Acupuncture and Herbal Medicine

Effectiveness of acupuncture in managing aromatase inhibitor-related arthralgia in breast cancer: a systematic review and meta-analysis

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Abstract

Objective: Breast cancer is the second most prevalent cause of mortality in women and the predominant malignancy type. However, breast cancer treatment faces challenges in managing aromatase inhibitor-induced arthralgia. Aromatase inhibitors have been shown to decrease recurrence risk in hormone receptor-positive cases; however, joint discomfort remains the primary adverse effect. Randomized clinical trials have evaluated the therapeutic outcomes of acupuncture for medication-related musculoskeletal complications. This comprehensive analysis sought to elucidate both the therapeutic efficacy and placebo responses associated with acupuncture intervention.

Methods: Two reviewers searched for randomized controlled trials (RCTs) in four English (PubMed, Embase, Web of Science, and the Cochrane Library) and four Chinese databases (CNKI, Wanfang Database, VIP, and SinoMed) from their inception to May 31, 2024. Methodological quality was assessed using the Cochrane risk of bias tool. Data were synthesized using random effects models and presented with forest plots.

Results: Seven trials involving 604 patients were included. The primary outcome and Brief Pain Inventory (BPI) score differed between the acupuncture and control groups (sham acupuncture or usual medication) in three subscales over the course of 6 weeks: worst pain: standardized mean difference (SMD) = –1.18, 95% confidence interval (CI): –1.74, –0.63, $P < 0.001$; pain-related interference: SMD = –0.87, 95% CI: –1.70, –0.05, $P = 0.038$; pain severity: SMD = –0.63, 95% CI: –1.22, –0.04, $P = 0.036$. No severe adverse events were reported in any study.

Conclusions: This meta-analysis showed that acupuncture is a safe and effective treatment for patients with breast cancer with aromatase inhibitor-induced arthralgia during the course of 6 weeks. Improvements in the blinding method and clarification of the total treatment recommendations and intervals need to be explored further.

Keywords: Acupuncture, Aromatase inhibitor-induced arthralgia, Breast cancer, Meta-analysis

Background

Breast cancer is the second most prevalent cause of mortality in women worldwide and constitutes the most frequently diagnosed malignancy[1]. Data from the International Agency for Research on Cancer indicates approximately 2.3 million new cases of female breast carcinoma are reported annually, establishing it as a predominant form of neoplastic disease[2]. Current clinical management typically involves localized interventions such as surgical resection and radiotherapy for disease containment. Comprehensive systemic therapeutic approaches, including endocrine (hormonal) treatments, chemotherapeutic agents, and molecularly targeted therapies, play crucial roles in both disease management and mitigation of metastatic potential[3].

For individuals diagnosed with estrogen receptor (ER)-positive or progesterone receptor (PR)-positive breast malignancies, extended therapeutic regimens

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involving aromatase inhibitors, such as tamoxifen over 5 to 10 years, demonstrate 50% reduction in disease recurrence rates[4]. Aromatase inhibitors (AIs), which are the standard treatment for early-stage breast cancer, can reduce the risk of recurrence in patients with hormone receptor-positive breast cancer[5]. The American Society of Clinical Oncology (ASCO) guidelines recommend that women with breast cancer should be treated with aromatase inhibitors for up to 10 years[6]. Despite these benefits, prolonged administration frequently induces adverse reactions including gastrointestinal disturbances, cutaneous eruptions, and musculoskeletal discomfort. Aromatase inhibitor-associated arthralgia (AIA) has emerged as the predominant treatment-limiting complication that significantly impacts medication adherence[7–9]. AIA development during therapeutic courses contributes to treatment discontinuation in nearly half of the patients who cease AI usage during the initial 12 months of therapy[10].

Current therapeutic strategies for the management of AIA primarily involve pharmacological agents and physical activity regimens. The American Cancer Society's clinical guidelines recommend interventions including regular exercise, body weight management, and specific medications (vitamin D supplements and bisphosphonates) to mitigate mild arthralgia symptoms[11]. Nevertheless, extended bisphosphonate administration is associated with an elevated risks of adverse effects, including acute-phase responses, gastrointestinal complications, and hepatorenal impairments[12]. Therefore, alternative therapies, such as acupuncture, yoga, and exercise, have been widely used to treat AIA in recent years[13].

As a vital element of Traditional Chinese Medicine, acupuncture has gained global recognition through the clarification of its pain-relieving mechanisms and validated therapeutic outcomes[14]. Therapeutic method activates endogenous opioid secretion within brainstem regions, subcortical networks, and limbic system structures[15–16] while simultaneously influencing the pituitary gland production of adrenocorticotropic hormone and cortisol[17]. Neuroimaging studies using functional magnetic resonance imaging (MRI) demonstrated that sustained acupuncture application produces rapid modulatory effects on the limbic circuitry and basal forebrain regions, which are critical neural substrates involved in human nociceptive processing[18]. Moreover, research has indicated that the sensation of *De qi* is related to the mechanical grasping of connective tissues under the skin, which induces unknown psychological changes[19]. Beyond analgesia, clinical evidence suggests that acupuncture exerts regulatory effects on hormonal imbalances involving estrogen levels[20], and that AIA pathogenesis is associated with a lack of estrogen[12]. Importantly, therapeutic outcomes of acupuncture may be significantly influenced by psychosocial elements, including treatment expectations, personal convictions, and the clinician-patient rapport established during therapy[21].

Multiple clinical trials utilizing randomized controlled designs have documented and analyzed the therapeutic effects of acupuncture in managing AIA-related conditions[22–28], and the Clinical Practice Guidelines recommend that acupuncture can relieve the side effects caused by AIs[10]. However, other studies have reported that it is ineffective for AIA[27]. There is no consensus on the role of acupuncture in the treatment of AIA in patients with breast cancer. Meta-analyses[29] on the effects of acupuncture on AIA have been published. However, a study[24] that included 226 patients showed that acupuncture helps relieve the symptoms of AIA, making it necessary to update the systematic review. Therefore, this investigation aimed to systematically assess both therapeutic outcomes and safety profiles of acupuncture therapy for AIA in patients with breast cancer, following the established meta-analytical reporting standards for the Systematic Reviews and Meta-Analysis Statement 2020[30] and Reporting Items for Systematic Reviews and Meta-Analyses of acupuncture: the PRISMA for acupuncture checklist[31].

Materials and methods

Registration

The protocol for this systematic review has been prospectively registered in PROSPERO (registration number: CRD42022370236).

Search strategy and selection criteria

A comprehensive search was conducted using eight major databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, SinoMed, and VIP. These resources were systematically explored from their inception to May 31, 2024. A detailed search methodology is provided in Supplemental Digital Content 1, https://links.lww.com/AHM/A190.

Inclusion criteria

The inclusion criteria for the literature were as follows: (1) study participants: Female patients undergoing aromatase inhibitor therapy for breast cancer who developed treatment-related musculoskeletal complications. (2) Interventions encompassing various acupuncture modalities such as traditional needle insertion, electrostimulation-enhanced techniques, auricular therapy, wrist-ankle needling approaches, scalp acupuncture protocols, and transcutaneous electrical acupoint stimulation, either as standalone treatments or in combination with standard care. Crucially, comparative studies maintain identical background therapies across the experimental and control groups, with acupuncture being the sole differentiating factor. (3) Control conditions comprising three categories: placebo acupuncture procedures, untreated waiting-list cohorts, and conventional therapeutic regimens. (4) Outcomes: The primary outcome was the Brief Pain Inventory (BPI) score used to assess joint pain severity. This validated assessment tool is widely recognized for its comprehensive and efficient measurement of pain-related parameters in clinical research settings. The worst pain, stiffness, pain severity, and pain-related interference scores (scale range: asymptomatic to severe, 0–10) were analyzed, and a reduction of ≥2 points on the maximum discomfort scale was deemed indicative of meaningful clinical

improvement[32]. Secondary outcomes included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Visual Analog Scale (VAS) score, and adverse events. (5) Type of study: This systematic review included randomized controlled trials (RCTs) on acupuncture in breast cancer patients with aromatase inhibitor-induced musculoskeletal symptoms.

Exclusion criteria

The exclusion criteria were (1) non-empirical research, including literature reviews, observational investigations, clinical trial protocols, case series reports, or animal experimentation; (2) incomplete manuscripts or studies with insufficient data documentation; (3) duplicate publications or previously disseminated research content.

Data extraction

Two researchers (Xinru Yuan and Yaman Zheng) independently evaluated the retrieved abstracts. Full-text assessments were performed using predefined inclusion and exclusion criteria to identify studies that warranted a detailed analysis. Discrepancies concerning study selection or eligibility criteria were resolved by a third researcher (Zheng Zhu). Relevant data from RCTs were independently extracted from the selected RCTs and cross-verified. Inconsistencies were resolved through team consultations or discussions with another investigator (Bo Chen). The extraction process captured key study elements, including publication titles, author information, participant demographics (number and age range), and measured outcomes. When incomplete data records were encountered, direct communication with the corresponding authors was initiated for clarification.

Quality assessment for the included studies

The Risk of Bias Assessment Tool was used to evaluate the methodological quality across all included RCTs. Two independent researchers (Liang Liu and Bomin Dou) evaluated seven critical dimensions: randomization procedures, allocation masking, participant and personnel blinding, outcome assessor blinding, handling of missing data, selective reporting tendencies, and potential miscellaneous biases. Each category was classified as high, low, or indeterminate based on predefined criteria.

Data analysis

Data analysis was conducted using the Stata 17.0 MP software. For continuous variables, the standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated. Dichotomous outcomes were evaluated using relative risk (RR) estimates with the corresponding 95% CIs. Study heterogeneity was assessed through χ^2 testing ($\alpha = 0.05$) supplemented by I^2 quantification. Pooled estimates were derived through random-effects modeling when I^2 values exceeded 50%, while fixed-effects approaches were applied for lower heterogeneity levels ($I^2 \leq 50\%$). The statistical significance threshold was set at $P < 0.05$. Substantial clinical heterogeneity prompted exploratory subgroup analyses to identify potential moderating factors.

Results

Selection of studies

The initial database searches retrieved 1,982 potentially relevant publications. Following duplicate removal, 1,447 unique records were subjected to a rigorous evaluation. Our team meticulously reviewed article titles and abstracts against predefined eligibility requirements, ultimately selecting seven RCTs for inclusion in the final analysis. The systematic screening procedure and outcome data are visually presented in the selection flowchart (Figure 1).

Study characteristics

A total of 604 patients were included in seven RCTs, and all studies reported comparable baselines. The study characteristics are shown in Tables 1 and 2. All patients were diagnosed with stage I to III breast cancer and hormone receptor-positive cancer and received AIs for >1 month. In terms of intervention methods, there were two RCTs[23,26] on simple intervention with body acupuncture, one RCT[22] on manipulation intervention after body acupuncture, and two RCTs[23,27] on a combination of body and ear acupuncture. In addition, warm[21], ear[24], and electroacupuncture[25] were investigated in one study. Regarding the selection of control measures, five RCTs[22–26] used conventional treatment as the control, and four RCTs[24,26–28] used sham acupuncture as the control. Furthermore, for the two three-arm RCTs, only a combined analysis of true sham acupuncture was performed. Five studies[22,24–28] reported BPI, two studies[25,27] reported WOMAC, two studies[23,27] reported VAS.

Quality assessment of included RCTs

The results of the risk of bias assessment are presented in Figures 2 and 3. Regarding randomization procedures, all seven trials documented randomization methods: five employed random number tables[22,24,26–28], and they were considered to be low-risk; one study was assigned as high risk because it recruited patients based on the order of visits[24]; and the randomization method of the remaining trial was unclear and was thus considered to be an unknown risk[22]. Two trials did not explicitly report allocation concealment and were considered to be of unknown risks[21–22]. For blinding of participants and personnel, three trials could not be blinded due to the selection of controls; hence, they were considered to be high risk[22–23,25]. For blinding of the outcome assessment, three trials referred to outcome evaluation, and the blinded method was considered an unknown risk[22–23,25]. All included trials demonstrated a low attrition bias risk through comprehensive documentation of incomplete data management. Selective reporting bias was deemed minimal across all studies as they comprehensively addressed predetermined outcomes. Seven investigations showed no detectable additional sources of bias, thus maintaining an undetermined risk classification.

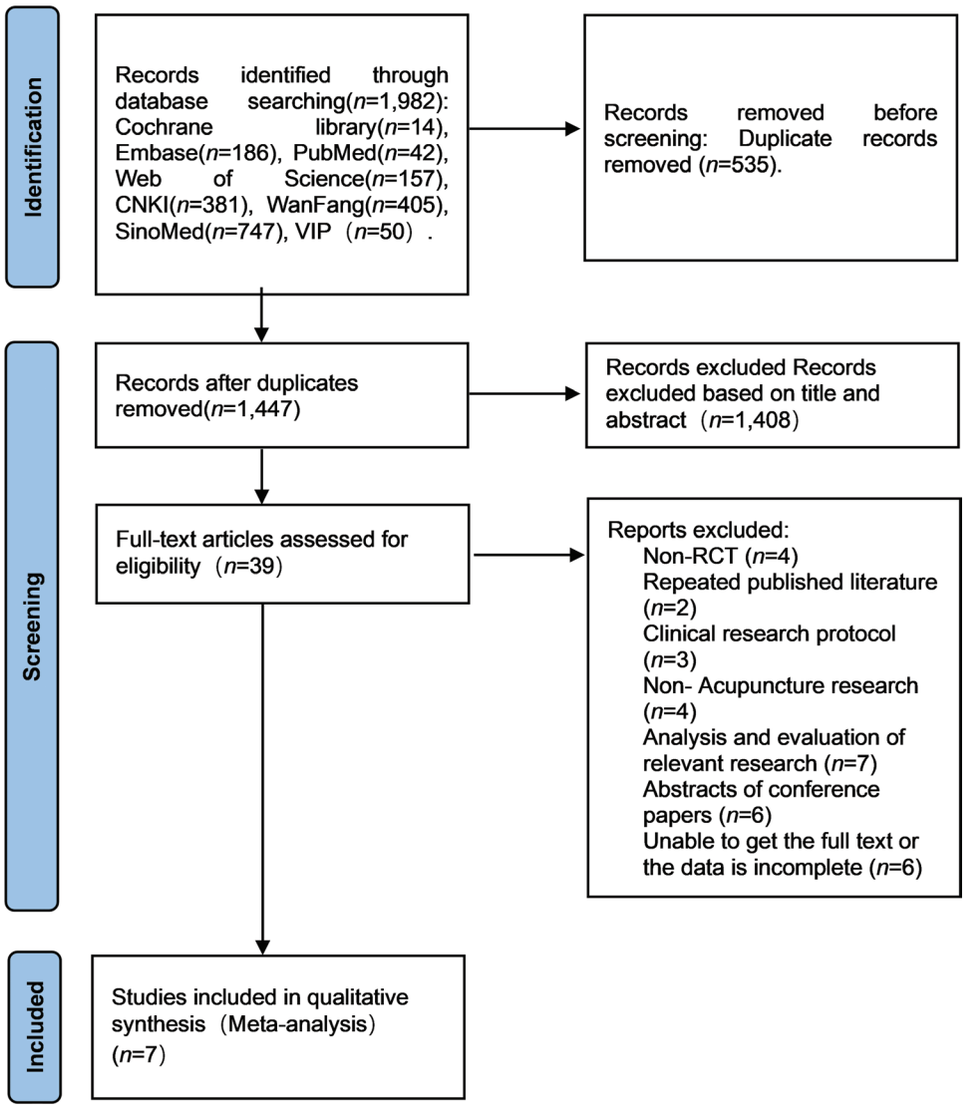


Figure 1. Study flow diagram. CNKI: China National Knowledge Infrastructure; RCT: Randomized controlled trial.

Outcomes analyses

BPI

Five RCTs reported pre- and post-treatment BPI[22,24–26,28]. The BPI is comprised of the following subscales: worst pain, pain-related interference, and pain severity. We analyzed each subscale in this study.

Four RCTs used the BPI-worst pain subscale for assessment[22,24–25,28], with subgroup analyses performed based on treatment duration. At the 3-week evaluation, the findings indicated enhanced therapeutic outcomes in the acupuncture cohort relative to the controls, with this intergroup disparity reaching statistical significance (SMD = –0.71, 95% CI: –1.12, –0.31, $P = 0.001$) as illustrated in Figure 4A. Subsequent analysis at 6 weeks revealed more pronounced clinical benefits in the acupuncture intervention group than in the standard care, demonstrating statistically significant differences (SMD = –1.18, 95% CI: –1.74, –0.63, $P < 0.001$), as depicted in Figure 4B. In contrast, longitudinal assessment at 12 weeks demonstrated comparable outcomes between treatment modalities, with no statistically significant disparity emerging (SMD = –1.04, 95% CI: –2.28, 0.21, $P = 0.104$) as shown in Figure 4C.

Four RCTs reported data on BPI pain-related interference[24–26,28], and we analyzed according to different courses. At 3 weeks, acupuncture was superior to the control, but the difference between the two groups was not statistically significant (SMD = –0.92, 95% CI: –2.23, 0.39, $P = 0.171$) (Figure 5A). During the course of 4 to 6 weeks, the results showed that acupuncture was superior to the control, and the difference between the two groups was statistically significant (SMD = –0.87, 95% CI: –1.70, –0.05, $P = 0.038$) (Figure 5B). For the course of over 8 weeks, the results showed that acupuncture was superior to the control, but the difference between the two groups was not statistically significant (SMD = –0.93, 95% CI: –2.25, 0.40, $P = 0.169$) (Figure 5C).

Four RCTs provided pre- and post-intervention measurements of BPI pain severity[22,24,26,28], with stratified analysis based on treatment duration. For interventions lasting 3 weeks, acupuncture demonstrated significantly greater efficacy compared to control conditions, revealing a clinically meaningful effect (SMD = –1.10, 95% CI: –1.78 to –0.41; $P = 0.002$) as illustrated in Figure 6A. When evaluating the 4- to 6-week treatment periods,

Table 1

Key characteristics of the studies included in the meta-analysis

Study	Inclusion criteria	Number of patients (T/C)	Average age (year)		Course of treatment (weeks)	Outcomes	Adverse effects
			T	C			
Liu 2020[22]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month; 3 ≤ VAS ≤ 7.	30/30	53.2 ± 5.9	55.9 ± 6.0	2, 4, 6	①	T: Minor burns to local skin (n = 1)
Li et al. 2019[23]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month; VAS ≥3.	36/36	58.21 ± 7.83	57.78 ± 7.54	12	②	No
Hershman et al. 2018[24]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month; BPI-WP ≥3.	110/59/57*	60.8 (34.1–80.6)	57.0 (40.6–77.5) 60.6 (27.1–76.0)	6, 12	①	T: presyncope (n = 1) C: presyncope (n = 1)
Ye et al. 2015[25]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month; BPI-WP ≥3.	31/33/30†	41–78	50–80 41–77	3, 6, 12	①	Not reported
Mao et al. 2014[26]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month; BPI-WP ≥4.	22/22/23*	57.5 ± 10.1	60.9 ± 6.5 60.6 ± 8.2	4, 8	①③	T: Pain at the needling site (n = 5) C: Pain at the needling site (n = 4)
Bao et al. 2013[27]	Breast cancer stages I–III; hormone receptor-positive cancer; took AIs for >1 month.	23/24	61 (45–85)	61 (44–82)	4, 8	②	No
Crew et al. 2010[28]	Breast cancer stages I–III; Hormone receptor-positive cancer; took AIs for >1 month; BPI-WP ≥3.	20/18	58 (44–77)	57 (37–77)	3, 6	①③	Not report

C: Control group; BPI: Brief Pain Inventory; T: Treatment group; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. ①BPI; ②VAS; ③WOMAC.

*The two control groups were sham acupuncture and waitlist control.

†The two control groups were routine injection medication and Routine oral medication.

Table 2

Intervention and control design characteristics of the included studies

	Intervention measures				Control measures		
Study	**Measure**	**Acupoints**	**Methods**	***De qi***	**Measure**	**Acupoints**	**Methods**
Liu 2020[22]	Needle warming through moxibustion + usual medication	①SP6, ST36, EX-LE4, ST35, and Ashi acupoints ②GB34, SP9, ST34, SP10, BL40, and Ashi acupoints two groups of points are alternately used	Twist to *De qi*, put 1 cm long moxa sticks on the needle tail, light the lower part of moxa until burned out, repeat moxibustion 1–2 times.	Yes	Usual medication	/	Oral calcium carbonate D3 tablets, 1,200 mg/time, once a day. All patients received the same health education during treatment.
Li et al. 2019[23]	Body acupuncture with manipulation + usual medication	Ashi acupoints, muscle tenderness points	Injection depth of 25–30 mm, until get *De qi* back needle to the subcutaneous, and then change the direction, the needle body tilt 15°–30°, respectively, oblique around the needle, repeat 1–2 times.	Yes	Usual medication	/	Oral calcium carbonate D3 tablets, 600 mg/time, once a day; Alfacalcalcitol soft capsule 0.5 μg/time, once/day.
Hershman et al. 2018[24]	Body acupuncture and auricular acupuncture	Main acupoints: LI4, GB41, GB34, SJ5, and SJ41; Selecting acupoints according to three Acupoints of the patient's most painful joint areas	The needle is inserted at the traditional depth and angle, and the needle is manually stimulated again during each acupuncture session.	Not described	SA: body sham and auricular sham acupuncture WLC: 10 true acupunctures were given at 24–52 weeks and no treatment was given before then	Non-acupuncture points	Minimally invasive, shallow needle insertion using thin and short needles.
Ye et al. 2015[25]	Auricular acupuncture	Main acupoints are auricular points of CO15, TF4, and AT4; selecting acupoints according to the painful joint areas	Use the 0.22 mm × 15 mm snap needle press auricular acupuncture	Yes	Usual medication	/	Injected hypo zoledronic acid every 6 months
Mao et al. 2014[26]	Electroacupuncture	To choose at least four local points around the joint with the most pain and another four distant points are used to address constitutional symptoms	The TENS unit provides 2 Hz electrical stimulation	Yes	SA: Streitberger sham needles. WLC: no treatment and 10 real acupuncture treatments after follow-up.	Same as intervention measures	Do not penetrate the skin without receiving electricity.
Bao et al. 2013[27]	Body acupuncture	CV4, CV6, CV12, LI4, MH6, GB34, ST36, KI3, and BL65	Park's needle, the injection was 0.5 inches	Not described	Sham needles	Selected 14 sham acupoints located at the midpoint of the line connecting 2 real acupoints	Non-penetrating retractable needles at non-acupuncture points
Crew et al. 2010[28]	Body acupuncture and auricular acupuncture	Acupoints located on full body and ears and joint-specific acupoints.	Standard acupuncture operation	Not described	Sham needles	Non-acupuncture points	Superficial needles insertion at non-acupuncture points

SA: Sham acupuncture group; TA: True acupuncture group; WLC: Waitlist control group.

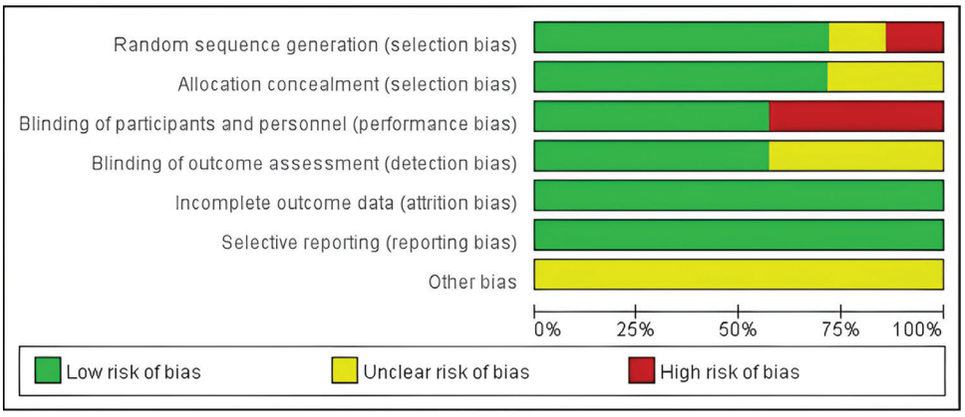


Figure 2. Risk of bias.

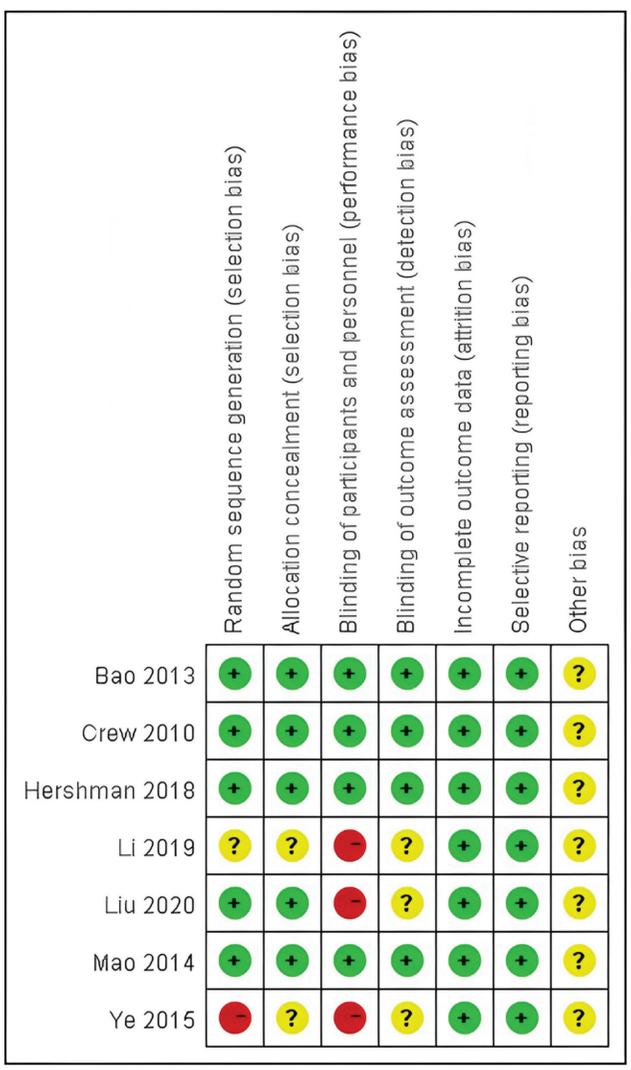


Figure 3. Risk of bias summary.

the intervention group maintained a marked therapeutic advantage over the controls, achieving statistical significance (SMD = –0.63, 95% CI: –1.22, –0.04; $P = 0.036$), as shown in Figure 6B. Extended interventions beyond 8 weeks yielded marginally favorable outcomes for acupuncture relative to controls, although between-group differences did not reach statistical thresholds (SMD = –0.20, 95% CI: –0.49 to 0.10; $P = 0.188$) (Figure 6C).

VAS

VAS outcomes from two studies[23,27] revealed no significant differences between acupuncture and control interventions (SMD = 0.58, 95% CI: –0.18 to 1.33, $P = 0.137$), as illustrated in Figure 7.

WOMAC

Two RCTs reported pre- and post-treatment WOMAC[26,28]. The WOMAC consists of four subscales as follows: pain, stiffness, function, and normalization. In this study, we analyzed each subscale and acupuncture was superior to control for each subscale, but there was no statistically significant difference between the two groups (pain: SMD = –0.67, 95% CI: –1.97 to 0.64, $P = 0.391$; stiffness: SMD = –0.75, 95% CI: –1.84 to 0.34, $P = 0.178$; function: SMD = –0.47 to 95% CI: –1.38 to 0.44, $P = 0.311$; normalization: SMD = –0.75, 95% CI: –2.08 to 0.58, $P = 0.269$) (Figure 8).

Adverse effects

Concerning the occurrence of adverse effects, two studies omitted documentation of adverse events[25,28], though none of the investigations documented severe adverse reactions. Among the documented cases, three investigations recorded adverse events, including localized dermal burns[22], presyncope[24], and pain[26]. Conversely, two studies reported the absence of such complications[23,27] (Table 1).

Discussion

This meta-analysis evaluated the effects of acupuncture on AIA in breast cancer patients. The results showed that acupuncture improved the BPI scores on the worst pain, pain severity, and pain severity subscales, especially over the course of 6 weeks. No serious adverse events were reported in any of the included studies. Acupuncture is an effective way to treat AIA with few side effects, especially labor pain, and reduces the degree to which pain interferes with the functioning of daily living. We found no statistical differences in the VAS and WOMAC scores,

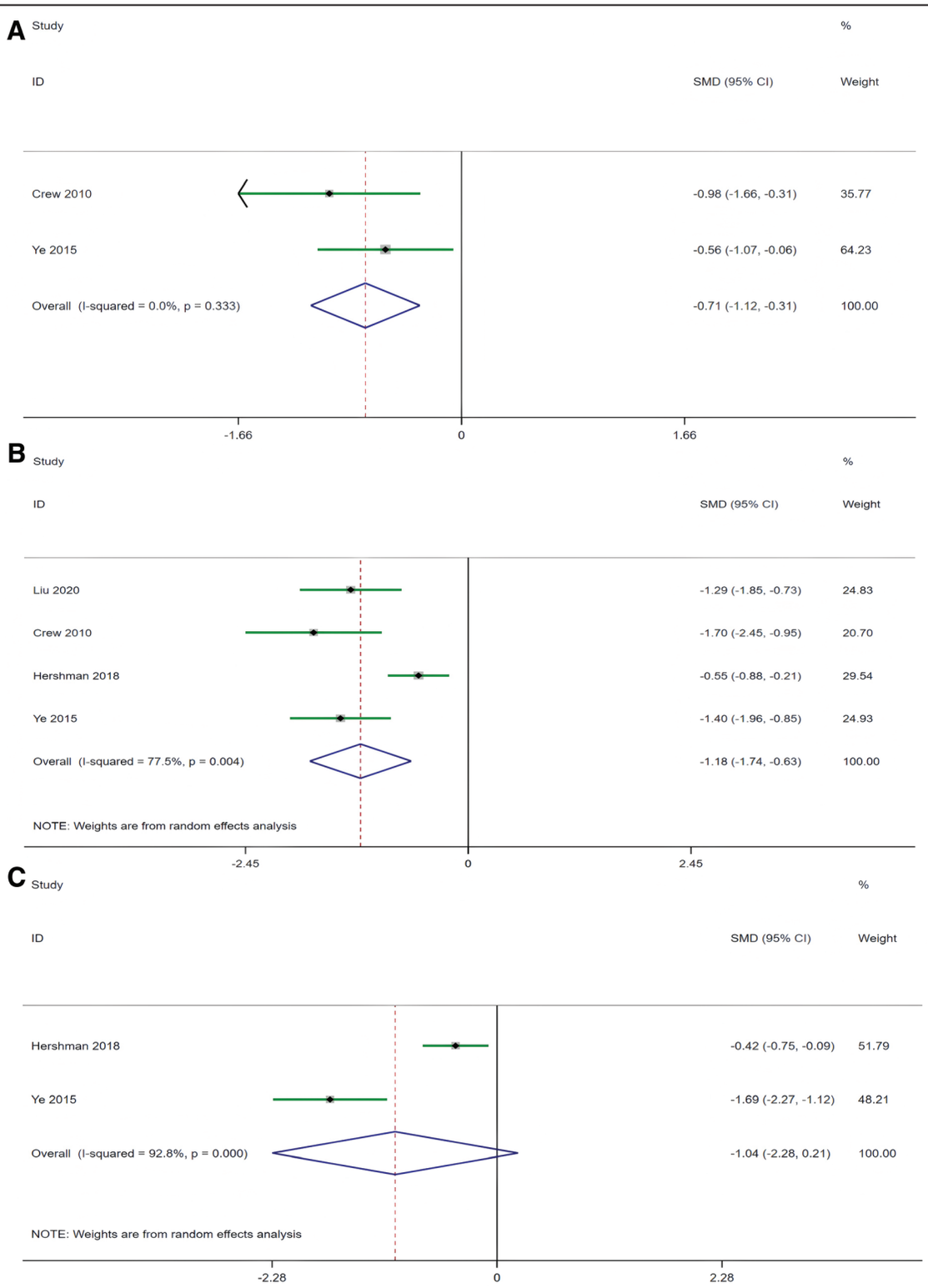


Figure 4. Forest plot of BPI-worst pain. Pooled BPI-worst pain in (A) 3 weeks; (B) 6 weeks; (C) 12 weeks. BPI: Brief Pain Inventory; CI: Confidence interval; SMD: Standardized mean difference.

which might be related to the small number of participants included in the analysis and large differences in intervention methods.

Among the seven included trials, four with sham acupuncture control were conducted in the United States, and the other three with conventional drug therapy as a control were conducted in China, where acupuncture therapy is the birthplace. The main reason for this difference is that the participants' familiarity with acupuncture therapy might have affected the implementation of blind therapy. Sham acupuncture was selected for the control group in acupuncture clinical trials to avoid the influence of placebo effects on the final outcome[33]. The efficacy of acupuncture therapy is the result of a combination of many factors; therefore, there are many factors that affect the final treatment outcome of acupuncture:

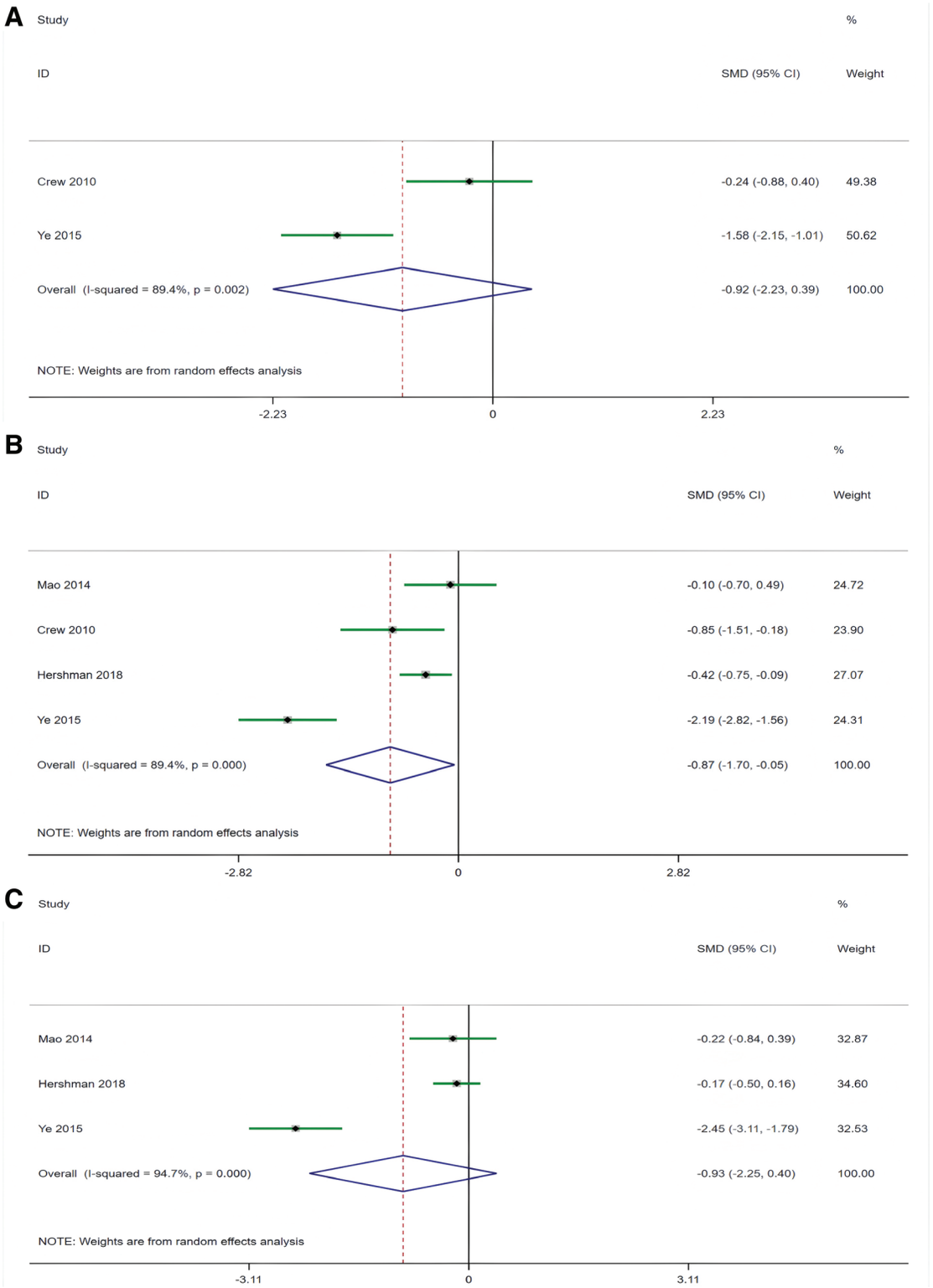


Figure 5. Forest plot of BPI pain-related interference. Pooled BPI pain-related interference (A) in 3 weeks; (B) in 4–6 weeks; (C) in ≥8 weeks. BPI: Brief Pain Inventory; CI: Confidence interval; SMD: Standardized mean difference.

reliance on professional knowledge, combination with other therapies, and highly personalized treatment plans. The efficacy of acupuncture is closely related to doctor–patient interaction[34]. Therefore, regardless of whether invasive[24,26,28] or non-penetrating sham acupuncture control[27] was used, the sham acupuncture control cannot completely rule out the placebo effects.

The effects of acupuncture and moxibustion in treating diseases occur through stimulation of specific acupoints that regulate bodily functions. These acupoints are connected by a network of meridians that play a crucial role in facilitating therapeutic effects[35]. The therapeutic effect of acupuncture results from the interaction between several factors, including the selection of

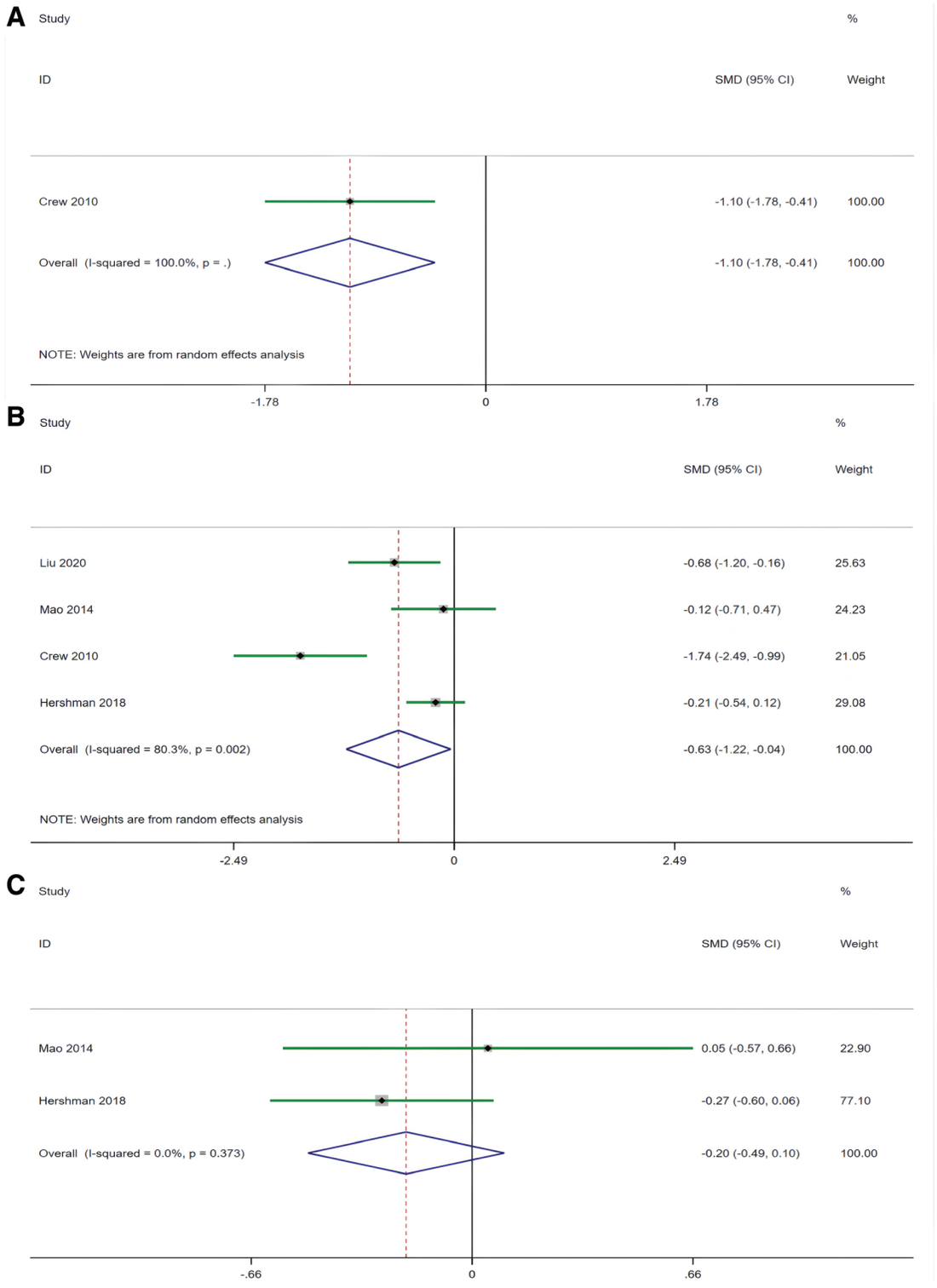


Figure 6. Forest plot of BPI pain-severity. Pooled BPI pain-severity (A) in 3 weeks; (B) in 4–6 weeks; (C) in ≥8 weeks. BPI: Brief Pain Inventory; CI: Confidence interval; SMD: Standardized mean difference.

acupuncture points, stimulation methods (body acupuncture, electric acupuncture, and ear acupuncture), and treatment time (single treatment time, number of courses, and total treatment time). Together, these factors constitute the multidimensional therapeutic effect of acupuncture, which fully reflects the complexity of acupuncture intervention[36]. Currently, there are many studies on the influence of acupuncture point selection and stimulation methods on acupuncture efficacy. However, there is a lack of studies on the relationship between treatment course and acupuncture efficacy. Therefore, determining a reasonable treatment course is important to improve the efficacy of acupuncture. There are no strict regulations on the length and interval of acupuncture treatment courses in clinical practice, which are usually determined according to the clinical experience of doctors, and there are no systematic research analyses, unified standards, or standardization. Maintaining and

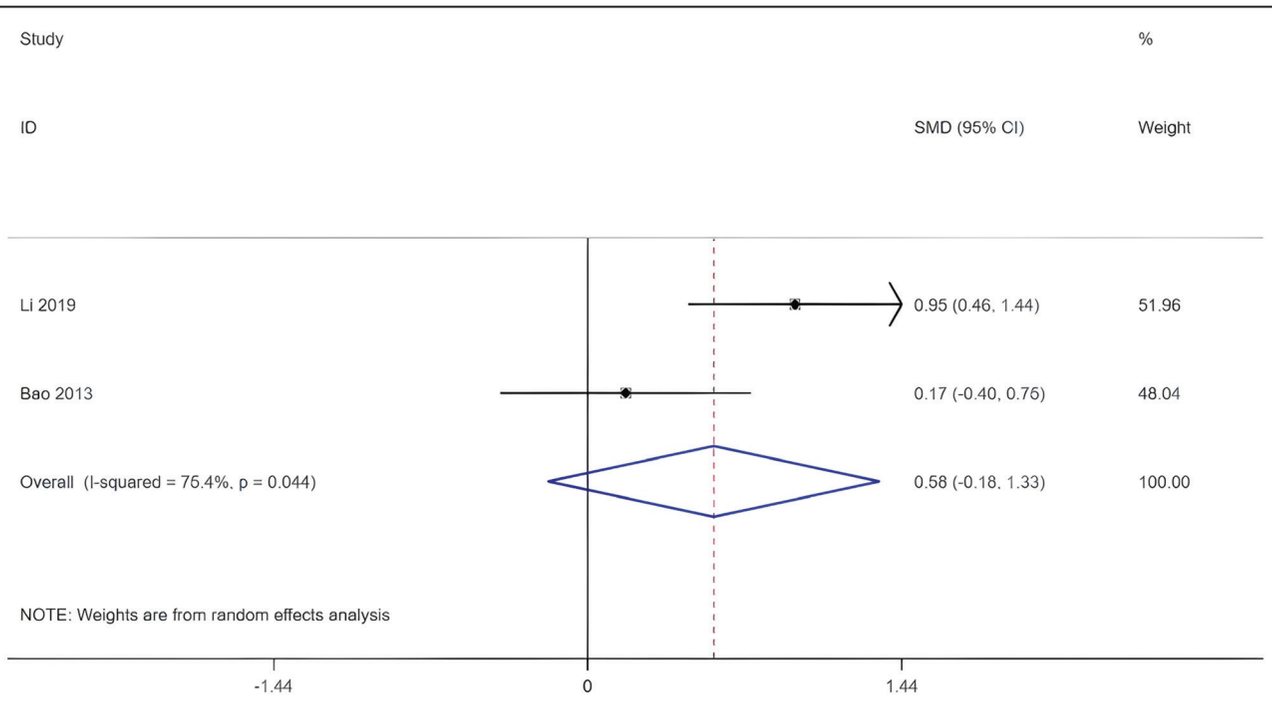


Figure 7. Forest plot of VAS. CI: Confidence interval; SMD: Sandardized mean difference; VAS: Visual Analog Scale.

accumulating acupuncture effects while reducing acupuncture tolerance requires scientific demarcation of the duration of acupuncture treatment.

Different acupuncture treatment courses (two, three, and five times per week) were used in the clinical trials included in this study, and the total lengths (cycles) were 6, 8, and 12 weeks[22–28]. Excessive acupuncture stimulation could cause patients to develop tolerance to acupuncture stimulation. When the acupuncture duration was >8 weeks, BPI scores were not statistically significant. Even for the two dimensions of BPI pain severity and worst pain, the differences between the treatment and control groups showed a decreasing trend. Acupuncture therapy mobilizes the body's inherent regulatory function to treat diseases by stimulating body surface points. The stimulation of acupuncture points is the beginning of the effect of acupuncture and the generation of acupuncture tolerance may be closely related[37]. The body's sensitivity to acupuncture changes from sensitivity to adaptation with an increase in acupuncture frequency and continuation of acupuncture time. When the body adapts to acupuncture stimulation, the original acupuncture points, stimulation intensity, and techniques cannot achieve the same results, or show poor efficacy, resulting in acupuncture tolerance[38]. Acupuncture has been very effective in the treatment of musculoskeletal pain[39]. However, the mechanism of acupuncture analgesia has not been elucidated, although there are many plausible theories, including hormonal changes, immune regulation, and endogenous opioid release[40]. Currently, it is unclear how long and how many acupuncture treatments can tolerate different types of chronic pain. Considering the economic burden on patients, determining the optimal treatment duration and frequency for AIA is imperative. Considering that there are few clinical studies on the course of acupuncture treatment for AIA, and that the results of the meta-analysis in this study were highly heterogeneous, large samples and high-quality clinical studies are needed to provide more valuable clinical evidence.

Clinical research aims to answer the most concerning or controversial questions, and the selection of research evaluation outcomes directly reflects this purpose[36]. Currently, there is no consensus on the outcomes of acupuncture clinical trials in patients with AIA, and no relevant core indicators have been published. This may have resulted in inconsistent findings and high heterogeneity, because only a few studies were included in the meta-analysis. Further clinical trials are needed to clarify the effects of acupuncture on VAS and WOMAC outcomes in patients with AIA. Furthermore, the core outcome set for acupuncture clinical trials in patients with AIA can help avoid data wastage during the study[41].

This study has some limitations. The principal drawbacks stem from the inclusion of studies characterized by small set of samples, short follow-up periods, and insufficient trial quantity. Notably, the current ASCO clinical guidelines advocate adjuvant aromatase inhibitor therapy durations exceeding 5 years, rendering existing short-duration studies inadequate for assessing the longitudinal efficacy of acupuncture against AI-associated symptoms. Furthermore, the predominant reliance on subjective patient-reported outcomes across all analyzed trials introduces potential measurement inaccuracies, as these self-assessment tools lack the objectivity of laboratory-based biomarkers. Additionally, the linguistic constraints of our search strategy resulted in the exclusive consideration of English and Chinese publications, potentially introducing a selection bias through the omission of relevant studies in other languages. Despite these methodological limitations, this systematic review provides valuable insights into the therapeutic potential of acupuncture

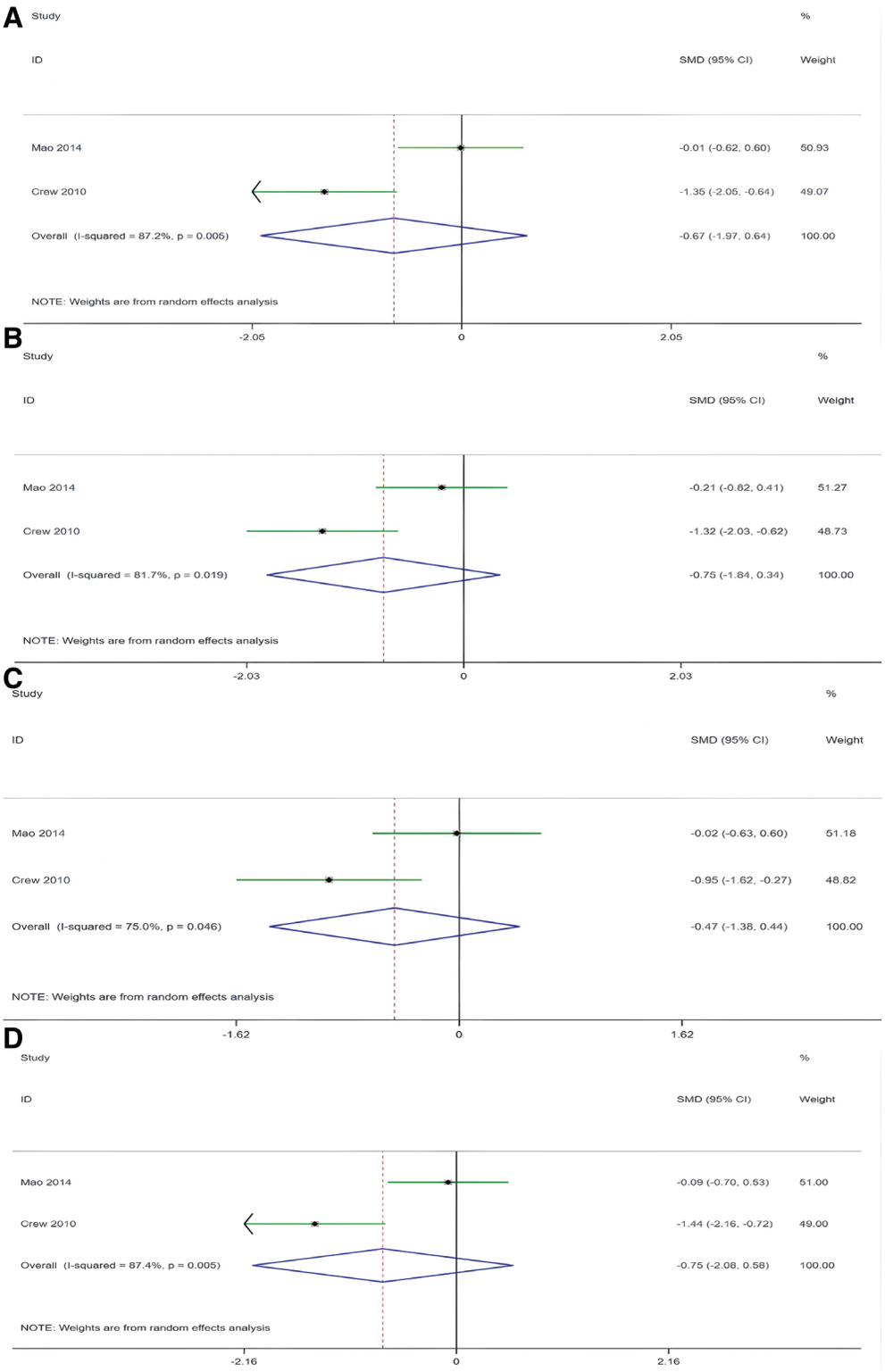


Figure 8. Forest plot of WOMAC. (A) Pain; (B) stiffness; (C) function; (D) normalization. CI: Confidence interval; SMD: Standardized mean difference; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

in managing aromatase inhibitor-induced arthralgia in patients with breast cancer.

Conclusions

In summary, this comprehensive analysis indicates that acupuncture therapy markedly enhances BPI outcomes in breast cancer patients experiencing AIA, particularly when administered over a 6-week treatment period. Notably, the WOMAC measurements showed no statistically significant differences between the groups. The intervention demonstrated a favorable safety profile with minimal adverse events. Subsequent research should focus on developing customized therapeutic protocols to establish optimal treatment duration and session frequency for AIA management. Future investigations

should employ enhanced blinding methodologies to better distinguish between the authentic therapeutic effects and placebo responses to both verum and simulated acupuncture.

Conflict of interest statement

Yi Guo is the editorial board member of this journal and other authors declare no conflict of interest.

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Author contributions

All authors listed have made substantial, direct, and intellectual contributions to the work. Bo Chen and Yi Guo designed the study. Zheng Zhu, Yaman Zheng, and Xinru Yuan reviewed the literature and drafted the main manuscript. Baomin Dou, Liang Liu, Pei Yong Loh, and Aoxiang Chen had helped with literature search, data extraction. Bo Chen, Zheng Zhu, Peihong Ma, and Zelin Chen conducted the data analysis. All authors edited and reviewed and the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

All datasets generated in this study are included in the manuscript and supplementary files.

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