 mm × 25 mm	30°	Bilateral U2, L2	1 h at a time, once a day	20 d
Lv ^[10] 2021	0.25 mm × 25 mm	30°	According to the location of the knee joint tenderness of the patient, select the L1–L6 areas of the affected side for treatment	1 h at a time, once a day	20 d
Huang ^[19] 2021	0.25 mm × 25 mm	30°	Ipsilateral L1, L4, L5	12 h at a time, once a day	6 w
Lv ^[20] 2021	0.25 mm × 25 mm	30°	L4–L5	30 min at a time, 3 times a week	4 w
Yang ^[21] 2020	0.25 mm × 25 mm	30°	Ipsilateral L1–L6	10–12 h at a time, once a day	3 w
Mei ^[22] 2020	0.25 mm × 40 mm	30°	Bilateral L1	30 min at a time, once a day	Start treatment 3 d before menstruation, continuous treatment for 5 d/m × 3
Fu ^[23] 2019	0.25 mm × 25 mm	30°	U2	Pull the needle in the morning of the second day, once a day	5 d/w × 4
Liu ^[24] 2019	0.25 mm × 25 mm	30°	Select the same position of wrist and ankle on both sides according to the area	1 h at a time	No mention
Gao ^[25] 2019	0.25 mm × 25 mm	30°	The symptoms of the same side of the same area acupoints	Patients with moderate pain 10 h at a time, patients with severe pain 12 h at a time, once a day	more than 3 w
Ying ^[26] 2019	1.5 inches	30°	Select points according to the specific pain site	2 h at a time, once a day	7 d × 2
Wu ^[27] 2019	1.5 inches	No mention	Bilateral U3, U4 (main); bilateral U2, U5 (auxiliary)	40 min at a time, once a day	10 times
Zhou ^[28] 2018	0.20 mm × 25 mm	20°–30°	Epigastric pain (ipsilateral U1–U2); flank pain (ipsilateral U3–U4); full abdominal pain (bilateral U1–U2 and L1–L3); chest pain (ipsilateral U2, U3); lower back pain (bilateral L5–L6); pain radiates to the shoulder, plus ipsilateral U4–U5; combined insomnia plus bilateral U1; combined with frequent urination plus bilateral L1	12 h at a time, once a day	10 d
Zhang ^[29] 2016	0.25 mm × 25 mm	30°	L2	30 min at a time, once a day	1 menstrual cycle × 3
Wang ^[30] 2013	0.30 mm × 40 mm	30°	Affected side L2–L5	30 min at a time, once a day	10 times × 2
He ^[31] 2009	0.30 mm × 40 mm	30°	L1–L2	30 min at a time, once a day	1 menstrual cycle × 3
Chan ^[32] 2009	No mention	15°–30°	L4–L6	30 min at a time, once a day	10 d × 2, 2 d between the two treatments
	A wrist-ankle acustimulator device	No mention	Unilateral neck pain stimulates the ipsilateral wrist, bilateral neck pain stimulates the non-dominant wrist, scilicet U1–U6	30 min at a time, twice a week	1 m

fact that the intervention personnel could not be uncertain about the intervention received by the participants. Only two studies had wrist-ankle acupuncture alone as

an intervention, while the rest included wrist-ankle acupuncture in combination with other therapies. In total, four studies reported cancer pain, five studies reported

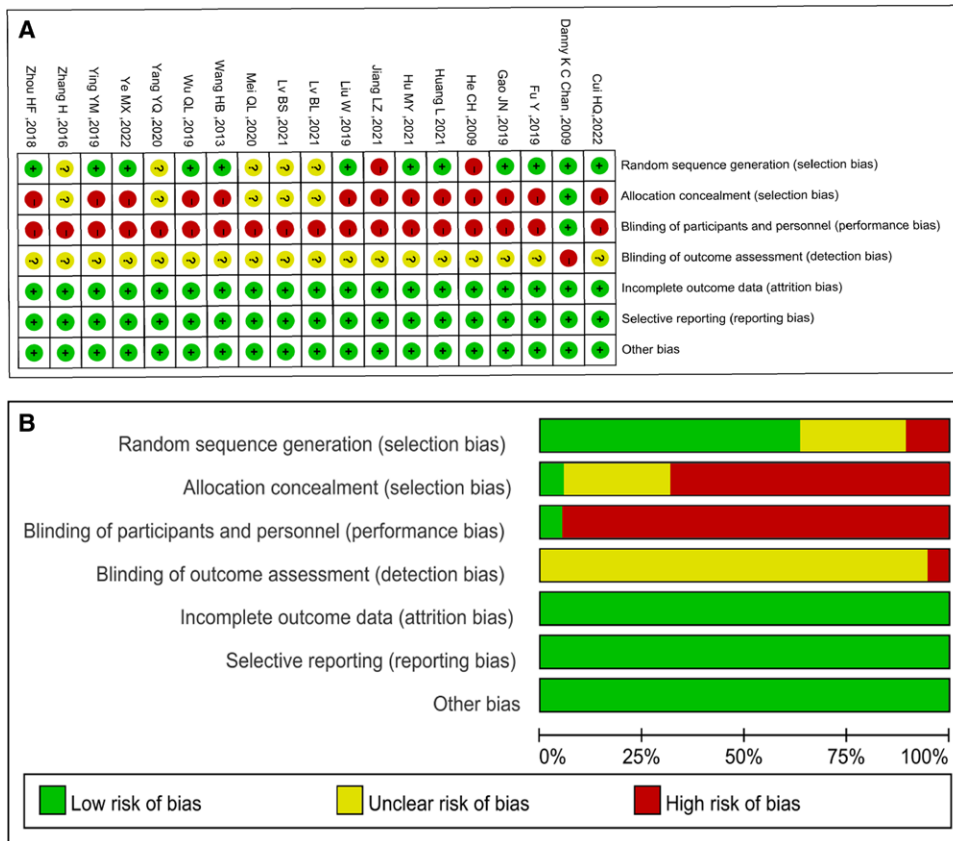


Figure 2. Risk of bias assessment using the Cochrane tools.

primary pain, eight studies reported chronic musculoskeletal pain, and two studies reported neuropathic pain.

Meta-analysis of pain score differences showed that WG was better than CG in reducing pain for chronic pain including chronic cancer, primary, musculoskeletal, and neuropathic pain. Overall meta-analysis of clinical efficacy showed that the clinical efficacy of WAA or WAA combined with other therapies was better than other treatments. Additionally, subgroup analysis of different measurement time points of outcomes showed that wrist-ankle acupuncture had good analgesic effect after 10 days, 2 weeks, 3 weeks, 1 month, 3 months. However, in the results of subgroup analysis, there was no statistical difference in clinical efficacy between the two groups for chronic musculoskeletal pain, which may be due to the superior clinical efficacy in the included studies over WG^[20]. Subgroup analysis was comparing WG and CG with oral drugs (such as western medicine and traditional Chinese medicine) or non-oral drugs (such as acupuncture, plaster and moxibustion, etc.) The results showed that the incidence of adverse reactions to carpal and ankle acupuncture was less than that of oral drugs, and the safety of wrist-ankle acupuncture was similar to non-oral drugs.

A 2014 meta-analysis by Li et al.^[33] showed that the analgesic effect of WAA or WAA combined with other therapies was significantly better than that of Western medicine, sham acupuncture, or body acupuncture. The meta-analysis only conducted subgroup analysis on the outcome of adverse reactions, and included a wide

range of pain categories. And the limited quantity and low quality of research quantity may lead to a lack of pertinence and persuasiveness of Li's study. However, this present study included studies on the treatment of chronic pain with WAA^[26,30] or WAA combined therapy^[10-13,18-25,27-29,31-32], and subgroup analysis was conducted for different outcomes, which was targeted and the results were more convincing and reliable.

Limitations

This present study also has the following limitations: First, the quality of the studies included in this meta-analysis is generally low, with incomplete reports on allocation concealment, random sequence generation, and blinding of outcome evaluators to subjects and intervention providers. Second, as WAA is a new type of acupuncture therapy, studies on wrist-ankle acupuncture outside of China are relatively immature with most of the selected studies being in Chinese literature. Clinical studies published in other languages may be omitted, which has a certain selectivity bias. Third, most of the interventions in the included studies were WAA combined with other treatments, and there were few studies in which WAA was used as a single treatment, which could not fully demonstrate that WAA could be used directly as an independent analgesic for chronic pain. Fourth, the small sample size in most of the studies may affect the strength of the argumentation of the analyzed results. Fifth, in addition to the inclusion of studies related to several types of common chronic pain,

Table 3
Meta-analysis summary of this study

Outcome	RR or SMD (95% CI)	Heterogeneity test			Overall effect test	
		<i>Q</i>	<i>P</i>	<i>I</i> (%)	<i>Z</i>	<i>P</i>
I						
Chronic cancer pain	-1.11 (-1.71 to -0.51)	20.31	0.0004	80	3.60	0.0003
Primary pain	-0.93 (-1.80 to -0.07)	68.95	<0.00001	93	2.12	0.03
Chronic musculoskeletal pain	-0.70 (-0.97 to -0.43)	19.48	0.007	64	5.03	<0.00001
Neuropathic pain	-0.91 (-1.70 to -0.11)	4.53	0.03	78	2.24	0.03
Total events	-0.88 (-1.15 to -0.60)	119.25	<0.00001	83	6.24	<0.00001
II						
Chronic cancer pain	1.21 (1.08 to 1.36)	1.27	0.94	0	3.32	0.0009
Primary pain	1.46 (1.21 to 1.75)	7.44	0.11	46	4.03	<0.00001
Chronic musculoskeletal pain	1.13 (0.94 to 1.37)	24.83	<0.0001	84	1.31	0.19
Neuropathic pain	1.10 (0.98 to 1.23)	0.46	0.50	0	1.62	0.11
Total events	1.23 (1.11 to 1.35)	55.92	<0.00001	70	4.14	<0.0001
III						
WAA vs. OD	-0.13 (-0.28 to 0.02)	11.8	0.02	66	1.69	0.09
WAA vs. NOD	0.00 (-0.03 to 0.03)	0.24	0.99	0	0.02	0.99
Total events	-0.04 (-0.1 to 0.03)	30.42	0.0004	70	1.14	0.25
IV						
10 d	-1.50 (-2.96 to -0.05)	39.19	<0.00001	95	2.03	0.04
2 w	-0.57 (-0.79 to -0.35)	5.75	0.33	13	5.08	<0.00001
3 w	-0.41 (-0.93 to 0.11)	27.21	<0.0001	85	1.54	0.12
1 m	-0.87 (-1.28 to -0.45)	7.24	0.06	59	4.07	<0.0001
3 m	-0.81 (-1.11 to -0.50)	1.11	0.57	0	5.18	<0.00001
Total events	-0.74 (-0.99 to -0.49)	102.39	<0.00001	80	5.88	<0.00001

OD: Oral drugs; RR: Relative risk; SMD: Standardized mean differences; WAA: Wrist-ankle acupuncture. CI: Confidence Interval; RD: Risk Difference; I: pain scores for different types of chronic pain. II: the total clinical efficacy of different types of chronic pain. III: likelihood of adverse events with WAA compared to oral or parenteral drug therapy. IV: pain score for different outcome measures times.

there are fewer clinical studies on other types of chronic pain. Sixth, patients with chronic pain had a variety of diseases, ages, course of disease, acupuncture points

used, combined therapy, etc, which further explained the reason for the high heterogeneity of meta-analysis results.

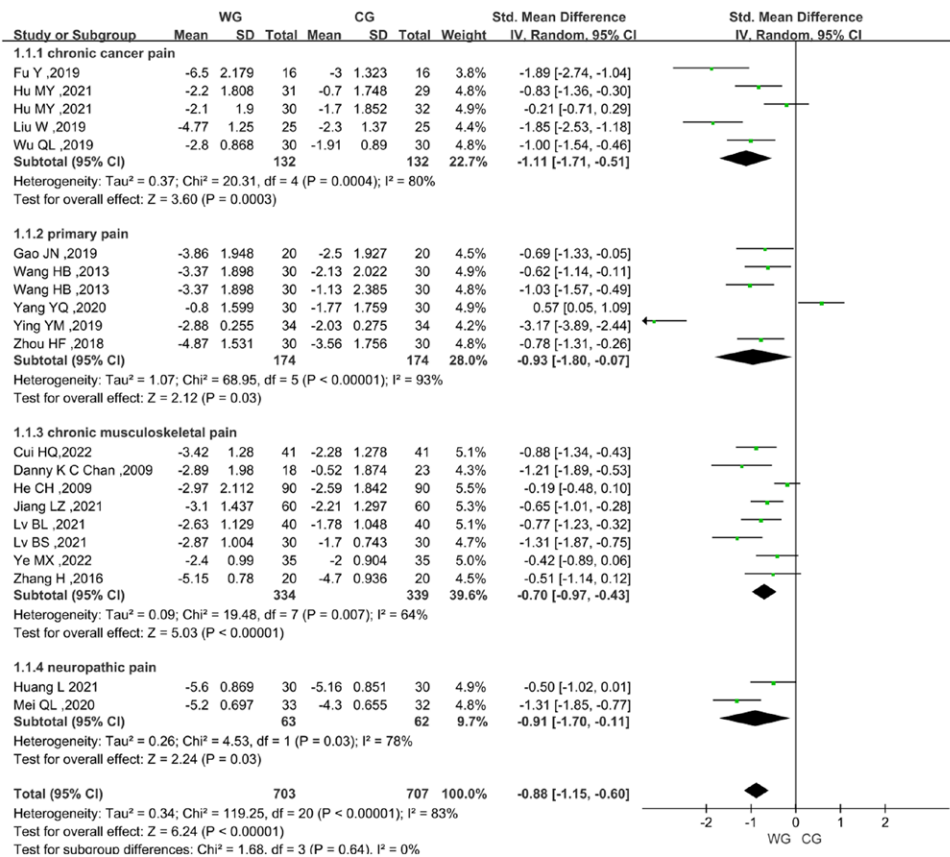


Figure 3. Forest plots for subgroup analysis of different chronic pain types:pain scores.

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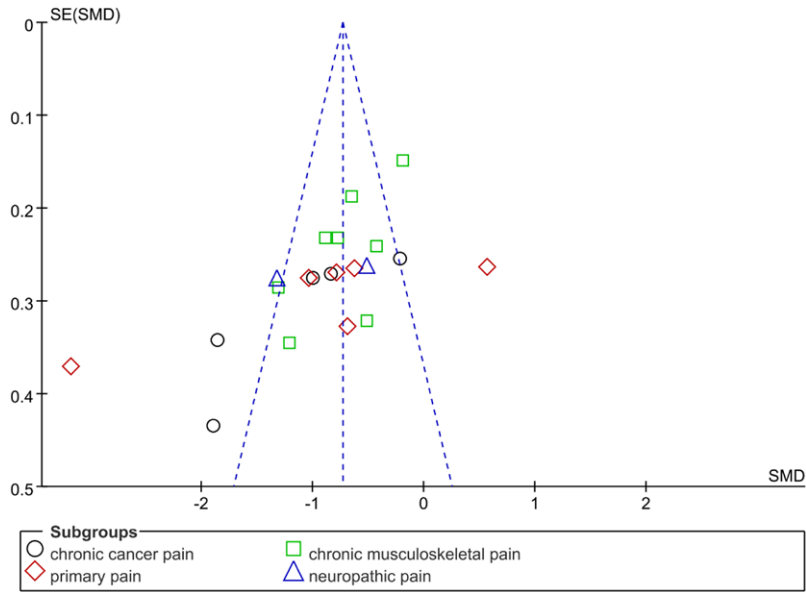


Figure 4. Funnel plots of pain scores.

Conclusion

In conclusion, this meta-analysis suggests that wrist-ankle acupuncture used independently or in conjunction with other types of treat has a positive effect on chronic pain, and can be used to treat pain clinically instead

of oral medication, in consideration of aspects such as adverse events and other factors. More high-quality, large-sample randomized controlled trials and clinical studies on WAA and other types of chronic pain need to be designed in the future to further validate the

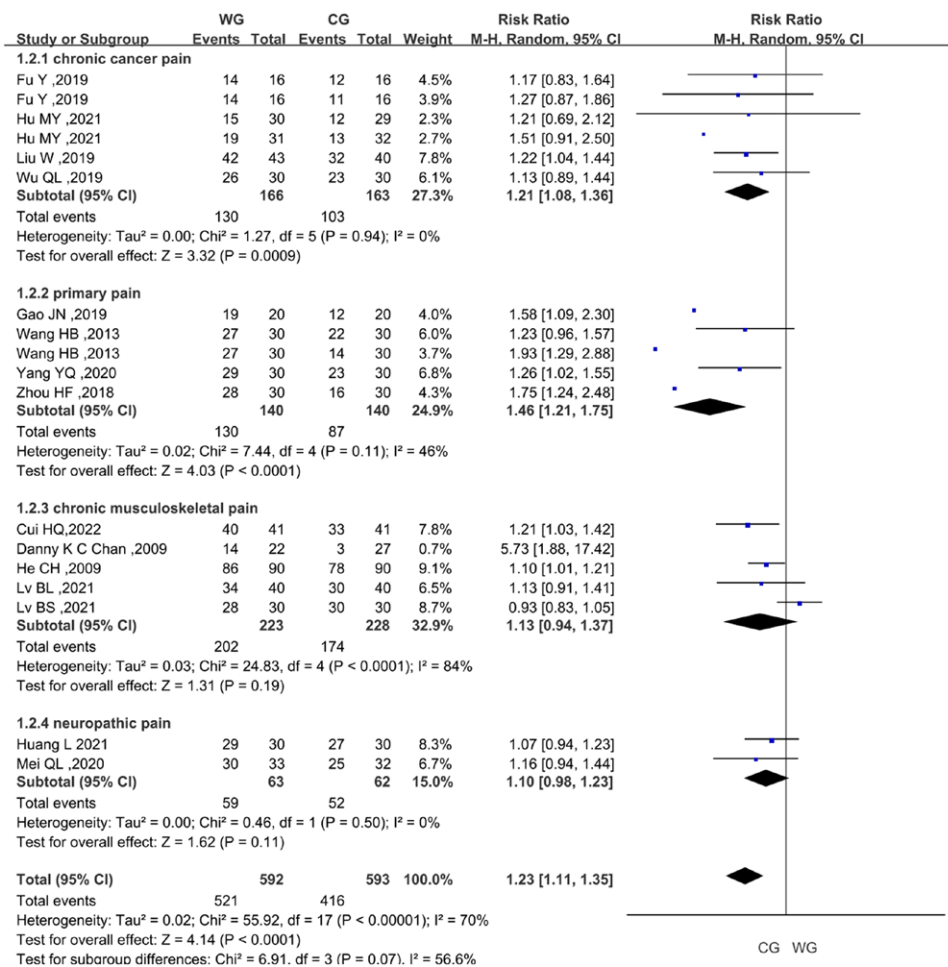


Figure 5. Forest plots for subgroup analysis of different chronic pain types:clinical efficacy (overall efficiency).

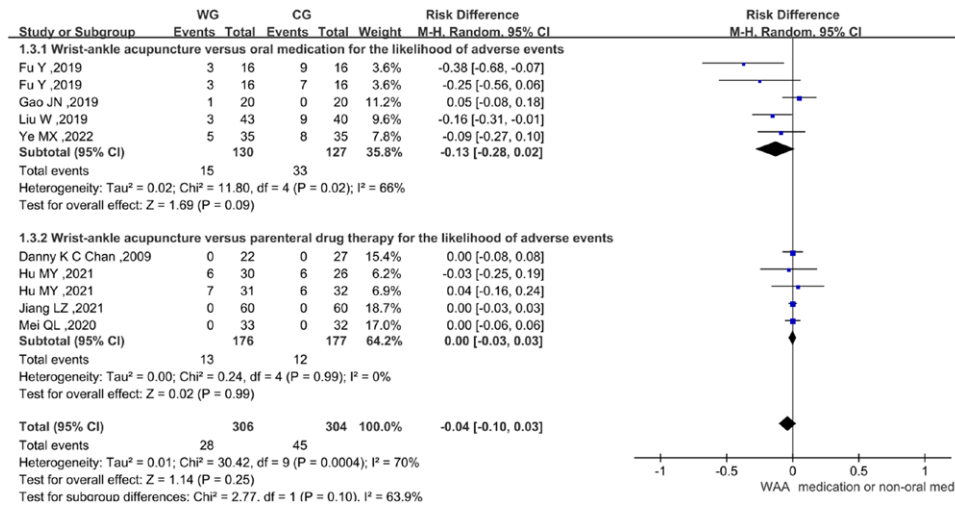


Figure 6. Forest plot of the occurrence of adverse events in wrist-ankle acupuncture therapy compared to oral drug or non-oral drug therapy.

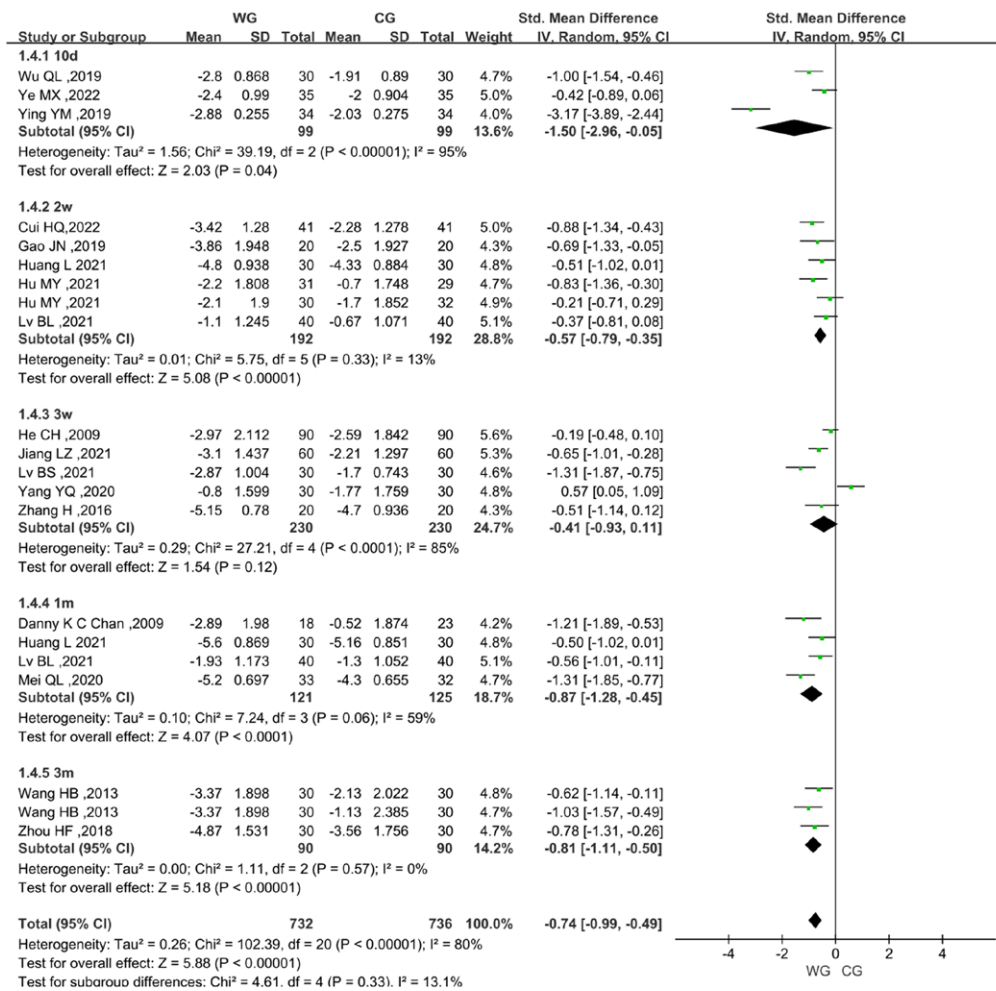


Figure 7. Forest plot of the pain difference score at different assessment time points.

pain-relieving efficacy of wrist-ankle acupuncture on chronic pain and provide new evidence-based data for clinical practice and application.

Conflict of interests statement

The authors declare no conflict of interest.

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Author contributions

Meihua Pan, Yanyan Lan, and Zhifu Wang conceived the manuscript idea. Meihua Pan and Yanyan Lan drafted

the manuscript. Meihua Pan analyzed the data and interpreted the results of analysis. Meihua Pan and Yanyan Lan filtered the articles and performed data extraction. Yanyan Lan assessed the risk of bias. Zhifu Wang provided critical version of the manuscript. All authors contributed to the revision of the manuscript and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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