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Complementary and alternative therapy for pain disorders: from bench to clinical practice

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Complementary and alternative therapy for pain disorders: from bench to clinical practice

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Editorial: Complementary and alternative therapy for pain disorders: from bench to clinical practice

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pain, complementary and alternative therapy, acupuncture, yoga, cupping, mechanism, efficacy, safety

Editorial on the Research Topic
Complementary and alternative therapy for pain disorders: from bench to clinical practice

1 Introduction

Pain disorders are a widespread clinical concern, affecting millions globally and leading to diminished quality of life and reduced productivity (1). While pharmacological treatments remain a cornerstone in pain management, they often present challenges, such as adverse side effects, drug tolerance, and insufficient relief for certain patients (2). These limitations have led to a growing exploration of complementary and alternative therapies (CATs) as non-pharmacological solutions for pain (3). This editorial consists of 17 recent studies authored by 149 researchers from five countries, highlighting the role of CATs—including acupuncture, yoga, and cupping—in addressing pain disorders. The discussion covers key aspects of CATs, such as their underlying mechanisms, clinical efficacy, and integration into conventional medical practice.

2 Mechanistic insights into complementary and alternative therapies

Understanding the underlying mechanisms of CATs is essential for their broader acceptance in clinical practice. Huang et al. investigated acupuncture's effects on chronic

spontaneous urticaria using functional MRI, identifying alterations in brain network function that may underlie its therapeutic effects. Similarly, Ye et al. explored the role of astrocyte activation in the somatosensory cortex as a mechanism for electroacupuncture's analgesic effects in acid-induced pain, providing a novel insight into how acupuncture may modulate pain pathways at the neurobiological level.

3 Evaluating the efficacy and safety of CATs across pain conditions

Several studies have assessed the efficacy of various CATs across different pain conditions, highlighting both potential benefits and areas where further research is needed. Wang L. et al. performed an evidence-mapping study on cupping therapy, which suggested that cupping may have beneficial effects on pain, although the overall quality of evidence was varied, ranging from low to moderate. Ko and Kim investigated the impact of acupuncture on pain and substance P levels in middle-aged women with chronic neck pain, demonstrating significant pain reduction and highlighting acupuncture's potential role in modulating neuropeptides associated with pain perception. Additionally, Zhang, Chang et al. reviewed systematic reviews on yoga for chronic low back pain, finding that yoga can be an effective and safe intervention, though the quality of the evidence was inconsistent.

4 Clinical applications of CATs in specific populations

Research has also focused on the application of CATs in specific patient populations, enhancing our understanding of their practical use in clinical settings. Zhang, Chen et al. studied auricular acupuncture as an adjunct for postoperative pain management in patients undergoing total knee arthroplasty (TKA). Their findings indicated significant reductions in postoperative pain and inflammation, supporting the use of acupuncture as a complementary therapy in surgical recovery. Liu et al. conducted a network meta-analysis to compare various acupuncture modalities combined with multimodal analgesia for post-TKA pain. This study demonstrated that these combined approaches offer superior pain relief and functional outcomes compared to multimodal analgesia alone, suggesting a beneficial role for acupuncture in enhancing postoperative pain management.

The Alberta Complementary Health Integration Project (ABCHIP) provided real-world evidence on the integration of acupuncture in treating pain and mental health concerns in vulnerable populations, such as youth and the elderly. Results indicated significant improvements in pain severity, sleep quality, and mental health measures, underscoring the potential of acupuncture as part of a holistic approach to patient care (Lu et al. (a)).

5 Expanding the applications of CATs

Beyond traditional applications, CATs are being explored for their potential benefits in managing complex conditions such as cancer-related pain and neurological disorders. Zhou et al. conducted a systematic review and meta-analysis on acupuncture point stimulation for stomach cancer pain, finding it to be more effective than standard medication-based approaches, thus supporting its use in oncology settings. Additionally, Zhang J. et al. detailed a protocol for a systematic review of fire needle therapy for cancer pain, aiming to clarify its efficacy and safety as an adjunctive treatment for cancer-related pain management. Wang Z. et al. explored the efficacy of acupuncture in managing facial nerve edema in patients with acute Bell's palsy, contributing to the understanding of acupuncture's role in acute neuropathic pain conditions.

6 CATs for osteoarthritis and chronic pain management

Osteoarthritis, particularly knee osteoarthritis (KOA), is a common chronic pain condition where CATs have shown potential benefits. Zhao et al. outlined a study protocol to evaluate the effectiveness of acupuncture and tuina in managing KOA, addressing the controversy surrounding their clinical application by providing structured evidence on short- and long-term outcomes. Qiu et al. proposed combining catgut embedding in acupoints with repetitive transcranial magnetic stimulation for treating postmenopausal osteoporosis, offering an innovative approach that merges neurostimulation with traditional therapies to address both pain and bone health.

7 Addressing pain and mental health with integrated therapies

The intersection of pain management and mental health is increasingly recognized, with studies exploring how CATs can address both domains simultaneously. Lu et al. (b) from the Alberta Complementary Health Integration Project highlighted the benefits of acupuncture in alleviating pain and improving mental health outcomes in a diverse patient population, demonstrating significant reductions in pain severity, anxiety, and depressive symptoms. Xiong et al.'s systematic review on acupuncture for myofascial pain syndrome confirmed its effectiveness in reducing pain, suggesting the need for further studies to optimize treatment protocols for best results.

8 Future directions and global trends in CATs research

Li et al.'s bibliometric analysis provided a comprehensive overview of global trends in acupuncture research for pain

management from 2010 to 2023, identifying key areas for future research such as standardization of treatment protocols and enhanced international collaboration. Song et al. reviewed the role of CATs in migraine treatment, detailing various mechanisms through which therapies like acupuncture and herbal treatments may alleviate migraine symptoms, thus expanding the understanding of CATs beyond traditional pain disorders.

9 Summary

This editorial synthesizes recent advancements in complementary and alternative therapies for pain disorders, highlighting their potential as effective, non-pharmacological treatment options. By bridging the gap between bench research and clinical application, these studies underscore the importance of continued investigation into CATs to improve their integration into mainstream healthcare. Future research should aim to enhance the quality of evidence, standardize treatment protocols, and foster interdisciplinary collaboration, ultimately leading to more comprehensive, patient-centered pain management strategies.

Author contributions

QZ: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. SY: Conceptualization, Data curation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. MF: Conceptualization, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. JY: Conceptualization, Data curation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. XL: Data curation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. HC: Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. H-TY: Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. DZ: Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. TX: Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. BG: Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Project administration, Supervision. GY: Conceptualization, Investigation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Conflict of interest

JY was employed by Shenzhen Frontiers in Chinese Medicine Research Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Brain network mechanism of acupuncture for chronic spontaneous urticaria: a functional magnetic resonance imaging study protocol

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Introduction: Chronic spontaneous urticaria (CSU) is a common skin condition that can significantly impact patients' quality of life. Although studies have demonstrated the efficacy of acupuncture in treating CSU, the underlying mechanisms remain unclear. Dysfunction within the brain's default mode network (DMN) represents a fundamental characteristic of central pathological changes associated with CSU. Therefore, it is hypothesized that improving brain network dysfunction could serve as a key mechanism through which acupuncture exerts its therapeutic effects. This study aims to provide evidence supporting this hypothesis.

Methods and analysis: This study, a parallel, randomized, sham-controlled functional neuroimaging investigation will be conducted in China. We aim to enroll 50 patients with CSU and 25 healthy controls, distributing them evenly between the acupuncture and sham acupuncture groups in a 1:1 ratio. The total observation period will span 6 weeks, including 2 weeks designated for the baseline phase and 4 weeks allocated for the clinical treatment phase. Prior to treatment, all participants will undergo magnetic resonance scanning, clinical index detection, and microbiota collection. Following treatment, the patients with CSU will be retested for these indicators. Using resting-state functional connectivity (rsFC) analysis, dynamic Functional Connection (dFC) analysis, and brain microstate extraction technology combined with correlation analysis of microbiota and clinical indicators, the regulatory mechanism of acupuncture on the brain network of CSU will be evaluated from multiple dimensions.

Ethics and dissemination: This trial was approved by the Biomedical Ethics Review Committee of the West China Hospital, Sichuan University (No. 2022-1255). Each participant will provide written informed consent to publish any potentially identifiable images or data.

Clinical trial registration: https://www.chictr.org.cn/, identifier: ChiCTR2200064563.

KEYWORDS

acupuncture, chronic spontaneous urticarial, microbiota, fMRI, randomized controlled trial, protocol

Introduction

Chronic urticaria (CU) is a skin disease characterized by reddish wheals and unbearable itching, with or without angioedema, lasting for ≥6 weeks. Chronic spontaneous urticaria (CSU) is the most common type of CU (71.2%) and is characterized by urticaria symptoms without inducing factors (1, 2). The prevalence of CU is particularly high within the Asian population (1.5%), with a higher prevalence among women than men (3). Owing to complicated conditions, recurrent symptoms, and few effective curative treatments, patients are often required to take high-cost drugs for an extended period. This significantly impacts their quality of life and places a considerable burden on both individuals and society (4, 5).

The latest clinical guidelines for urticaria state that modern second-generation H1-antihistamines should be employed as first-line treatment drugs (2). Despite this, the guidelines do not provide specific recommendations for individual specific drugs due to insufficient research on the effectiveness and safety evaluation of all second-generation H1-antihistamines. Furthermore, the guidelines recommend using omalizumab or cyclosporine for patients who have an inadequate response to second-generation H1-antihistamines. However, there are still some patients who do not benefit from these medications (6, 7). The Taiwanese Dermatological Association consensus proposes that non-pharmacological therapies are also an important approach in alleviating urticaria (8). As an nondrug alternative therapy, acupuncture has been widely used to treat pruritic dermatoses, including CSU, and has demonstrated curative effects (9, 10). However, due to a lack of high-quality evidence supporting its use and insufficient elucidation on the mechanisms underlying acupuncture's effects, recent clinical practice guidelines do not recommend or report the beneficial effect of acupuncture on CSU (11, 12). Therefore, further research is needed to provide additional evidence.

Given the multi-target and holistic regulatory characteristics of acupuncture, single-mechanism studies cannot fully elucidate the mechanism underlying its therapeutic effects. Therefore, the objective of this study is to explore the potential therapeutic targets of acupuncture by examining a systematic onset mechanism on CSU. Functional magnetic resonance imaging (fMRI) studies have demonstrated that during episodes of dermatotic itch in patients, the primary afferent nerves from the skin projects itch signals to the thalamus. These signals activate the brain's default mode network (DMN) (13, 14), leading to abnormal functional connectivity. It has been established that DMN brain dysfunction represents an important characteristic of central pathological changes in CSU (15, 16). Moreover, Characteristic changes have been reported in the intestinal microbial population of patients with CSU (17), which may aggravate inflammatory responses and immune dysfunction (18). Similar to gut microbiota, the skin microbiota is closely associated with chronic inflammatory skin diseases (19–21). It plays a regulatory role in modulating immune responses within the skin to prevent inflammation (22). Furthermore, a bidirectional interaction between the microbiota and brain function, often referred to as the "Microbiota-Brain Axis," has been identified (23). This interaction may potentially contribute to the pathogenesis of certain chronic inflammatory skin conditions like rosacea (24), and can influence neurophysiology and behavior, including anxiety and depression. These effects involve complex mechanisms involving the immune system, neuroendocrine system, and metabolism (25). However, a comprehensive understanding of these mechanisms remain elusive. Another objective of this study is to enhance the understanding of the underlying pathological mechanisms involved in CSU from diverse perspectives.

Recent studies on brain networks have shown that DMN largely overlaps with acupuncture response areas (26, 27). That is, verum acupuncture can regulate the DMN and increase the functional connectivity of the DMN with the sensorimotor network, pain emotion, and memory-related brain regions. Moreover, acupuncture can exert therapeutic effects by modulating microbiota (28, 29). These underlying mechanisms also play a crucial role in both the development and resolution of CSU. Accordingly, we have designed a randomized sham acupuncture-controlled trial. fMRI will serve as the primary research method while the key DMN brain regions regulated by acupuncture for CSU treatment will represent the seed points. Furthermore, we plan to analyze the microbiota and clinical indicators. The primary objective of this study is thus to systematically elucidate the brain network mechanism associated with the treatment of CSU by acupuncture. Our goal is to provide robust scientific evidence to support the clinical application of acupuncture as a treatment modality for CSU.

Methods and analysis

Study design

This is a parallel randomized sham-controlled functional neuroimaging study. Fifty CSU patients and 25 matched healthy subjects will be randomly assigned to the verum or sham acupuncture groups at a 1:1 ratio. The total observation period of this study is 6 weeks, including a baseline period of 2 weeks and a clinical treatment period of 4 weeks. Before treatment, all participants ($n = 75$) will undergo clinical index evaluation, magnetic resonance scanning, and microflora collection. Following treatment, only the CSU patients will be reassessed for these indicators. The study flow chart is presented in Figure 1, and the schedule of enrolment, interventions, and assessments is shown in Table 1. This trial will be reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Recruitment and informed consent

Participants will be recruited from the West China Hospital of Sichuan University from 1 January 2022 to 31 December 2023.

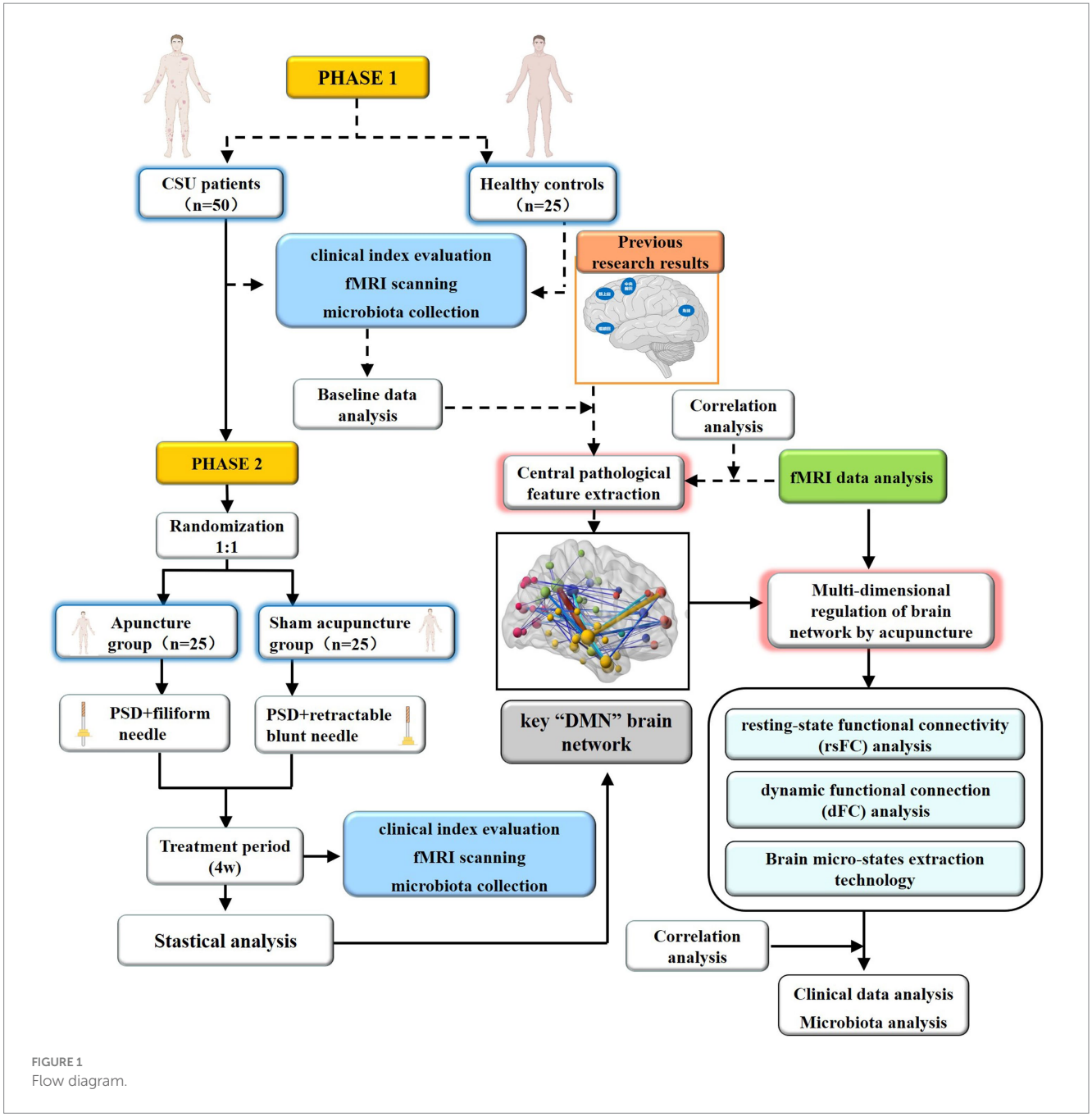

FIGURE 1
Flow diagram.

Different strategies will be used to recruit potential participants, including posters and social media advertisements. Researchers will ensure that the participants are fully informed regarding the research procedures, benefits, and potential risks. Those who agree to participate will provide written informed consent before beginning the study and will be made aware that they can withdraw at any time.

Participants

CSU patients

Diagnosis criteria

According to the diagnostic criteria of CSU in "the International EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines for the definition, classification, diagnosis, and management of urticaria" (2021 edition) (2): (1) repeat appearance of wheals, (2) with/without angioedema, (3) wheal episodes ≥2 times per week, (4) recurrent attacks ≥6 weeks, and (5) spontaneous wheals induced by nonspecific stimulation factors.

Inclusion criteria

The study will enroll patients who meet the following criteria (1) meet the diagnostic criteria of CSU as defined in "The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria" (2); (2) right-handedness of either sex, aged between 18 and 70 years, with a minimum of 6 years of education; (3) urticaria activity score 7 (UAS7) > 14; (4) no metal implants, no fMRI scanning contraindications; (5) patients who

TABLE 1 Schedule of enrolment, interventions, and assessments.

Time point	Enrolment	Baseline	Treatment period	
	Week-1	Week 0	Week 2	Week 4
Enrolment				
Eligibility screen	√			
Informed consent	√			
Inclusion/exclusion criteria	√			
Expectation of acupuncture	√			
Physical examination	√	√	√	√
Medication record	√	√	√	√
Treatment record	√	√	√	√
Intervention groups				
Verum acupuncture			←	→
Sham acupuncture				
Assessments				
UAS7/VAS		√	√	√
PSQI/DLQI		√	√	√
HAMA/HAMD		√	√	√
SAS/SDS		√	√	√
Skin wheal measures		√	√	√
IgE/CRP		√		√
fMRI		√		√
Gut/skin microbiota		√		√
Safety				
Safety evaluation			√	√
Adverse events				√
Effects self-assessment				√
Patient compliance				√
Blinding assessment				√

have not taken any antihistamines within 2 weeks before entering the study, and have not used steroid hormones or immunosuppressants within the last month; (6) no acupuncture treatment within 3 months before entering the study, no participation in other ongoing clinical studies; (7) and patient who have provided signed informed consent and volunteered to participate in this study.

Exclusion criteria

Patients who meet any of the following criteria will be excluded: (1) claustrophobic or other fMRI scanning contraindications; (2) unable to understand or record in the urticaria diary; (3) pregnant or lactating; (4) severe primary diseases, such as cardiovascular, liver, kidney, digestive, or hematopoietic conditions; (5) progressive malignant tumors or other severe wasting diseases that increase the risk of concurrent infection and bleeding; (6) unconscious, unable to express subjective symptoms independently, or diagnosed with a psychiatric illness; (7) and patients who have participated in similar research within the past month.

Healthy controls

Inclusion criteria

Participants who meet all of the following criteria will be included in this study: (1) have not participated in similar research within 1 month; (2) right-handedness of either sex; between the ages of 18 and 70 years, with a minimum of 6 years of education; (3) no history of urticaria or other allergic diseases; (4) no drug use for at least 15 days before entering the study; (5) no metal implants, no fMRI scanning contraindications; (6) all physiological indexes are common, no functional or organic diseases; (7) No participation in similar or other clinical studies; (8) volunteer for this study and provide signed informed consent.

Exclusion criteria

Participants who meet any of the following criteria will be excluded: (1) CSU disease history or allergic constitution; (2) pregnant or lactating; (3) Hamilton anxiety scale score (HAMA) > 7 or Hamilton depression scale score (HAMD) > 7; (4) metal implants,

fMRI examination contraindications like claustrophobia; (5) severe asymmetry of skull anatomical structure or apparent lesions detected while scanning; (6) unconscious or unable to express subjective symptoms independently.

Randomization and blinding

Eligible patients will be randomly assigned to the acupuncture or sham acupuncture group at a 1:1 ratio. Statistical analysis will be performed using SPSS software (version 22.0) to generate random sequences with a random number table. The random distribution cards will contain random numbers, serial numbers, and groups, packed in opaque numbered envelopes. The envelope will be unsealed following study enrolment. Owing to the particularity of acupuncture research, it is difficult to blind the acupuncture operators. As such, fake acupuncture devices and separate treatment rooms will be used for each patient to blind them as much as possible. Moreover, the "three separations strategy" will be strictly adhered to by researchers, operators, and statisticians throughout the research process. Efficacy evaluation, data analysis, and statistics will be completed by third parties blinded to the groupings.

Interventions

Patients in the acupuncture and sham acupuncture groups will receive treatment for 4 weeks, five times per week for the first 2 weeks, and three times per week for the next 2 weeks, for a total of 16 treatments. The acupuncture group will be treated with filiform needles (Huatuo brand, 0.25 × 40 mm), whereas the sham group will be treated with retractable blunt needles (AcuPrime brand, 0.25 × 40 mm). A Park sham device (PSD) (DONGBANG Acupuncture Inc.) will be used to achieve patient blinding in both groups. Acupuncturists with a doctor's qualification certificate and more than 5 years of experience will complete the treatment sessions. Before the formal start of the study, we will conduct a unified training and assessment of related acupuncture operations.

Acupuncture group

The acupuncture group will be treated with "PSD + filiform needle" combined equipment. The acupoint selection plan refers to the Chinese textbook *Acupuncture and moxibustion Science* and expert opinions (30). Bilateral acupoints: LI11 (Quchi), SP10 (Xuehai), SP6 (Sanyinjiao), ST36 (Zusanli), ST25 (Tian Shu), and HT7 (Shenmen); single acupoint: CV12 (Zhongwan). The acupoint locations are shown in Figure 2. The patients will be placed in the supine position. The operator will remove the release paper from the PSD surface and insert the needle through the device with the needle tip exposed at the end. After disinfecting the acupoints and inserting the needles, the PSD will be fixed. After inserting the needle (20–40 mm, vertically), the lifting-thrusting method will be applied to induce and maintain the Deqi sensation (frequency: 60–90 times/min, amplitude: 3–5 mm). The needles will be retained for 30 min.

Sham acupuncture group

The sham group will be treated with the "PSD + retractable blunt needle" combined equipment. Non-meridian and non-acupoint points will be selected (Figure 2). The retractable blunt needle has a hollow handle, and the needle tip is flat and blunt. Upon insertion, the body of the needle retracts into the hollow needle handle and does not penetrate the acupoints, remaining on the skin surface without causing deqi sensations. The needle will be retained for 30 min without needle manipulation. The remaining operating procedures will be performed in the same manner as that described for the acupuncture group.

Outcome measures

Primary outcome measure

Urticaria activity score 7

The UAS7—a fundamental scale for evaluating urticaria symptoms (2)—assesses the number of wheals and degree of itching. Owing to the frequent and varying attacks of urticaria, we recommend daily recording. Subsequently, a total score of seven consecutive days will be used to evaluate urticaria activity.

Secondary outcome measures

Visual analog scale

The VAS will be used to evaluate the degree of urticarial itching in subjects over 1 week. More specifically, the participants will use a 10 cm horizontal line marked from 0 (no itching) to 10 (intolerable itching) to indicate their itching sensation. The degree of itching will be evaluated by measuring the distance from 0 to the mark. As CSU attacks occur more than once a day, the record is based on the highest daily VAS itching score.

Dermatology life quality index

The DLQI will be used to evaluate quality of life. This index covers six areas: symptoms and feelings, daily activities, leisure, work and school, interpersonal relationships, and the impact of treatment on everyday life (31).

Pittsburgh sleep quality index

The PSQI comprises nine questions used to evaluate the effect of CSU on sleep quality. The evaluation includes sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, sleeping pills, and daytime dysfunction (32).

Hamilton anxiety/depression scale

The Hamilton Anxiety Scale (HAMA) consists of 14 items (33), whereas the Hamilton Depression Scale (HAMD)_comprises 17 items (34). Both of these scales will be employed to evaluate the impact of CSU on the mental health of patients.

Self-rating anxiety/depression scale

The Self-rating anxiety scale (SAS) (35) and Self-rating depression scale (SDS) (36) are both self-report questionnaires consisting of 20 items each, designed to assess levels of anxiety and depression. Both have been widely used in mental health assessments among patients with various skin and other medical conditions (37).

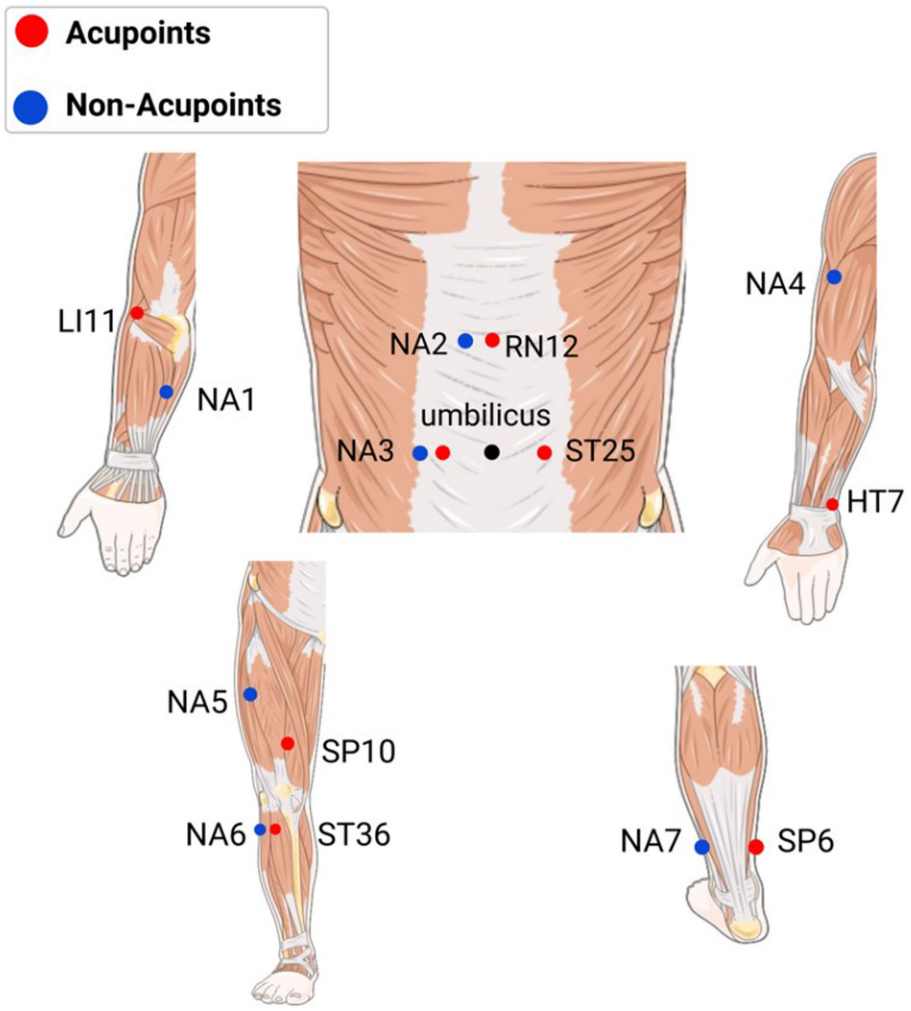

FIGURE 2
Location of acupoints and non-acupoints. NA1: midpoint between the medial epicondyle of the humerus and the ulnar malleolus, on the ulnar margin. NA2: 1.2 cun beside CV12. NA3: 1 cun lateral to ST25, the midpoint of ST25 and SP15. NA4: inner anterior edge of the arm, at the junction of the deltoid and biceps. NA5: on the thigh, 0.8 cun medial to the midpoint of the line connecting the anterior superior iliac spine and the outer superior angle of basis patellae. NA6: 1 cun lateral to ST36, between the stomach and gallbladder meridian. NA7: 3 cun above the prominence of the lateral malleolus, between the stomach and gallbladder meridian.

Skin wheal measures

Infrared thermometers (Cofoe; Cofoe Medical Technology Co., LTD) will be used to measure the skin temperature of wheals. We will also use skin analyzers (RealBubee, Ningbo Realbubee Medical Equipment Co., LTD) to measure skin moisture, oil, and elasticity, as well as Vernier calipers to measure each wheal's maximum length and vertical diameter. The arithmetic mean of the measured values will be recorded as the typical value.

Serum laboratory testing

Patients with CSU exhibit higher levels of serum-specific IgE and C-reactive protein (CRP) compared to healthy controls (38, 39). Therefore, CSU patients will receive fasting hemospasia before and after treatment to detect serum-specific IgE and CRP levels.

Gut microbiota collection

Stool samplers will be used to collect specimens from the middle of the stool (approximately 3 g) at the hospital. Samples will then be placed in a 10 mL centrifuge tube and immediately stored at −80°C. The genomic DNA of samples will be extracted by cetyltrimethylammonium bromide (CTAB) or sodium dodecyl sulfate (SDS) methods, while agarose gel electrophoresis will be employed to assess the purity and concentration of the extracted DNA. Subsequently, DNA will be collected in a centrifuge tube and diluted with sterile water to 1 ng/μL for further analysis.

Skin microbiota collection

A sterile cotton swab soaked with normal saline will be applied to the skin surface (patients: skin at the wheals; healthy persons:

corresponding normal skin). The sampling surface will be wiped smoothly in the horizontal and vertical directions, respectively. Subsequently, the bottom of the cotton swab head will be cut off at three sampling points, placed in a 15 mL centrifuge tube, and stored at −80°C. The DNA extraction and detection methods were the same as those for gut microbiota collection.

fMRI outcome measures

We will use a Siemens' 3.0 T superconducting magnetic resonance scanner and a 12-channel head coil for magnetic resonance scanning. All subjects will be scanned with the same parameters, and the same operator will be responsible for routine operations. An operator instruction manual will be produced to standardize the operation process and communication with the subjects. The various factors that can impact the magnetic resonance scanning (MRS) process will be strictly regulated. That is, the scanning time will be unified and the interference of the environment, equipment, technicians, and psychology on the subjects' brain function imaging data will be limited, improving data reliability. The scanning parameters will be as follows: repetition time (TR): 2,000 ms, echo time (TE): 30 ms, field of view (FOV): $240 \times 240\,mm^2$, slice thickness (ST): 4 mm, number of slices (NOS): 40, matrix: 64×64, flip angle (FA): 90°.

Safety assessment

If adverse events, such as dizziness, pain, bleeding, or haematoma occur after acupuncture, researchers will deal with them in a timely manner by inviting expert to consult when necessary to ensure the safety of the participants. The event's occurrence time, symptoms, signs, severity, duration, and treatment methods will be recorded in the report forms and analyzed. The ethics committee will then evaluate whether the trial should be suspended.

Sample size

Due to the particularity of the neuroimaging mechanism, the clinical sample calculation method is not applicable. According to fMRI sample size research, each group should include at least 6–12 patients (40), while the statistical data of 20 subjects resembles that of large sample data for 130 subjects (41). Considering the uncertain factors in this study, including the loss or elimination of subjects and unavailable data due to head movements, we included 50 patients and 25 matched healthy persons in this study.

Statistical analysis

Clinical data analysis

All baseline and clinical response index data will be analyzed using the SPSS software (version 22.0). Measurement data will be expressed as mean ± SD. Following the normality test, an independent samples *t*-test will be used if the criteria of normal distribution and homogeneity of variance are met. Otherwise, a non-parametric test (Mann–Whitney U-test) will be used. Count data will be analyzed by the two-sided χ^2 test. A $p < 0.05$ will be considered significant.

fMRI data analysis

Neuroimaging data preprocessing

The DICOM software (version 1.3.5) will be used to convert the BOLD fMRI data into an analyzable NIFTI file. Preprocessing will be based on the MATLAB 2013b software platform with DPARSF V1.0 and SPM12 software. The preprocessing steps include removing the first 10 time points, time-layer correction, head-motion correction, spatial standardization, smoothing, delinear trends, noise filtering, and regression covariates.

Region of interest

Our previous studies found that multiple "DMN" core brain regions are closely related to urticaria, dyssomnia, and mood disorders. Their MNI coordinates are as follows: orbitofrontal cortex ($X = -45$, $Y = 24$, $Z = -12$), superior frontal cortex ($X = -15$, $Y = 33$, $Z = 54$), precentral gyrus ($X = 48$, $Y = 9$, $Z = 33$), angular gyrus ($X = 45$, $Y = -48$, $Z = 33$), and hippocampal gyrus ($X = -18$, $Y = -12$, $Z = -9$). These five brain regions were selected as regions of interest (ROI) to complete the resting-state, dynamic functional connectivity, and microstate analyzes.

Resting-state functional connectivity analysis

Based on the MATLAB 2013 software platform, the SPM12 software package will be used to perform the statistical analysis of brain functional connectivity. The whole-brain functional connectivity algorithm will be used to calculate the average time-series of all voxels at seed points. Next, all average time-series will be calculated individually with the Pearson correlation coefficient or the whole-brain voxel time-series. The correlation coefficient between the voxel and seed point can be obtained for each whole-brain voxel and transformed into an approximate Gaussian distribution data value using the Fisher-Z transform. Brain regions with significant statistical relationships will be identified according to a specific threshold and will be considered to have a resting-state functional connection with the seed points.

Dynamic functional connection analysis

The Dynamic BC 2.4 toolkit will be employed to analyze the dynamic functional connectivity network, and the sliding window correlation (SWC) method to analyze the dFC characteristics. Based on previous experience, a window length of 30TR (60 s) and a sliding step size of 1TR will be applied to generate 200-time windows. For each window, the intravoxel time-series Pearson correlation of the ROI will be individually calculated. Subsequently, each subject will produce a sequence of sliding window correlation coefficients, which will be transformed to a normal distribution using Fisher's z-conform. The variation in the correlation coefficient time-series will be represented by calculating the standard deviation of the *z*-value for each voxel to characterize the dFC variability. Time means, standard deviations, and coefficients of variation will be used to analyze the specific attributes of dFC.

Brain micro-states extraction technology

Based on the dynamic functional connectivity network extraction, the k-means clustering method will be used in the dynamic functional connectivity matrix by cluster analysis to obtain the microstates of

dynamic functional connectivity. Next, we will study brain functional connectivity changes in these microstates. The K-means algorithm uses a simple iterative strategy to divide the dataset into K nonoverlapping clusters. First, we will obtain the whole-brain dynamic functional connection vectors of all participants via vectorization in the upper triangular matrix of the dynamic functional connection matrix. Then, all functional connection vectors with strong variability (>1 SD) will be selected as clustering samples. The average diameter of each clustering result will be calculated to obtain the optimal number of clusters. The results will then be transformed into matrix form by running the standard k-means algorithm with the optimal clustering number on each subject's dynamic functional connection vector. After summarizing, all clustering medians for each group will be used to represent the results for each group, i.e., the "micro-state." Second, the time-series characteristics of the dFC microstates will be analyzed. The specific indicators include the average residence time of the microstate, conversion time, and stability.

Microbiota analysis

Clinical skin and intestinal flora DNA will be analyzed using 16S rDNA amplicon sequencing to determine the microbial composition of the samples. 16S rRNA gene sequencing will be performed using Novogene (Beijing, China), according to the manufacturer's instructions. Raw data obtained by sequencing will then be spliced and filtered to obtain clean data. The DADA2 method will be employed to reduce noise based on the effective data, and sequences with abundances <5 will be filtered out to obtain the final amplicon sequence variants (ASVs).

For the ASVs obtained, species annotation will be performed on representative sequences to obtain the corresponding species information and abundance distribution. Simultaneously, the abundance, alpha diversity calculation, Venn diagrams, and petaline graphs of ASVs will be analyzed to obtain species richness and evenness information. Additionally, multiple sequence alignment of ASVs will be carried out to construct a phylogenetic tree. Principal coordinate analysis (PCoA), principal component analysis (PCA), nonmetric multi-dimensional scaling (NMDS), other dimension reduction analysis, and sample phylogenetic tree display will be applied to explore the differences in community structure between CSU patients and healthy people, and between the acupuncture group and sham acupuncture group. To further explore the community structure differences among grouped samples, statistical analysis methods, including *t*-test, MetaStat, and LEfSe, will be employed to test the significance of species composition and community structure of grouped samples.

Correlation analysis

The interactions between brain functional connectivity, microbiota, and clinical indicators in patients will be analyzed using MATLAB (version R2015b), which will calculate the Spearman correlation. An effect size of $r = 0.10$ is considered small (explained by 1% variance), 0.30 is medium (explained by 9% variance), and 0.50 is large (explained by 25% variance). The Z test and Fisher's r-to-z transformation will be used to evaluate the differences in correlation coefficients between the acupuncture and sham acupuncture groups. Statistical significance is set at $p < 0.05$. Cytoscape (v. 3.8.2) will be employed to construct a visual network of interactions between brain functional connectivity, microbiota, and clinical indicators.

Data management and quality control

The clinical data will be recorded in a case report form (CRF) by a trained researcher. Another researcher will confirm the accuracy and completeness of the recorded information and record the relevant data in a password-protected Excel file. All CRF data will be stored in a locked cabinet for at least 5 years. The Biomedical Ethics Review Committee of West China Hospital, Sichuan University will regularly review the progress of the study and monitor the research data to ensure authenticity and reliability.

Discussion

We hypothesized that the brain network mechanism of acupuncture serves as the multi-dimensional regulator of the key "DMN" brain network in CSU. To test this hypothesis, we will employ BOLD fMRI as the primary research method, as well as rsFC with strong spatial characterization, dFC with high sensitivity to time-varying characteristics, and microstate extraction as the main analysis methods. In this way, we aim to explore the pathological features of brain networks in patients with CSU in three dimensions: time, space, and microstates.

Microstate extraction technology will be used to identify subtle changes in the deep layers of the dynamic brain network. The "microstate" is a transient stable state found in many dFC studies (42). Specifically, the brain rapidly evolves into another state after maintaining a particular state for 80–120 ms; different states reappear over time. This analysis method has high sensitivity and specificity and can capture hidden dynamic changes based on dFC analysis.

In addition to studying the brain network, we will evaluate changes in the microbiota. Specific relationships between gut microbiota and CSU have been proven. Similar to the intestine, many skin microbiota are related to pruritus diseases (43). However, the direct relationship between skin microbiota and CSU remains unclear. Therefore, in this study, we evaluated the gut and skin microbiota to explain the pathological characteristics of CSU from a microbiota perspective.

Given the complexity of CSU pathogenesis, it is not sufficient to explore its mechanism using a single peripheral or central mechanism. Moreover, due to the overall regulatory characteristics of acupuncture, it is difficult to systematically explain the acupuncture treatment mechanism of CSU from a single perspective. Nevertheless, gut microbiota is significantly associated with multiple brain network functional connections, including DMN (44). Hence, this study will exploit the key brain networks of CSU as a breakthrough point to explore the acupuncture treatment mechanism for CSU in the "brain-gut-skin" context. Compared to previous acupuncture central mechanism studies for CSU treatment that only focused on single brain regions, we will explore the mechanism using rsFC, dFC, and microstate extraction to evaluate brain function while combining microbiota and clinical symptom index correlation analyzes. Hence, this study is expected to provide scientific and objective visual evidence for the clinical application of acupuncture in CSU treatment and promote further development of basic research on CSU treatment.

This study has certain limitations. First, the acupuncturists cannot be blinded due to the particularity of the acupuncture procedure, which may cause bias. Second, because of the skin sensitivity of patients with CSU, the blunt needles used in the sham acupuncture group may stimulate the patients' skin, resulting in unpredictable

changes in the neuroendocrine network, which may affect the experimental results. Third, as a single-center study, the number of samples will be small, and the results may not be extrapolated owing to the single operator, research equipment, and inclusion of patients.

Author contributions

XH: Formal analysis. JX: Formal analysis. YY: Data curation. XD: Supervision. LL: Data curation. NL: Resources. YL: Funding acquisition. SW: Conceptualization. LZ: Conceptualization, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effect of acupuncture on pain and substance P levels in middle-aged women with chronic neck pain

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Chronic neck pain is a leading health issue affecting a significant proportion of the global population. Multiple treatment options for chronic neck pain include anti-inflammatory drugs and analgesics. Acupuncture has been widely used for the treatment of chronic pain. In this study, we aimed to determine the efficacy of acupuncture for female patients with chronic neck pain. Twenty-three participants were enrolled in the study, and participants waited 4 weeks without acupuncture treatment and then received 4 weeks of treatment. One-way ANOVA with repeated measures was used to determine differences in the visual analogue scale (VAS), neck disability index (NDI), and substance P (SP) over time. The subjects' pain intensity and degree of disability due to neck pain were measured as primary outcomes. SP in the blood was also analyzed as a secondary outcome. There was no significant difference between the VAS score and NDI value of baseline and after 4 weeks waiting. However, there was an improvement in both VAS and NDI after 4 weeks treatment. SP level was decreased after 4 weeks treatment. We could conclude that acupuncture is effective in alleviating chronic neck pain. Moreover, our findings revealed the efficacy of acupuncture on chronic pain with potential underlying biological mechanisms.

KEYWORDS

acupuncture, chronic neck pain, substance P, middle-aged women, neck disability index

1. Introduction

Neck pain is a highly prevalent musculoskeletal disorder affecting individuals, families and healthcare systems of countries with substantial economic burdens. The Global Burden of Disease Study between 1990 and 2017 studied trends and prevalence of neck pain, and neck pain was reported as a serious public health problem, still affecting a significant proportion of the global population (1, 2). Popular analgesics such as non-steroidal anti-inflammatory drugs, acetaminophen, and cyclooxygenase 2 inhibitors relieve pain by suppressing the inflammatory process and have been commonly used as pharmacological interventions for musculoskeletal diseases, including neck pain (3, 4).

There are also non-pharmacological treatments such as physiotherapy, manual treatment, and massage therapy (5–7). Acupuncture has been gaining increasing interest for its favorable clinical outcomes in various chronic pains (8–10). Studies have shown a significant improvement in the visual analogue scale (VAS) score in subjects with acute or chronic musculoskeletal diseases such as low back pain after receiving acupuncture treatments (11–13). Nevertheless, there are still controversies over the clinical mechanisms by which insertion and stimulation by needles alleviate chronic pain.

Substance P (SP) is a mediator involved in various physiological processes, such as neuroinflammation and pain transmission (14, 15). It is broadly distributed in both the central

and peripheral nervous system, and some studies have reported control of diseases, such as inflammatory muscle pain, cancer, and colitis, by mediating SP levels in animal models (16, 17). It has been hypothesized that neurological stimulation by needles at acupoints would cause physiological changes, mediating SP in serum (18).

The effect of acupuncture on chronic neck pain and its underlying mechanism is not well explored. In this study, we aimed to investigate the effect of acupuncture on chronic neck pain with different measurements and to further examine the potential biological connection between pain and SP level.

2. Methods

2.1. Study participants

Participant recruitment was performed through advertisement using local flyers in Goyang City, Gyeonggi-do and Seoul City, South Korea, from April 2018 to February 2019. A pre-screening survey was conducted on volunteered participants by assessing numeric pain scale (0–10 points), current medication, and questionnaires based on inclusion and exclusion criteria. Eligible participants were women aged between 40 to 60 years having neck pain for more than 12 weeks (VAS score ≥30.0 mm) (19). The inclusion criteria for participation were the absence of radiating pain and medication or other pain-related treatments. The exclusion criteria were pregnancy, spondylolisthesis, spondylitis, and infectious diseases, potentially affecting the treatment outcome.

2.2. Ethical approval and consent

Ethical approval for this study was obtained from the Institutional Review Board of Kyonggi University (KGU-20171222-HR-026). This study was registered with the Korean Clinical Trial Registry and WHO Clinical Trial Registry (KCT0005363, registered April 3rd, 2018, https://cris.nih.go.kr/cris/en/). The study procedures and potential risks were explained to each participant, and written informed consent was obtained prior to the study enrollment.

2.3. Study procedures

We primarily screened 29 participants to be enrolled in the study. After the first blood sampling (20), two participants dropped out due to perceived discomfort in blood sampling. Four participants withdrew from the study due to not being able to comply with the treatment schedule. Twenty-three subjects were ultimately included in the study and the further outcome analysis (Figure 1). All the outcome measures were assessed by an independent investigator. The investigator was also blinded to the treatment procedure and each patient's treatment.

2.4. Acupuncture protocol

All the subjects received acupuncture treatment at two proximal acupoints (GV14 and GV16) and ten acupoints (BL10, GB20, GB12, GB21, TE3, TE17, ST10, SI3, SI14, and SI15), which are bilaterally symmetric. Acupoints were located near the head, cervical vertebrae, neck and shoulder (Figure 2). The practitioner used disposable sterile needles (0.25 × 0.30 mm) and inserted the needles to a depth of 10–20 mm using a guide tube. The needles remained in the acupoints for 15 min, and each treatment session took approximately 20 min, with relaxation time before and after each treatment. A licensed oriental medicine doctor performed all the acupuncture treatments.

2.5. Primary outcome measures

2.5.1. Visual analogue scale

Neck pain intensity was evaluated using VAS. Patients marked the point on a 10 cm horizontal line that best estimated their intensity of pain. The left end (0.0 cm) represented "no pain," and the right end (10.0 cm) represented "extreme pain" (21). The measurements from the left end of the scale to the patients' marks were recorded in centimeters and analyzed as their pain intensity.

2.5.2. Neck disability index

Neck pain-related disability was assessed by the Korean version of NDI to determine patients' perceived pain levels and degree of interference with daily activities (22). The NDI questionnaire covers ten items: pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. Each item is scored on a 0 (no disability) to 5 (full disability) scale with a maximum total score of 50 points or 100% (23). If a subject responded that they do not drive, we recorded the NDI out of 45 and converted the score to a percentage.

The VAS and NDI measures were completed by each subject before the 4 weeks waiting (baseline), after the 4 weeks waiting (week 4), and after the 4 weeks treatment (week 8).

2.6. Secondary outcome measures

Blood sampling was conducted at three different time points (baseline, week 4, and week 8). The blood from each subject was collected into anticoagulant (EDTA)-treated tubes and prepared by centrifuging the whole blood at 3000 RPM for 15 min at 4°C. Plasma was then transferred into a new microtube and stored at −80°C until analysis. Serum SP levels were measured by enzyme-linked immunosorbent assay (ELISA) (KGE007, R&D, United States) and multimode plate reader (VICTOR Nivo, PerkinElmer, United States).

2.7. Statistical analysis

All data were analyzed using SPSS version 24.0 (IBM SPSS Statistics, Armonk, NY, United States). Statistical significance was set at $p < 0.05$ for all analyses. An independent t-test or chi-square test was performed to compare all variables at baseline between groups. One-way ANOVA with repeated measures at three different time points as main factors were used to test whether pain level significantly differed from baseline in VAS, NDI, and serum SP levels.

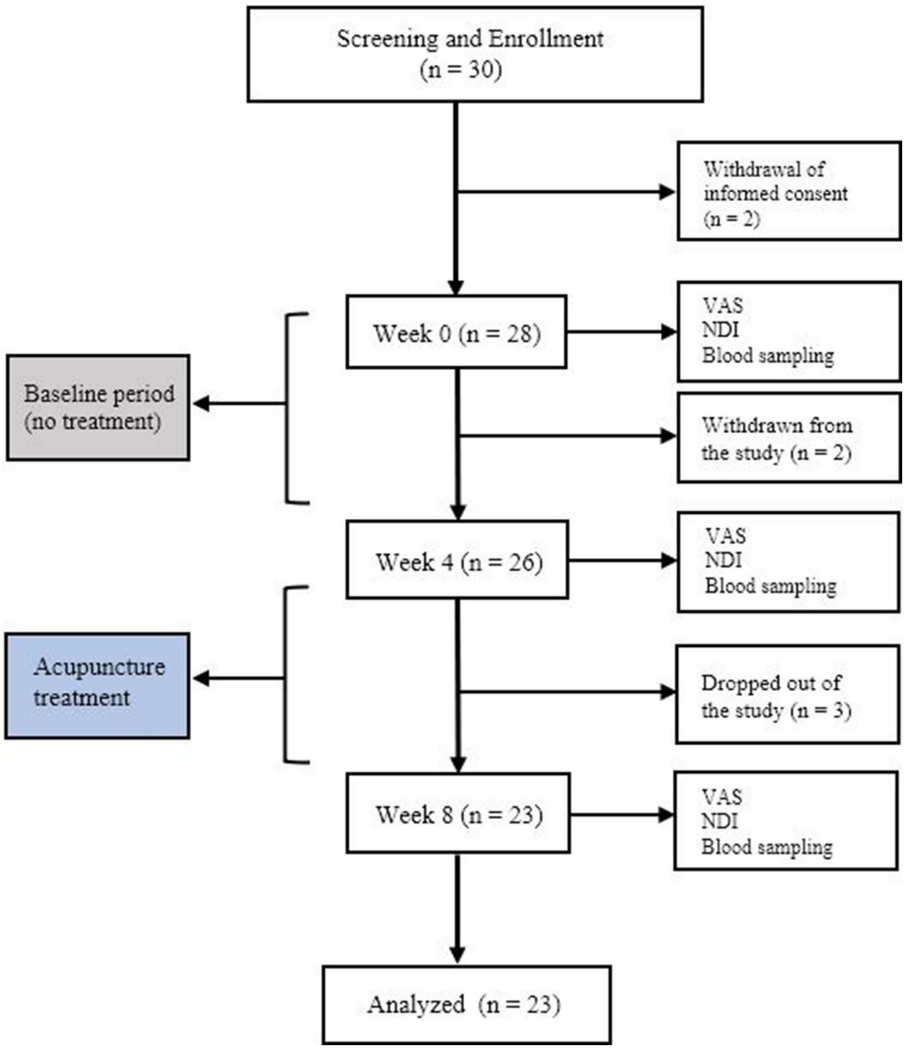

FIGURE 1
Flow chart of the current study.

When a group-by-time interaction was significant, the significance of the difference from baseline was tested by paired *t*-test in each group. The Greenhouse–Geisser correction was applied upon violating the assumption of Mauchly's test of sphericity.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the subjects, including age, body mass index (BMI), current medication, and duration of neck pain, are displayed in Table 1. The average age of the subjects ($n = 23$) was 54.17, and the average BMI was 24.28. Duration of neck pain was less than 3 years for all the subjects, with a mean of 2.65 years. Eighteen subjects (78.3%) were not on any medications, and the types of medication that five subjects (21.7%) had been taking were hypertension and hyperlipidemia medicine.

3.2. Primary outcomes

Pain intensity measured using VAS showed no significant differences between measurement values at baseline and week 4 ($p = 0.102$). There was also no significant difference between the baseline NDI score and the score after 4 weeks-waiting ($p = 0.618$). According to the test of within-subjects effect for VAS result, a significant improvement in pain was observed after 4 weeks-treatment compared to the value after 4 weeks-waiting ($p < 0.001$). In addition, there was also a significant difference in NDI score between the score measured after 4 weeks-waiting and after 4 weeks-treatment ($p < 0.001$) (Figures 3A,B).

3.3. Secondary outcome

The results of one-way ANOVA with repeated measures showed no significantly different changes in SP between baseline value and after the 4 weeks-waiting ($p = 0.736$). However, there was a significant

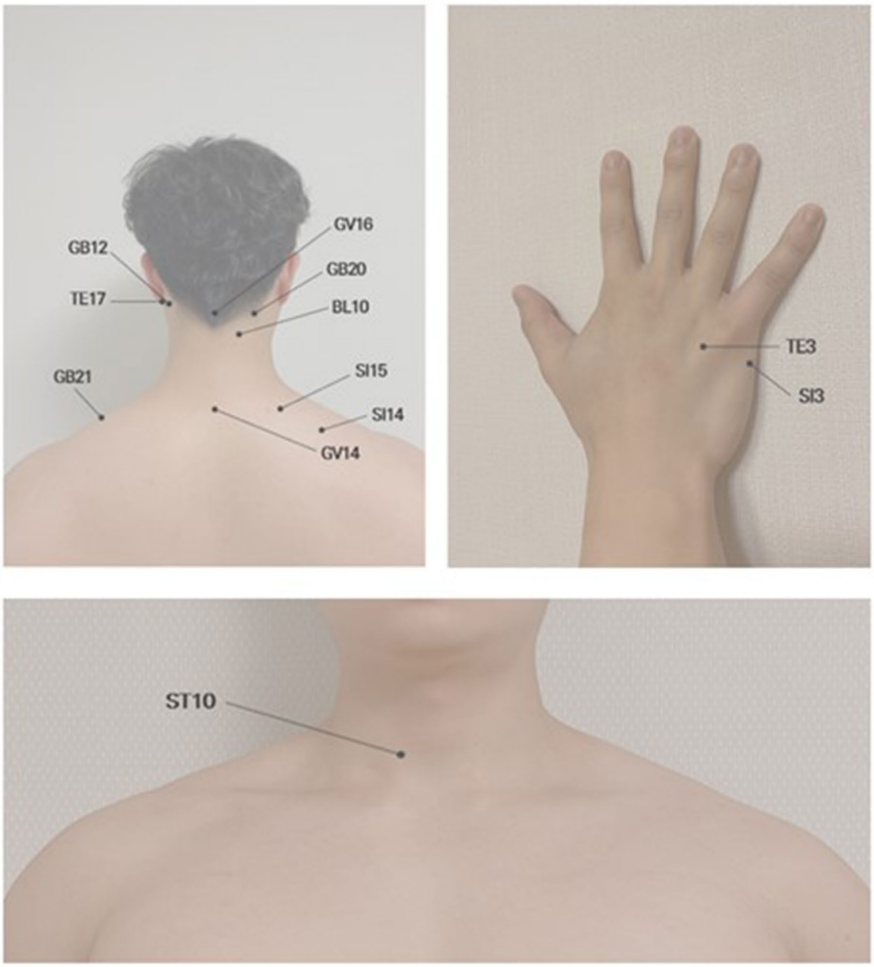

FIGURE 2
Location of the 2 distal acupoints and 10 proximal acupoints used in the current study.

TABLE 1 Baseline characteristics of enrolled subjects.

Age (years)	54.17 ± 5.29
Body mass index (kg/m^2)	24.28 ± 3.71
Duration of pain (years)	2.65 ± 2.79
Current medication	
No	18 (78.3%)
Yes	5 (21.7%)
Hypertension	4
Hyperlipidemia	2

Data are presented as mean ± standard deviation or %.

change in SP value after 4 weeks-treatment compared to the value examined prior to the treatments ($p < 0.05$) (Figure 3C).

4. Discussion

We observed efficacy of acupuncture on chronic neck pain by assessing perceived pain and changes of SP level in serum. There was no significant difference in the comparison of VAS score at baseline vs. after 4 weeks-waiting. After 4 weeks-acupuncture intervention on the subjects with chronic neck pain, there was significant alleviation in pain intensity as VAS decreased from 53.96 mm to 31.65 mm. Subjects also reported that their overall disability level in daily life had diminished after treatments (15.46 ± 10.65) compared to before treatments (26.69 ± 13.45). For pain assessment, patient-reported outcome measures have been widely applied in clinical trials. By self-evaluating pain intensity, patients can subjectively detect their pain over time (24). Our primary outcome data obtained from VAS and NDI also shows how effectively acupuncture improved pain in patients with chronic neck pain.

A growing number of studies demonstrate reliable evidence of the effect of acupuncture on various diseases despite ongoing controversies over acupuncture treatment. Several studies examined the effect of acupuncture treatment on different types of pain. Acupuncture treatment significantly decreased VAS score in Whiplash patients compared to the no-treatment control group (25). In our study, the VAS and NDI were decreased by an average of −22.31 mm and −11.24%, respectively, after 4 weeks of acupuncture intervention. According to the results we obtain from two different self-evaluations, the pain-relief effect of acupuncture on acute pain is also evident in chronic neck pain.

In previous pain-related research, a multitude of biomarkers have been studied to understand complex neurobiological mechanisms of pain. SP is an undecapeptide belonging to the tachykinin peptide family. It is

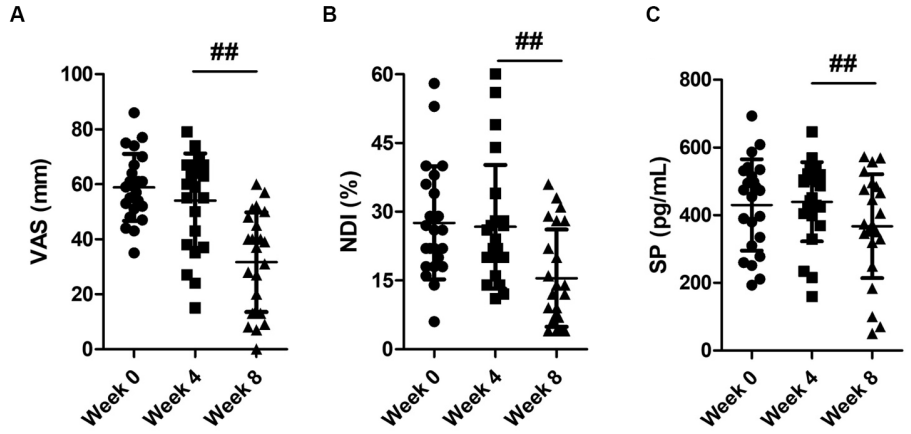

FIGURE 3
Changes in **(A)** visual analogue scale (VAS), **(B)** neck disability index (NDI), and **(C)** substance P (SP) level. Data are presented as mean ± standard deviation. The significance of the within-subject factor (time) was tested by one-way ANOVA with repeated measures. $^{\#\#}p < 0.001$: week 4 vs. week 8.

widely distributed in the central and peripheral nervous systems and released upon nociceptive stimulation. SP is involved in numerous neuronal signaling pathways and plays a pivotal role as a neurotransmitter and a neuromodulator (26, 27). However, the effect of acupuncture on SP has not been well understood in patients with chronic neck pain. Inflammatory biomarkers often reflect the degree of inflammation. We explored the change in SP level to objectively measure pain and make a reliable connection between pain modulation and acupuncture treatment for chronic neck pain. The painful perception can occur by various factor, which means it could stimulate different neural pathways. Interestingly, in this study, SP levels significantly decreased after acupuncture intervention in subjects with chronic neck pain, whereas there was no significant difference in SP levels between baseline and week 4. Based on both primary and secondary outcomes, a correlation between the effect of acupuncture and changes in SP levels can be suggested. However, there were limited subjects and healthy comparison group to further suggest more concrete underlying mechanism. We still need to further investigate how acupuncture played a regulatory role in central sensitization which led to SP level changes and also identify whether SP level is directly or indirectly involved in potential therapeutic mechanisms of acupuncture such as segmental inhibition, release of endogenous opioid, and adrenergic and 5 HT pathway.

This study assessed the impact of acupuncture treatment chronic neck pain in a single group over time. It allowed us to minimize subjects' variation and to compare pain modulation. Although more studies with larger sample sizes and the inclusion of a healthy control group are expected to provide more reliable evidence of the effect of acupuncture on pain regulation in general, our findings suggested the beneficial effect of acupuncture on chronic neck pain and potential pain relief mechanism.

5. Conclusion

The present study suggests that acupuncture alleviates chronic neck pain by managing pain intensity and improving neck pain-induced disabilities in daily life. However, it is still necessary to further investigate the biological mechanism underlying the role of acupuncture in pain relief based on the secondary outcome of this study.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Kyonggi University (KGU-20171222-HR-026). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JK: Investigation, Writing – original draft. S-NK: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of cupping therapy on pain outcomes: an evidence-mapping study

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Objective: Cupping therapy is an ancient technique of healing used to treat a variety of ailments. An evidence-mapping study was conducted to summarize the existing evidence of cupping therapy for pain-related outcomes and indicate the effect and the quality of evidence to provide a comprehensive view of what is known.

Methods: PubMed, Cochrane Library, Embase, and Web of Science were searched to collect the meta-analyses investigating the association between cupping therapy and pain-related outcomes. The methodological quality was assessed by using the AMSTAR 2 tool. Significant outcomes ($p < 0.05$) were assessed using the GRADE system. The summary of evidence is presented by bubble plots and human evidence mapping.

Results: Fourteen meta-analyses covering five distinct pain-related conditions were identified and assessed for methodological quality using the AMSTAR 2, which categorized the quality as critically low (36%), low (50.0%), moderate (7%), and high (7%). In accordance with the GRADE system, no high-quality evidence was found that demonstrates the efficacy of cupping therapy for pain-related outcomes. Specifically, for neck pain, there were two moderate-quality, four low-quality, and two very low-quality evidence, while only one very low-quality evidence supports its efficacy in treating herpes zoster and one low-quality evidence for chronic back pain. Additionally, for low back pain, there were two moderate-quality, one low-quality, and four very low-quality evidence, and for knee osteoarthritis, three moderate-quality evidence suggest that cupping therapy may alleviate pain score.

Conclusion: The available evidence of very low-to-moderate quality suggests that cupping therapy is effective in managing chronic pain, knee osteoarthritis, low back pain, neck pain, chronic back pain, and herpes zoster. Moreover, it represents a promising, safe, and effective non-pharmacological therapy that warrants wider application and promotion.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021255879, identifier: CRD42021255879.

KEYWORDS

cupping therapy, pain-related conditions, systematic review, meta-analysis, evidence mapping

1. Introduction

The definition of pain has been revised to an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage according to the International Association for the Study of Pain (IASP) (1). Pain is the principal reason why individuals seek medical care, with three of the top ten reasons being osteoarthritis, back pain, and headaches (2). Chronic pain poses a significant personal and economic burden, affecting over 30% of the global population and causing psychological distress and sleep issues (3). The Global Burden of Diseases study identified low back pain and migraine as two of the five leading causes of years lived with disability (YLDs) (4). In China, the annual total treatment cost of chronic pain may surpass 500 billion yuan (approximately 685 billion dollars) (5). Although many medications may have limited effectiveness, they often come with significant side effects that can be compounded (6). As a result, alternative complementary treatments are increasingly crucial in the management of pain-related conditions. The demand for complementary and integrative medicine approaches has been on the rise, including mind–body interventions, acupuncture therapy, and other traditional Chinese medicine (TCM) practices (7). Among these, cupping therapy stands out due to its simplicity, safety, and efficacy. Cupping therapy has been widely used in various fields of medicine, including internal medicine, external medicine, gynecology, pediatrics, and particularly in conditions related to pain, skin diseases, knee osteoarthritis, migraines, and other ailments (8).

Cupping therapy, an ancient healing modality, has long been a mainstay in TCM, as well as being documented in the historical records of other regions, including ancient Egypt, Greece, and India. This valuable therapeutic technique has been utilized for thousands of years, and its benefits have been recognized and applied worldwide. It is not only a part of TCM but also recorded in ancient Egypt, Greece, India, and other regions. It is a precious asset to people and has been used worldwide. Cupping therapy involves the application of cups to targeted acupoints or specific skin regions, which creates a negative pressure (9, 10). The modalities of cupping can be broadly classified into dry cupping, wet cupping, massage cupping, etc. (11).

Cupping therapy, initially used as a pain relief method, has now been extended to a broad range of medical conditions (12). Recent evidence shows that this therapy may offer potential benefits for a variety of conditions such as myofascial pain (13), low back pain, ankylosing spondylitis, knee osteoarthritis, neck pain, herpes zoster, migraine, plaque psoriasis, and chronic urticaria (14). For pain-related conditions, cupping might be used as a useful intervention because it decreases the pain level and improves blood flow to the affected area with low adverse effects (15). A clinical study has confirmed that cupping was more effective in improving pain and functional disability in people with persistent non-specific low back pain when compared to sham therapy (16). A single session of dry cupping therapy may be an effective short-term treatment method for immediately reducing pain (17). However, it is worth noting that there exist clinical research findings that do not align with this conclusion. Cupping therapy was not superior to sham cupping for improving pain, physical function, mobility, quality of life, psychological symptoms, or medication use in people with non-specific chronic low back pain (18). Despite this, the National Center for Complementary and Integrative Health (NCCIH) (U.S.) states that although cupping therapy may have some effect in reducing pain, the available evidence is currently insufficient (19). Moreover, although research on this form of therapy has increased, there remains a lack of comprehensive surveys that summarize the efficacy of cupping therapy in managing pain-related conditions. To bridge this gap, the present study endeavors to furnish a comprehensive evaluation of related meta-analyses pertaining to cupping therapy, with a particular focus on the outcomes of pain, as well as to carry out evidence mapping. The primary aim of this study was to provide insights for forthcoming research endeavors.

2. Methods

2.1. Protocol and registration

The protocol of this evidence mapping was registered at the PROSPERO (CRD 42021255879).

2.2. Data sources and search strategy

PubMed, Cochrane Library, Embase, and Web of Science were searched to identify the systematic reviews with meta-analyses on the relationship between cupping therapy and any pain-related conditions published from inception until 15 April 2023. Medical Subject Heading (MeSH) terms and their variants were used for the search strategy for the following terms: "cupping therapy," "cupping," "cupping treatment," "meta-analysis," "meta-analysis as topic," "systematic review." Only published articles in English were considered. We also conducted an extensive review of the pertinent literature, encompassing a range of narrative synopses within the domain. Such a comprehensive approach allowed us to ensure that no substantive sources were overlooked. The details of the search strategies for all databases are given in Supplementary Table S1.

2.3. Inclusion and exclusion criteria

All systematic reviews with meta-analysis related to cupping therapy (including but not limited to dry cupping, wet cupping, moving cupping, etc.) for any pain-related outcomes were included. Conference abstracts, letters, protocols, overviews, and systematic reviews without quantitative meta-analysis were excluded.

2.4. Study selection

All records identified from four databases were imported into Endnote X9 software, and duplicate records removed before screening. After eliminating duplicates, two authors (LW and XL) independently read the titles, abstracts, or full text until all studies are confirmed. Ambiguity was resolved by group discussion.

2.5. Data extraction

For each eligible study, two authors (LW and ZC) extracted the following data independently: first author, publication year, country, study type, type of disease or disorder, number of studies, sample size, intervention, comparison, outcome, type of metric with 95%

confidence interval [CI] (i.e., odds ratio [OR], relative risk [RR], risk ratio [HR], standardized mean deviation [SMD], mean deviation [MD]), adverse effect, and the main findings. Ambiguity was resolved by group discussion with the other author (AZ).

2.6. Methodological quality assessment

A measurement tool to assess systematic reviews 2 (AMSTAR 2) (20), which contains 16 items, was used to assess the methodological quality and ranks the quality from critical low to high of the included studies. Two researchers (LW and ZC) independently evaluated the quality of the included studies. The items of the AMSTAR 2 checklist are shown in Supplementary Table S2.

2.7. Evidence quality assessment

We used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (21) to assess the quality of evidence for each outcome on four degrees (high, moderate, low, and very low quality) by two reviewers (LW and XL) independently. Any disagreement between reviewers was resolved by discussion, and consistent results were reached finally.

2.8. Evidence mapping presentation

The evidence mapping findings were depicted using bubble plots in a graphical form. Each bubble in the chart denotes clinical evidence from studies that explored the efficacy of cupping for specific pain-related conditions and clinical indications. Excel 2021 was utilized to design the evidence mapping. The X-axis indicates the effect size of the primary outcome visual analog scale (VAS) ($p < 0.05$), while the Y-axis denotes the number of articles. The size of the bubbles corresponds to the total population's sample size for the effects of cupping, with bigger bubbles representing a larger sample size. The colors symbolize the different interventions of cupping and non-cupping groups. In addition, we aimed to summarize all the distinct qualities of evidence relating to different pain conditions in human evidence mapping.

3. Results

3.1. Study selection

A total of 265 records were identified. After removing duplicates and screening the titles and abstracts, there were 19 potentially eligible studies. We finally included 14 studies (22–35) after assessing for eligibility including five types of pain-related conditions. The study selection process is shown in Figure 1.

3.2. Study characteristics

Five studies (23, 26, 28, 30, 31) contained less than ten original studies, while twelve (85.7%) studies (23–30, 32–35) had a combined total sample of over 500 participants. The majority of studies, eight (57.1%) in total (23, 26, 29–31, 33–35), were conducted in China, followed by two (25, 28) in Korea, and one each in Germany (24), Brazil (27), Australia (32), and Iran (22). The included studies investigated various conditions, including low back pain ($n = 4$), neck pain ($n = 3$), knee osteoarthritis ($n = 2$), chronic back pain ($n = 1$), migraine ($n = 1$), chronic pain ($n = 1$), pain-related conditions ($n = 1$), musculoskeletal pain ($n = 1$), and herpes zoster ($n = 1$). The characteristics of included studies are shown in Table 1.

3.3. Methodology quality

One high-quality study (24) and one moderate-quality study (26) were included. However, five studies (22, 23, 25, 27, 32) were rated as critically low quality, and seven studies (28–31, 33–35) were rated as low quality. The primary reasons for these downgraded ratings were noted as the absence of registration and protocols (item 2), poor information regarding the source of funding for the original studies in the systematic review and meta-analysis (item 10), and an inadequate explanation of the risk of bias when discussing the results of the review (item 13). The assessment of methodology quality of included studies by AMSTAR 2 is presented in Figure 2.

3.4. Evidence quality

Among the 21 outcomes, the quality of evidence was rated as moderate quality, low quality, and very low quality. Eight moderate-quality evidence are for knee osteoarthritis ($n = 3$), neck pain ($n = 2$), low back pain ($n = 2$), and chronic pain ($n = 1$). Six low-quality evidence are for neck pain ($n = 4$), chronic back pain ($n = 1$), and low back pain ($n = 1$). Seven very low-quality evidence are for low back pain ($n = 4$), neck pain ($n = 2$), and herpes zoster ($n = 1$). On the basis of two moderate-quality, four low-quality, and two very low-quality evidence, cupping therapy is found to be effective for treating neck pain. Similarly, two moderate-quality, one low-quality, and four very low-quality evidence support the efficacy of cupping therapy in alleviating low back pain. Additionally, three moderate-quality evidence indicate that cupping therapy is useful in managing knee osteoarthritis, while only one very low-quality evidence supports its efficacy in treating herpes zoster and one low-quality evidence for chronic back pain. Furthermore, one moderate-quality evidence supports the use of cupping therapy in managing chronic pain. Table 2 and Supplementary Table S3 provide a detailed account of the GRADE assessment.

3.5. Evidence mapping

Figure 3 displays the outcomes of the evidence mapping, which graphically presents the evidence in the form of bubbles. The findings of the evidence mapping revealed that cupping therapy effectively alleviates pain (measured via VAS scores) for neck pain, low back pain, and knee osteoarthritis.

Figure 4 further elucidates the evidence quality for specific pain conditions. For neck pain, there exist two moderate-quality, four low-quality, and two very low-quality evidence. There exists one

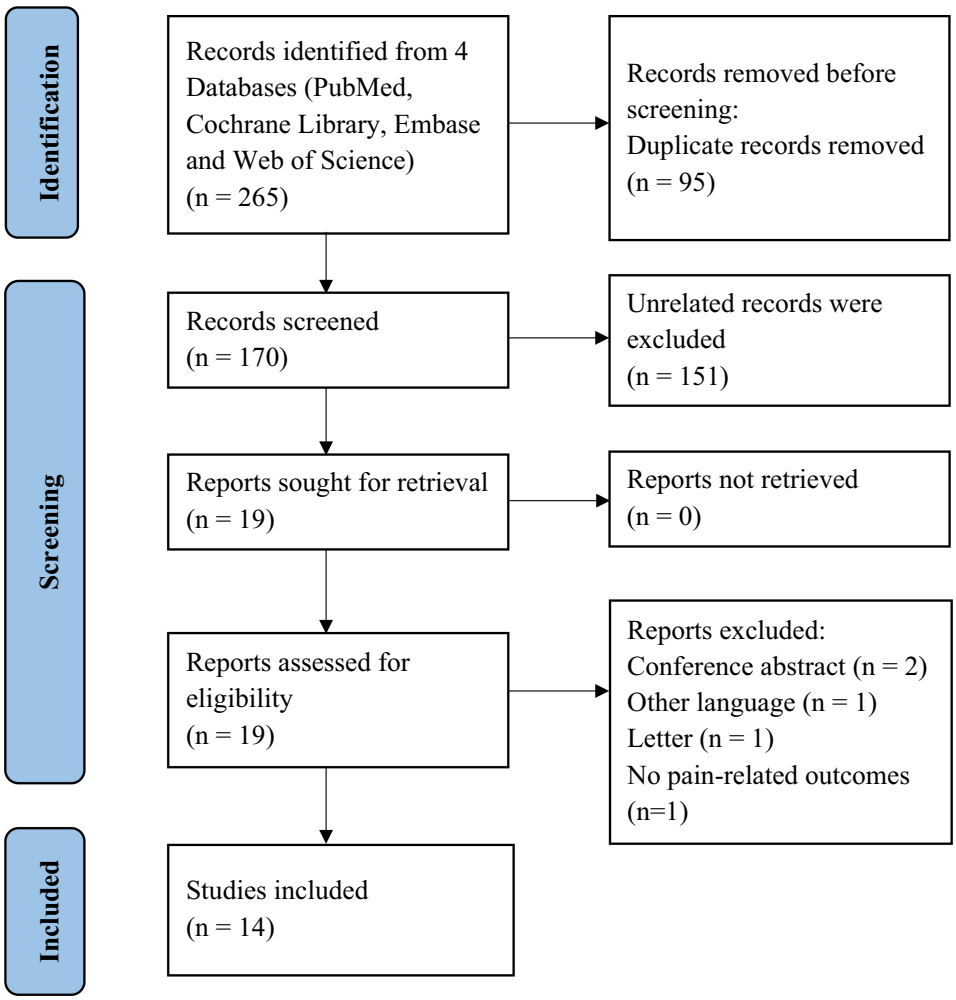

FIGURE 1
Flow chart of the literature search and screening process.

low-quality evidence for chronic back pain and one very low-quality evidence for herpes zoster that demonstrates cupping therapy's effectiveness. Moreover, there are two moderate-quality, one low-quality, and four very low-quality evidence for low back pain, while for knee osteoarthritis, three moderate-quality evidence indicate that cupping therapy can alleviate osteoarthritis pain.

4. Discussion

4.1. Main findings

In the present evidence-mapping study, comprising 14 meta-analyses, the findings highlight the effectiveness of cupping therapy for various pain-related conditions. This comprehensive overview of systematic reviews summarizes the evidence on the efficacy of cupping therapy for several different pain conditions (chronic back pain, knee osteoarthritis, low back pain, neck pain, and herpes zoster). However, none of the meta-analyses provided high-quality evidence on the effectiveness of cupping therapy on pain-related outcomes. In addition, this study shows that cupping therapy is supported by moderate-quality evidence in the relief of a wide range of pain conditions, including chronic pain, knee osteoarthritis pain, low back pain, and neck pain. Some very low to low-quality evidence supports that cupping therapy for chronic back pain, low back pain, neck pain, and herpes zoster. The quality of current evidence provides good support for the clinical use of cupping therapy and direction for future cupping therapy to play a role in the treatment of other pain outcomes.

4.2. Potential mechanism of cupping therapy

Cupping therapy is an integral part of TCM, in which its effectiveness is increasingly recognized and substantiated by modern clinical medicine, but its physiological mechanisms have no consensus. The mechanisms of cupping therapy that have been proposed include the promotion of blood circulation, neurological reflex, the gate theory of pain, inflammation-immune reaction, and skin tension increase (36).

4.2.1. Neural

There is converging evidence that cupping therapy can induce comfort and relaxation on a systemic level, and the resulting increase

TABLE 1 Characteristics of included studies.

Study	Country	Clinical condition	No. of databases searched	No. of studies	No. of participants	Outcome	Tool for risk of bias assessment
Cramer et al. (24)	Germany	Chronic pain	3	18	1,172	Pain intensity	ROB tool
Moura et al. (27)	Brazil	Chronic back pain	7	16	1,049	Pain intensity score	Jadad scale
Wang 2018 (30)	China	Knee osteoarthritis	7	5	535	VAS, WOMAC-pain	ROB tool
Seo et al. (28)	Korea	Migraine	8	6	510	VAS	ROB tool
Li et al. (26)	China	Knee osteoarthritis	7	7	661	VAS, WOMAC-pain	ROB tool
Zhang et al. (35)	China	Pain-related conditions	6	23	2,845	VAS	ROB tool
Wood et al. (32)	Australia	Musculoskeletal pain	7	21	1,049	VAS, NRS, SMPQ, PPT	Downs & Black (D&B) quality assessment scale
Kim et al. (25)	Korea	Neck pain	9	18	1,683	VAS, NPQ	ROB tool
Wang et al. (31)	China	Low back pain	3	6	458	VAS, MPPI	Jadad scale
Azizkhani et al. (22)	Iran	Non-specific neck pain	10	10	441	VAS	ROB tool
Cao et al. (23)	China	Herpes zoster	5	8	651	Number of patients with PHN after treatment	Agency for Healthcare Research and Quality
Yuan et al. (34)	China	Neck Pain and Low Back Pain	7	11	666	VAS	Cochrane Back Review Group
Shen et al. (29)	China	Low Back Pain	5	10	690	VAS, PPI	ROB tool
Xie et al. (33)	China	Non-specific low back pain	7	13	1,088	VAS, NRS	ROB tool

MPPI, McGill present pain index; NPQ, Northwick Park Neck Pain Questionnaire; NRS, numerical rating scale; PHN, postherpetic neuralgia; PPI, present pain intensity; PPT, pain pressure threshold; ROB, risk of bias; SMPQ, Short Form McGill Pain Questionnaire; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

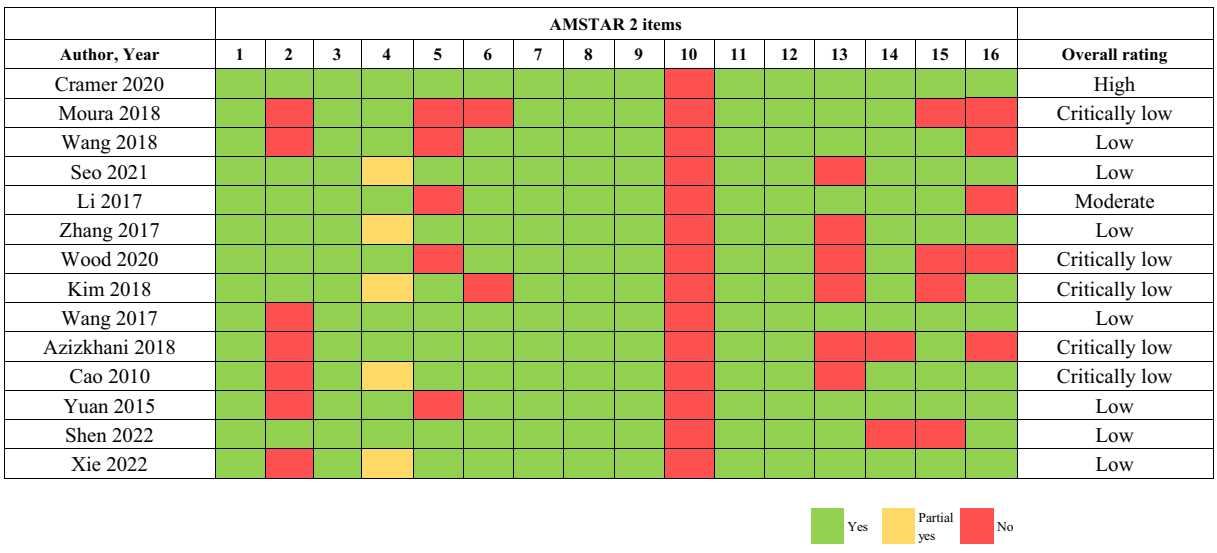

FIGURE 2
AMSTAR 2 quality assessment.

TABLE 2 Evidence quality of cupping therapy and pain-related outcomes.

Study	Condition	NO. of studies	NO. of participants	Outcome	Metrics	ES (95%) CI	I^2 (%)	Comparison	Evidence quality
Cramer et al. (24)	Chronic Pain	13	718	Pain intensity	SMD	−1.03 [−1.41, −0.65]	81	Cupping vs. no treatment	⊕⊕⊕○ Moderate
Moura et al. (27)	Chronic back pain	10	595	Pain intensity score	AD	−1.59 [−2.07, −1.10]	67.7	Cupping therapy compared to one or more of the following groups: sham, active treatment, waiting list, standard medical treatment, or no treatment	⊕⊕○○ Low
Wang et al. (30)	Knee osteoarthritis	2	211	VAS	MD	−1.79 [−2.40, −1.18]	0	Dry cupping therapy + Western medicine vs. Western medicine	⊕⊕⊕○ Moderate
		2	211	WOMAC-Pain	MD	−0.73 [−1.03, −0.43]	0	Dry cupping therapy + Western medicine vs. Western medicine	⊕⊕⊕○ Moderate
Li et al. (26)	Knee osteoarthritis	2	211	WOMAC-pain	MD	−1.10 [−1.61, −0.41]	0	Dry cupping therapy + Western medicine vs. Western medicine	⊕⊕⊕○ Moderate
Wood et al. (32)	Musculoskeletal pain (non-specific neck pain)	5	239	VAS	MD	−1.29 [−2.05, −0.53]	94	Dry cupping vs. no treatment	⊕○○○ Very low
		4	191	PPT	SMD	−0.40 [−0.69, −0.11]	0	Dry cupping vs. no treatment	⊕⊕○○ Low
	Musculoskeletal pain (low back pain)	2	196	VAS	MD	−19.38 [−28.09, −10.66]	59	Dry cupping vs. comparative or control group	⊕○○○ Very low
		2	160	SMPQ	MD	−11.20 [−13.76, −8.64]	76	Dry cupping vs. comparative or control group	⊕○○○ Very low
Kim et al. (25)	Neck pain	5	241	VAS	MD	−2.42 [−3.98, −0.86]	93	Cupping vs. no treatment	⊕○○○ Very low
		9	870	VAS	MD	−0.89 [−1.42, −0.37]	88	Cupping vs. active control	⊕⊕○○ Low
		1	95	NPQ	MD	3.59 [2.02, 5.16]	/	Cupping vs. active control	⊕⊕○○ Low
		5	534	VAS	MD	−0.87 [−1.14, −0.61]	19	Cupping + active control vs. active control	⊕⊕⊕○ Moderate
Wang et al. (31)	Low back pain	4	280	VAS	SMD	−0.73 [−1.42, −0.04]	87	Cupping vs. medication or usual care	⊕○○○ Very low
Azizkhani et al. (22)	non-specific neck pain	5	282	VAS	MD	−0.84 [−1.22, −0.46]	54.7	Cupping therapy vs. other or no treatment	⊕⊕○○ Low
Cao et al. (23)	Herpes zoster	3	326	Number of patients with PHN after treatment	RR	0.11 [0.02, 0.56]	0	Wet cupping versus medications	⊕○○○ Very low
Yuan et al. (34)	Chronic neck pain	2	93	VAS	WMD	−19.0 [−27.61, −10.58]	0	Cupping vs. waitlist	⊕⊕⊕○ Moderate

(Continued)

TABLE 2 (Continued)

Study	Condition	NO. of studies	NO. of participants	Outcome	Metrics	ES (95%) CI	I^2 (%)	Comparison	Evidence quality
	Chronic low back pain	7	430	VAS	WMD	−0.54 [−0.89, −0.19]	84.5	Cupping vs. medications	⊕⊕⊕ ○Moderate
Shen et al. (29)	Low Back Pain	3	146	VAS	MD	−1.54 [−1.81, −1.26]	0	et cupping vs. non-cupping group	⊕⊕○ ○Low
		4	275	PPI	MD	−2.22 [−3.92, −0.52]	97	wet cupping vs. non-cupping group	⊕○○ ○Very low
Xie et al. (33)	Non-specific low back pain	9	736	VAS	MD	−1.43 [−2.31, −0.54]	95	blood pricking and cupping vs. other treatments	⊕⊕⊕ ○Moderate

AD, absolute difference; CI, confidence interval; ES, effect size; MD, mean deviation; MPPI, McGill present pain index; NPQ, Northwick Park Neck Pain Questionnaire; NRS, numerical rating scale; PHN, postherpetic neuralgia; PPI, present pain intensity; PPT, pain pressure threshold; RR, risk ratio; SMD, standard mean deviation; SMPQ, Short Form McGill Pain Questionnaire; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

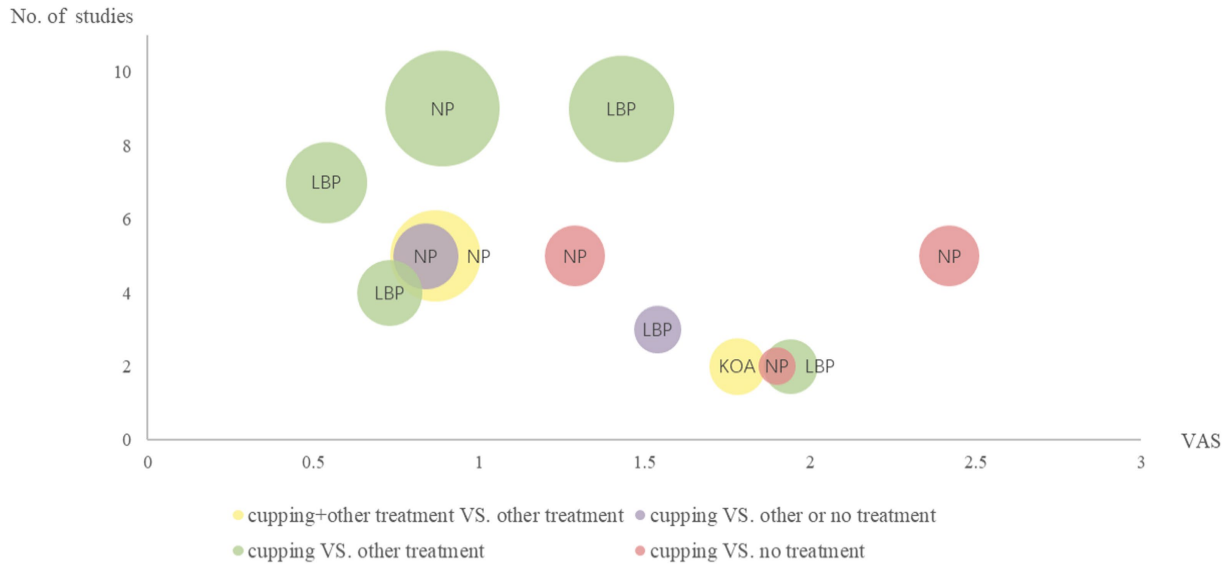

FIGURE 3
Evidence mapping of cupping therapy. KOA, knee osteoarthritis; NP, neck pain; LBP, low back pain; VAS, visual analog scale. The size of the bubbles corresponds to the total population's sample size for the effects of cupping, with bigger bubbles representing a larger sample size. The colors symbolize the different interventions of cupping and non-cupping groups.

in endogenous opioid production in the brain leads to improved pain control (37). Furthermore, cupping therapy has been found to increase immediate pressure pain thresholds in certain areas (38). In addition, the study has revealed that wet cupping therapy can decrease pain in rats *via* the upregulation of heat shock protein 70 (HSP70) and β-endorphin expression (39).

4.2.2. Hematological

Studies have demonstrated that cupping therapy can augment blood volume and tissue oxygenation at the affected site, whereas reductions in those parameters were observed in the surrounding tissue (40). Moreover, the drawing force in cupping may bring about alteration in blood flow dynamics along with the variation in dermal vascular arrangement. Cupping could positively affect erythrocyte diapedesis from superficial dermal venules. The extravasated erythrocyte may play a mediating role in the proteolytic degradation cascade of hemoglobin. The hemoglobin-derived hemorphins engage opioid receptor signaling and induce the local analgesic effect of cupping (41).

4.2.3. Immune

A study suggests that the mechanism of cupping therapy is that cupping regulates local immunomodulation. The microenvironment is changed when stimulating the surface of the skin, and physical signals transform into biological signals, which also interact with each other in the body. These signaling cascades activate the neuroendocrine-immune system, which produces the therapeutic effect (42).

The mechanisms of cupping therapy for pain reduction are closely related to pain gate theory, diffuse noxious inhibitory controls theory, and reflex zone theory. In summary, several theories have been proposed to explain the effects produced by cupping therapy, and

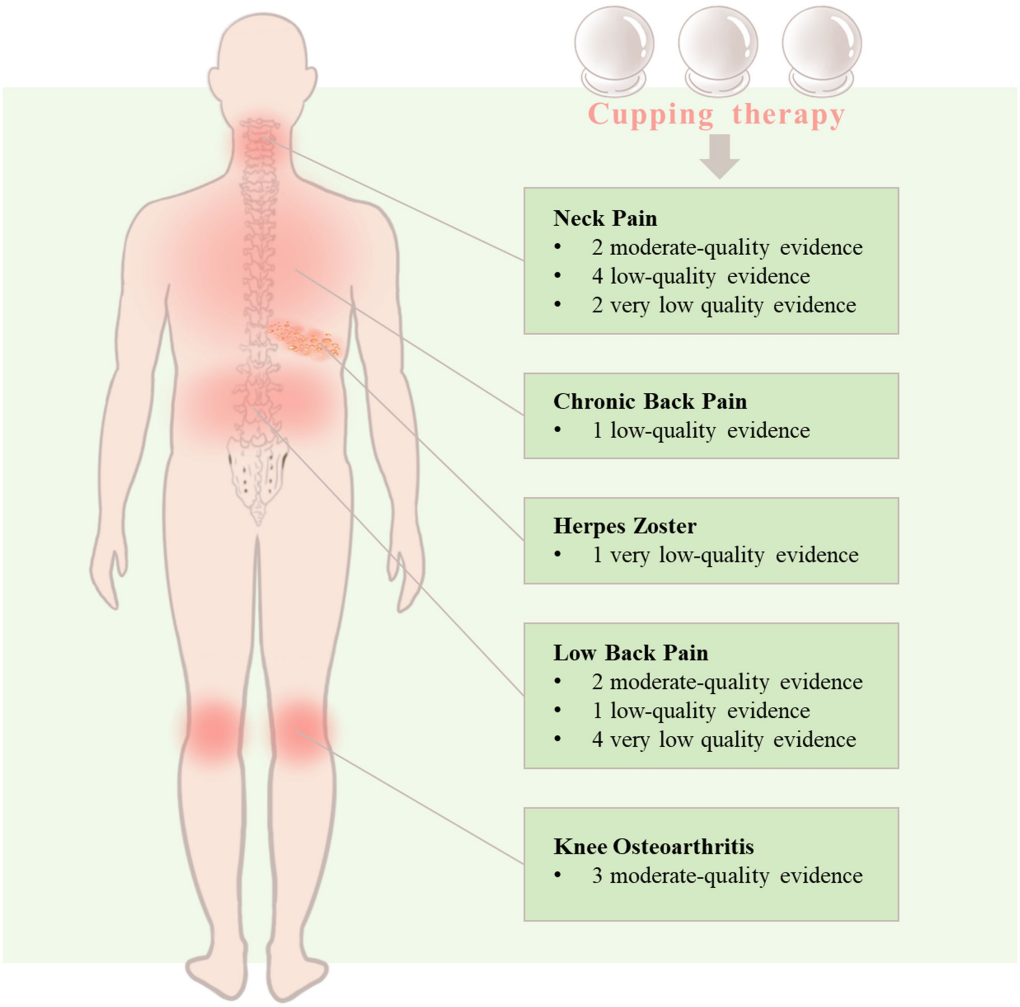

FIGURE 4
Grade distribution of evidence of cupping therapy for pain-related conditions.

these theories may overlap or alternate, producing various therapeutic effects in a specific disease (43).

4.3. Strengths and limitations

To sum up, our study presents the inaugural overview and evidence mapping of cupping therapy for pain-related outcomes, which comprehensively summarizes the extant evidence. The available evidence quality for the effectiveness of cupping therapy ranges from very low to moderate, with an absence of high-quality evidence. Future research endeavors should concentrate on elucidating the underlying mechanisms of cupping therapy, prioritizing avoidance of adverse events, and optimizing the design and execution of clinical investigations.

Unlike the protocol, our study was limited to pain-related outcomes. The rest of the methods and steps basically followed the contents of the protocol. First of all, the increase of the literature of cupping therapy for pain makes it possible to conduct an evidence mapping. Furthermore, there is consensus among authors that in registration, outcomes cover diverse diseases, but focusing on a certain area after literature screening could better reduce bias. Therefore, we proceeded with the evaluation of pain-related outcomes. We utilized stringent inclusion criteria and restricted our review to English-language literature, which may have increased the likelihood of missing relevant studies. Furthermore, we focused solely on pain-related outcomes, potentially neglecting the impact of cupping therapy on other symptoms, such as functional activities. It is worth noting that non-specific and chronic neck pain were included in our analysis under the umbrella term "neck pain," while non-specific and chronic low back pain were considered collectively as "low back pain." Nonetheless, it is essential for better-quality research to validate the current evidence.

5. Conclusion

Cupping therapy appears to be a promising treatment modality for various pain-related disorders. It is effective in the treatment of chronic pain, knee osteoarthritis, low back pain, neck pain, chronic back pain, and herpes zoster. However, the quality of the evidence supporting these outcomes is mostly low quality, with moderate-quality evidence

still less available and no high-quality. Therefore, to strengthen these findings, more high-quality clinical studies are also needed to obtain a higher level of evidence. Nonetheless, the potential benefits of cupping therapy in clinical practice make it a valuable intervention for further research and implementation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LW: Software, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology. ZC: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. XL: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. AZ: Conceptualization, Investigation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1266712/full#supplementary-material

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Efficacy and safety of yoga for the management of chronic low back pain: an overview of systematic reviews

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Background: Yoga is a non-pharmacological conservative therapeutic modality that can be employed for the management of chronic low back pain (CLBP). In this overview, we have summarized and evaluated data from current systematic reviews (SRs) on the use of yoga for CLBP.

Methods: We comprehensively searched SRs on the use of yoga for CLBP in nine electronic databases from inception to September 2023. The methodological quality was evaluated using the Assessment of Multiple Systematic Review Scale-2 (AMSTAR-2). The reporting quality of the included SRs was evaluated using the Preferred Reporting Item for Systematic Review and Meta-Analysis-2020 (PRISMA-2020), and the quality of data was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Two independent researchers performed the screening, data extraction, and quality assessment process of SRs.

Results: A total of 13 SRs were included. The results of the AMSTAR-2 indicated that the methodological quality of the included studies was relatively low. The PRISMA-2020 checklist evaluation results indicated that methodological limitations in reporting, especially regarding data processing and presentation, were the main weaknesses. The GRADE assessment indicated that 30 outcomes were rated moderate, 42 were rated low level, and 20 were rated very low level. Downgrading factors were mainly due to the limitations of the included studies.

Conclusion: Yoga appears to be an effective and safe non-pharmacological therapeutic modality for the Management of CLBP. Currently, it may exhibit better efficacy in improving pain and functional disability associated with CLBP. However, the methodological quality and quality of evidence for SRs/MAs in the included studies were generally low, and these results should be interpreted cautiously.

KEYWORDS

chronic low back pain, systematic review, GRADE, AMSTAR-2, yoga

1. Introduction

Low back pain (LBP) is a prevalent clinical concern and symptom, which is defined as pain or discomfort in the area between the lower rib and the gluteal folds (1). The global population prevalence rate of LBP has reached 7.3% (2). The lifetime prevalence rate of LBP can be as high as 47% in low-income countries such as Africa (3). A systematic review shows that running can decrease the incidence of LBP and can serve as a protective factor for preventing the onset of LBP (4). The etiology of LBP is complex and not completely understood; neurological, bladder dysfunction, loss of anal sphincter tone, and saddle anesthesia are factors that can contribute to the onset of LBP (5). Clinicians can identify potential pathologies that resemble musculoskeletal conditions through the use of screening and differential diagnosis. More emphasis should be placed on patients with signs and symptoms that resemble severe pathology in the thoracolumbar region, such as LBP due to post-traumatic thoracolumbar fracture (6), and other potential non-musculoskeletal causes of LBP including LBP due to secondary peripheral arterial disease (7). Chronic low back pain (CLBP) is LBP lasting 3 months or longer. More than 70% of people experience CLBP at least once in their lifetime (8). CLBP can cause physical diseases and lead to anxiety and depression, thus decreasing the quality of life (9). CLBP has become a significant public health concern. The resulting inability to work, disability, and medical expenditure have imposed a substantial financial burden on individuals and society (10).

Presently available biomedical therapies for CLBP are expensive, have poor long-term efficacy, and may cause adverse side effects (11). Therefore, many patients with CLBP prefer alternative treatments. Recent practice guidelines from the American College of Physicians suggest that non-pharmacological therapeutic modalities can be considered if standard medical treatments fail to alleviate LBP (12). Exercise is strongly recommended as a non-pharmacological intervention because it can effectively relieve pain (13). Yoga has garnered widespread attention as a characteristic meditative movement therapy that integrates body and mind (14). Yoga originated in ancient India and has a history of over 4,000 years. Yoga comprises several key components, such as physical posture (asana), controlled breathing techniques (pranayama), relaxation, and meditation (dhyana) (15). The inherent nature of yoga is characterized as gentle and soothing. It can improve the strength of the back muscles and alleviate pain while promoting the extension, flexibility, and balance of the body tissue of the spinal vertebra (16). Yoga can improve physical functions. One study has shown that yoga can decrease anxiety and improve self-efficacy and pain acceptance (17). This is particularly helpful because CLBP occurs due to a complex interplay of biological, psychological, and social factors, and the availability of emotional support from practicing yoga can improve the confidence of the patients in overcoming the disease (18). Furthermore, the underlying mechanism of action of yoga is linked to contextual factors, which are the result of a combination of personal, disease-related, and environmental factors (19), where pain-induced contextual factors can be conceptualized as triggers of placebo and nocebo effects (20). Particularly in musculoskeletal disorder (MSK)-associated pain, the mood and expectations of the patient can affect MSK pain (21). Previous studies have shown that physiotherapy for MSK can effectively ameliorate pain when patients redirect their attention away from the disease compared with when patients focus on the pain (22).

Many clinical studies, systematic reviews (SRs), and reviews have reported the efficacy of yoga in the treatment of CLBP. However, adequate and unified data are not available. An overview of SRs can be performed to comprehensively collect and evaluate the relevant systematic evaluation of the treatment, etiology, diagnosis, and prognosis of the same disease or health problem. This can provide more robust, high-quality evidence for clinicians and promote their decision-making ability (23). In this study, we evaluated and objectively summarized the efficacy and safety of yoga in treating CLBP by overviewing SRs to provide clinicians with evidence of synthesis that can serve as a basis for decision-making.

2. Methods

This overview was performed according to the Cochrane Handbook for SRs of Interventions (24) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (25).

2.1. Inclusion and exclusion criteria

Inclusion criteria for the overview were established using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework, which were as follows: (a) Participants: Adults over 18 years of age who are diagnosed with CLBP and patients diagnosed with chronic non-specific LBP based on the LBP diagnostic criteria were included (1). CLBP refers to low back pain over 3 months, and 85% of chronic back pain was non-specific, with no clear pathoanatomic explanation. (b) Interventions: yoga or combined with other therapies. (c) Comparator: Treatments other than yoga, such as other exercise therapy, placebo, health education, and blank control, to fulfill the research conditions. (d) Outcomes: the primary outcome was pain relief. Secondary outcomes included disability function, quality of life, and adverse effects of yoga for managing CLBP. (e) Study design: SRs with or without meta-analysis (MAs) of randomized controlled trials (RCTs) were included. In these studies, yoga was used as a treatment modality for managing CLBP.

Exclusion criteria for the overview were as follows: (a) incomplete information or incorrect data in a systematic review,

Abbreviations: CLBP, chronic low back pain; SR, systematic review; AMSTAR-2, Assessment of Multiple Systematic Reviews scale-2; PRISMA-2020, Preferred Reporting Item for Systematic Review and Meta-analysis-2020; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LBP, low back pain; MSK, musculoskeletal disorders; PEDro, Physiotherapy Evidence Database; CNKI, China Knowledge Network; CBM, Chinese Biomedical Databases; CCA, corrected covered area; RCT, randomized controlled trial; VAS, visual analog scale; MD, mean difference; RD, risk difference; MAs, meta-analysis; GROOVE, Guidance for the Review of Overviews of Reviews.

(b) duplicated SRs/MAs, (c) for updated reviews, non-latest works of literature will be excluded, (d) systematic review with network meta-analysis or indirect comparison, and (e) dissertation or conference papers.

2.2. Search strategy

Computer searches of PubMed, EMBASE, Cochrane Library, Web of Science, Physiotherapy Evidence Database (PEDro), China Knowledge Network (CNKI), VIP, Wanfang Database, and Chinese Biomedical Databases (CBM) were conducted to collect systematic evaluations of yoga for CLBP. The retrieval time has been updated from the database inception to September 2023. The search used a combination of subject headings and free words. Key phrases included "yoga," "low back pain," "back pain," "lumbar disc herniation," "meta-analysis," or "systematic review." Furthermore, we also searched conference abstracts and reference lists of all retrieved articles to avoid missing relevant SRs/MAs. The search strategy for PubMed is shown in Table 1. More search strategies are mentioned in Appendix 1.

2.3. Study selection and data abstraction

The systematic review literature obtained from the search was imported into NoteExpress. Two reviewers (XS-Z and TY-C) independently performed two rounds of screening by reading the title, abstract, and complete text. Any disagreements among the reviewers were resolved by discussion or by consulting with an experienced, authoritative third reviewer (XL) to reach a final decision. The content of data extraction included author, year, publication language, number of included studies, sample size, intervention and control measures, quality assessment tool, outcome indicators, and principal conclusions.

We retrieved the original research studies for each system evaluation using an Excel spreadsheet and used the Guidance for the Review of Overviews of Reviews (GROOVE) to evaluate the degree of overlap. OVErviews (GROOVE) (26) is a user-friendly tool, wherein the matrices of evidence and the calculation of the corrected covered area (CCA) are one of the most exhaustive methods for measuring overlap. The CCA value from 0 to 5 represents slight overlap, 6–10 represents moderate overlap, 11–15 represents high overlap, and >15 represents a very high degree of overlap.

2.4. Quality appraisal and assessment of evidence

Two trained and qualified reviewers, XS-Z and TY-C, used the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), Preferred Reporting Item for Systematic Review and Meta-Analysis-2020 (PRISMA-2020), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to evaluate the methodological, reporting, and evidence quality of the included studies, respectively. Any disagreements between the two reviewers were resolved by consulting an experienced, authoritative third reviewer (XL).

2.4.1. Methodological assessment tool—AMSTAR-2 scale

AMSTAR-2 (27) was used to evaluate the quality of the methodology included in SR, which contains 16 items. Each item was rated as "yes," "partially yes," and "no," and the methodological quality was divided into four categories of "high," "moderate," "low," and "very low" based on the evaluation results of the grade of the key items (items 2, 4, 7, 9, 11, 13, and 15). AMSTAR-2 scale categorized the methodological quality of the systematic evaluation/meta-analysis into the following four levels: (a) high quality, characterized as no or one non-critical weakness; (b) moderate quality, characterized as more than one non-critical weakness; (c) low quality: characterized as one critical flaw with or without non-critical weaknesses; and (d) critically low quality, characterized as more than one critical flaw with or without non-critical weaknesses.

2.4.2. Report quality assessment tool—PRISMA-2020 statement

PRISMA-2020 (28) was used to evaluate the reporting specifications in SRs, containing 27 main items and 42 sub-items. The complete report of each item was recorded as "1 point." Some reports were recorded as "0.5 point," and no report was recorded as "0 point." A report with completeness of more than 80% (33–42 points) was considered "relatively complete" and rated as high quality. If the completeness of the report was above 60% (25–32 points), it was considered "the report has certain defects" and rated as medium quality. If the completeness of the report was below 60% (<25 points), it was considered a "relatively serious lack of information" and rated as low quality (29).

2.4.3. Evidence quality assessment—GRADE system

The GRADE (30) was used to comprehensively evaluate the quality of the outcome indicators. Initially, RCT-derived evidence was considered to be of high quality; however, confidence in such evidence may decrease due to the following five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence was graded based on the confidence in approaching the estimated efficacy with real efficacy as follows: (a) high quality (very confident in efficacy); (b) medium quality (confidence was average, and a significant difference may be present between actual and estimated efficacy); (c) low quality (limited confidence, and a significant difference between actual and estimated efficacy); and (d) extremely low quality (with almost no confidence, and a significant difference may be present between actual and estimated efficacy).

TABLE 1 Search strategy for PubMed.

Query	Search term
#1	Yoga [MeSH Terms]
#2	(yogic [Title/Abstract])) OR (yogi [Title/Abstract])) OR (yog* [Title/Abstract]))
#3	#1 OR #2
#4	Low Back Pain [Mesh]
#5	Low back pain[Title/Abstract]) OR (low back pains[Title/Abstract])) OR (lumbago[Title/Abstract])) OR (lower back pain[Title/Abstract])) OR (lower back pains[Title/Abstract])) OR (low back ache[Title/Abstract])) OR (low back aches[Title/Abstract])) OR (low backache[Title/Abstract])) OR (low backaches[Title/Abstract])) OR (lumbar pain[Title/Abstract])) OR (herniated disk[Title/Abstract])) OR (herniated disc[Title/Abstract])) OR (hernia intervertebral disc[Title/Abstract])) OR (lumbar degenerat* [Title/Abstract])) OR (backache[Title/Abstract])) OR (back disorders[Title/Abstract])) OR (sciatica[Title/Abstract])) OR (coccyx[Title/Abstract])) OR (coccy* [Title/Abstract])) OR (spondylosis[Title/Abstract])
#6	#4 OR #5
#7	"Systematic Review" [Publication Type]) OR ("Systematic Reviews as Topic"[Mesh])) OR ("Meta-Analysis" [Publication Type])) OR ("Meta-Analysis as Topic"[Mesh])) OR (Systematic review [Title/Abstract])) OR (Meta-analysis [Title/Abstract])
#8	#3 AND #6AND #7

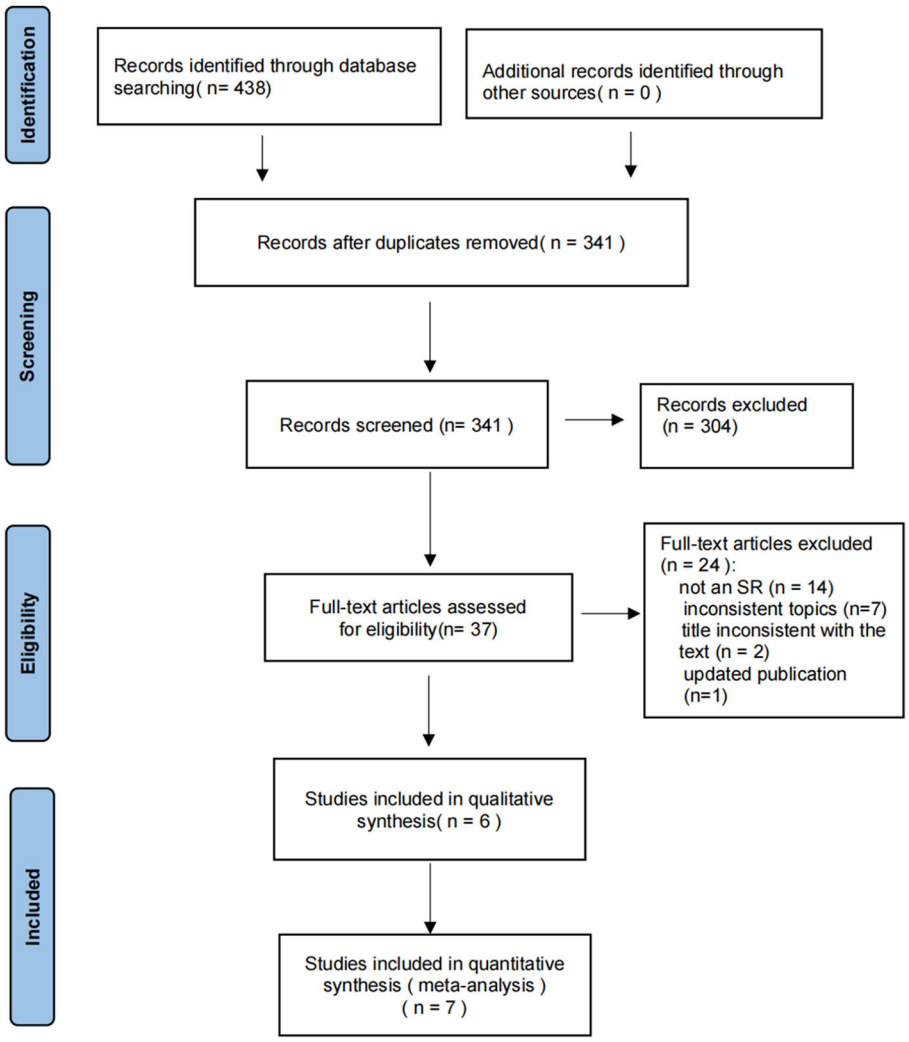

FIGURE 1
Flow diagram of the literature selection.

3. Results

3.1. Literature search

Based on the established search strategy, we performed a preliminary search and searched 438 articles across nine databases from database inception to September 2023. After eliminating duplicate 97 articles, we obtained 341 studies. We then screened the titles and abstracts and excluded 304 studies. The complete texts of the remaining 37 studies were read, and after a detailed review, 24 studies with no SR, inconsistent topics, titles inconsistent with the text, or updated publication were excluded. Finally, 13 SRs (31–43) fulfilled the inclusion criteria and were selected for analysis, which included seven MAs and six qualitative analyses. The process and results of the literature screening are shown in Figure 1.

3.2. Characteristics of SRs

The characteristics of the included SRs are shown in Table 2. Of the 13 SRs, two SRs (31, 32) were published in Chinese, whereas 11 SRs (33–43) were published in English. The publication date ranged from 2011 for the earliest SR to 2022 for the most recent. The number of RCTs included in each SR ranged from 4 to 27 and the number of patients participating in the RCTs ranged from 403 to 2,702. The methodological quality of the RCTs was assessed in all 13 SRs using different tools. Two SRs (31, 43) used the Jadad scale, one SR (40) used the PEDro scale, seven SRs (32–36, 39, 42) used the Cochrane risk of bias tool, and three SRs (37, 38, 41) used other methods. The interventions in the treatment groups primarily involved yoga, either alone or as a combination with other therapies. The control groups received physical exercise, education, usual care, or no treatment. A total of 12 SRs used pain as the endpoint outcome. A total of 11 SRs (31–34, 36–38, 40–43) used physical function and disability as the endpoint outcome, six SRs (31, 33, 34, 36, 40, 42) used quality of life as the endpoint outcome, and six SRs (33, 34, 36, 37, 42, 43) used adverse events as the endpoint outcome. All studies concluded that yoga can improve CLBP and functional disability to varying degrees.

3.3. Methodological quality of included SRs

The overall quality of the SRs was graded using AMSTAR-2 based on seven critical domains. Only one SR (36) was rated as high-quality evidence, two SRs (33, 34) were as low quality, and the remaining 10 SRs (31, 32, 35, 37–43) were rated as critically low quality. These SRs had deficiencies in the following key areas: three SRs (33, 34, 36) had registered protocols (Item 2), two SRs (36, 43) used comprehensive literature search strategies, the other 11 (31–35, 37–42) SRs had not searched gray literature (Item 4), only one SR (36) provided a list of excluded studies with reasons (Item 7), five SRs (31, 37, 39–41) did not use appropriate tools to assess the risk of bias (Item 9), six SRs (31, 37, 39–41, 43) did not perform meta-analysis (Item 11), five SRs (33, 34, 36, 40, 42) considered risk of bias in interpretations (Item 13), and finally six SRs (32–36, 42) assessed publication bias using funnel plots (Item 15). The absence of these key domains decreased the literature quality. For other items, 10 SRs (31–35, 38–40, 42, 43) did not report study settings and follow-up, which was rated as "Partial yes" for Item 8. Six SRs (31, 37, 39–41, 43) without meta-analysis were rated as "no meta-analysis" for Item 12. The main methodological limitations were the absence of a clear rationale for the inclusion criteria and a list of excluded studies. Details of evaluations for other items are shown in Table 3.

3.4. Reporting quality of included SRs

The PRISMA-2020 checklist contains 42 items, with a maximum score of 42 points. Based on the scores, two SRs (34, 36) were relatively complete and rated as high quality, two SRs (33, 42) had certain defects and were rated as medium quality, and the remaining nine SRs (31, 32, 35, 37–41, 43) had serious defects and were rated as low quality. In the case of the titles, nine SRs (31, 33, 34, 36, 39–43) fulfilled the criteria. None of the SRs completely reported all elements of the abstracts. The introduction section was comprehensive in all SRs. In the methods, two SRs (36, 41) had more comprehensive search details, and six SRs (31, 37, 39–41, 43) did not describe data processing for pooling and analyses. Finally, only one SR (36) provided a list of excluded studies in the results and four SRs (33, 34, 36, 42) evaluated outcome heterogeneity sources and bias risks. In the discussion section, all SRs (31–43) reported research limitations to varying degrees. Altogether, only two SRs (34, 36) had relatively completed reporting across all checklist items. The included SRs were generally of low reporting quality primarily due to methodological limitations in reporting, especially regarding data processing and presentation. Furthermore, the reporting on additional information, such as funding, conflicts of interest, and data access, was not transparent and had major inadequacies. The specific scores are shown in Table 4, and the categorization of reporting quality is shown in Table 5.

3.5. Evidence quality classification using GRADE

The pooled results of seven SRs (32–36, 38, 42) on the efficacy of yoga for CLBP regarding 4 outcomes, including pain, disability function, quality of life, and adverse events, were presented. The quality of evidence for the 92 outcomes was evaluated using GRADE. Moderate-quality evidence was obtained for 30 of the 92 outcomes (32.6%), low-quality evidence for 42 of 92 (45.7%), and very low-quality evidence for 20 of 92 (21.7%). Serious flaws in randomization, concealment, and blinding methods of the RCTs contained in the included literature were the main factors behind the downgrade. Other downgrading factors such as imprecision, publication bias, and inconsistency negatively affected the strength of the evidence. Further details are presented in Tables 6–9.

TABLE 2 Characteristics of included systematic reviews.

References	Country	No. of included RCTs	Interventions	Comparisons	Quality assessment tools	Outcomes	Overall conclusions
Zhang and Hu (31)	China	19 (1,660)	Yoga	No treatment, placebo, other conservative therapy, or another exercise	Jada scale	Pain intensity, functional disability, quality of life	Yoga therapy can effectively alleviate patients' back pain and improve their dysfunction, and the curative effect is long-term
Kang et al. (32)	China	14 (1,684)	Yoga	Conservative therapy	Cochrane risk of bias tool	Functional disability	Available evidence shows that yoga can achieve better results in the treatment of lower back pain
Dennis et al. (33)	Germany	27 (2,702)	Yoga	No treatment, usual care, other passive treatments, or any active treatment	Cochrane risk of bias tool	Pain, back-specific disability, quality of life, adverse events	Yoga revealed robust short- and long-term effects for pain, disability, and physical function when compared to non-exercise controls and no significantly different effects when compared to exercise controls
Zhu et al. (34)	China	18 (1,852)	Yoga or in combination with other treatments	No treatment, a minimal intervention (e.g., education and booklets), usual care, or other active treatments	Cochrane risk of bias tool	Pain, disability, quality of life, adverse events	Yoga might decrease pain from the short term to the intermediate term and improve functional disability status from the short term to the long term compared with non-exercise (e.g., usual care and education)
Sang (35)	Korea	6 (523)	Yoga	No intervention, or any other intervention	Cochrane risk of bias tool	Pain intensity	Yoga programs could significantly reduce CNSLBP
Wieland et al. (36)	USA	21 (2,223)	Yoga	Any other intervention or no intervention	Cochrane risk of bias tool	Back-specific functional status, pain, clinical improvement, mental or physical quality of life, depression, adverse events	There is low- to moderate-certainty evidence that yoga compared to no exercise results in small and clinically unimportant improvements in back-related function and pain
Douglas et al. (37)	USA	10 (1,053)	Yoga	No treatment, another exercise, education, usual care	Evidence criteria	Physical function and disability, pain, psychological, adverse events	Yoga appears to be an effective and safe intervention for chronic low back pain
Susan and Beggs (38)	UK	8 (743)	Yoga	No treatment, another exercise, education, usual care	CLEAR NPT	Pain, functional disability	Yoga may be an efficacious adjunctive treatment for CLBP
Manoj and Haider (39)	USA	13 (1,386)	Yoga	No treatment, physical exercise, education, usual care, etc.	Cochrane risk of bias tool	Pain	Yoga as part of the intervention can be a reduction in low back pain
Alison et al. (40)	USA	10 (1, 024)	Yoga	No treatment, usual care, a self-care book, stretching, or other forms of exercise	PEDro scale	Pain, disability, quality of life	Evidence demonstrates moderate support for yoga as an effective treatment for LBP
Christopher (41)	UK	4 (711)	Yoga	Other care modalities	CASP reviewer checklist	Pain, functional disability	Yoga is an effective management tool for CLBP, it is effective in improving back function
Holger et al. (42)	Germany	10 (967)	Yoga	No treatment, usual care, or any active treatment	Cochrane risk of bias tool	Pain, back-specific disability, generic disability, health-related quality of life, adverse events	Yoga can be recommended as an additional therapy for chronic low back pain patients
Paul and Ernst (43)	UK	7 (403)	Yoga	Usual care, physical exercises, education, or no treatment	Jada scale	Pain, functional disability, Beck Depression Inventory, adverse events	Yoga has the potential to alleviate low back pain

LBP, low back pain; CLBP, chronic low back pain; CNSLBP, chronic non-specific lower back pain; CLEAR NPT, checkist to evaluate a report of a non-pharmacological trial; PEDro, Physiotherapy Evidence Database; CASP, Critical Appraisal Skills Programme.

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TABLE 3 Result of the AMSTAR-2 assessments.

First author	Type of study/ publication year	AMSTAR-2 quality items																AMSTAR-2 classification
		Q1	Q2*	Q3	Q4*	Q5	Q6	Q7*	Q8	Q9*	Q10	Q11*	Q12	Q13*	Q14	Q15*	Q16	
Zhang	SR/2016	Y	N	N	PY	Y	N	N	PY	PY	N	NM	NM	N	N	NM	N	Critically low
Kang	SR/MA/2020	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	N	Critically low
Dennis	SR/MA/2022	Y	Y	N	PY	N	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y	Low
Zhu	SR/MA/2020	Y	Y	N	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	N	Low
Sang	SR/MA/2020	Y	N	N	PY	N	N	N	PY	Y	N	N	N	N	N	Y	N	Critically low
Wieland	SR/MA/2022	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Douglas	SR/2016	Y	N	N	PY	N	N	N	N	N	N	NM	NM	N	N	NM	N	Critically low
Susan	SR/MA/2013	Y	N	N	PY	N	N	N	PY	Y	N	Y	Y	N	Y	N	N	Critically low
Manoj	SR/2013	N	N	N	PY	N	N	N	PY	N	Y	NM	NM	N	N	NM	Y	Critically low
Alison	SR/2013	N	N	N	PY	Y	N	N	PY	Y	N	NM	NM	Y	N	N	N	Critically low
Christopher	SR/2013	Y	N	N	N	N	N	N	N	N	N	NM	NM	N	N	NM	N	Critically low
Holger	SR/MA/2013	Y	N	N	PY	N	Y	N	PY	Y	N	Y	N	Y	N	Y	N	Critically low
Paul	SR/2011	N	N	N	Y	N	N	N	PY	Y	N	NM	NM	N	Y	NM	N	Critically low

SR, systematic review; Y, yes; N, no; PY, partial yes; MA, meta-analysis; NM, no meta-analysis.
Q1: Did the research questions and inclusion criteria for the review include the components of PICO?
Q2*: Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?
Q4*: Did the review authors use a comprehensive literature search strategy?
Q5: Did the review authors perform study selection in duplicate?
Q6: Did the review authors perform data extraction in duplicate?
Q7*: Did the review authors provide a list of excluded studies and justify the exclusions?
Q8: Did the review authors describe the included studies in adequate detail?
Q9*: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
Q10: Did the review authors report on the sources of funding for the studies included in the review?
Q11*: If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13*: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
Q15*: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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TABLE 4 Results of the PRISMA-2020 checklist.

Item	Zhang and Hu (31)	Kang et al. (32)	Dennis et al. (33)	Zhu et al. (34)	Sang (35)	Wieland et al. (36)	Douglas et al. (37)	Susan and Beggs (38)	Manoj and Haider (39)	Alison et al. (40)	Christopher (41)	Holger et al. (42)	Paul and Ernst (43)
Item 1	1	0	1	1	0	1	0	0	1	1	1	1	1
Item 2	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Item 3	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1
Item 4	0.5	1	1	1	1	1	1	1	1	1	1	1	1
Item 5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	0.5
Item 6	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	1	0.5	0.5
Item 7	0	0	0	0	0	1	0	0	0	0	1	0	0
Item 8	0.5	0.5	0.5	1	0	1	0	0	0	0.5	0	0.5	0
Item 9	0	0	0.5	1	0	1	0	0	0	0	0	0.5	0.5
Item 10a	0	0	0	1	0	1	0	0	0	1	0	0	0
Item 10b	0.5	1	1	1	1	0.5	0	1	0	1	0	1	0
Item 11	0.5	0.5	1	1	0.5	1	0	0	0	1	0	1	0.5
Item 12	0	1	1	1	1	1	0	1	0	1	0	1	0
Item 13a	0	0	1	0	0	1	0	0	0	0	0	1	0
Item 13b	0	0	1	1	0	1	0	0	0	0	0	1	0
Item 13c	0	0	1	1	0	1	0	0	0	0	0	1	0
Item 13d	1	1	1	1	1	1	0	1	0	0	0	1	1
Item 13e	0	1	1	1	1	1	0	1	0	0	0	1	0
Item 13f	0	0	1	1	0	1	0	0	0	0	0	1	0
Item 14	0	0	1	1	1	1	0	0	0	0	0	1	0
Item 15	0	0	0	1	0	1	0	1	0	0	0	0	1
Item 16a	1	1	1	1	1	1	1	1	1	1	1	1	1
Item 16b	0	0	0	0	0	1	0	0	0	0	0	0	0
Item 17	1	1	1	1	1	1	1	1	1	1	1	1	1
Item 18	1	1	0.5	1	1	1	0	0	0	0	0	1	0
Item 19	0	1	1	1	1	1	0	1	0	1	0	1	0

(Continued)

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TABLE 4 (Continued)

Item	Zhang and Hu (31)	Kang et al. (32)	Dennis et al. (33)	Zhu et al. (34)	Sang (35)	Wieland et al. (36)	Douglas et al. (37)	Susan and Beggs (38)	Manoj and Haider (39)	Alison et al. (40)	Christopher (41)	Holger et al. (42)	Paul and Ernst (43)
Item 20a	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	0	0.5	0.5	1	0.5
Item 20b	1	1	1	1	1	1	1	1	0	1	1	1	1
Item 20c	0	1	1	1	0	1	0	0	0	0	0	1	0
Item 20d	0	0	1	1	0	1	0	0	0	0	0	1	0
Item 21	0	0	1	1	1	1	0	0	0	0	0	1	0
Item 22	0	0	1	1	0	1	0	1	0	0	0	0	1
Item 23a	1	0	1	1	0	1	1	1	1	1	1	1	1
Item 23b	1	1	1	1	1	1	1	1	1	1	1	1	1
Item 23c	1	1	1	1	1	1	1	1	1	1	1	1	1
Item 23d	1	0	0	1	1	1	1	1	1	1	1	1	1
Item 24a	0	0	1	1	0	0	0	0	0	0	0	0	0
Item 24b	0	0	0	1	0	0	0	0	0	0	0	0	0
Item 24c	0	0	0	1	0	1	0	0	0	0	0	0	0
Item 25	0	0	1	1	0	1	1	0	1	0	0	0	1
Item 26	0	0	1	1	0	1	0	0	1	0	0	0	0
Item 27	0	0	0	0	0	1	0	0	0	0	0	0	0
Total score	14.5	16.5	28.5	36	18.5	38.5	12.5	18	12.5	16.5	13.5	28.5	17

Full conformity is recorded as 1 point, partial conformity is recorded as 0.5 point, and no conformity is recorded as 0 point. Items corresponding to the evaluation theme: item 1 for the title; item 2 for the abstract; items 3–4 for the introduction; items 5–15 for the method; items 16a—22 for the results; items 23a—27 for the discussion.

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3.6. Efficacy evaluation

3.6.1. Effects of yoga on pain relief

MAs were performed on six SRs (33–36, 38, 42) on the effect of yoga in relieving pain in cases of CLBP. A total of 25 pieces of evidence were obtained, including eight moderate, nine low, and eight very low-quality pieces of evidence. Pain was primarily measured using the visual analog scale (VAS). Out of the six studies, three SRs (33, 34, 36) with moderate-quality evidence showed that yoga considerably reduced pain compared with that reduced by non-exercise and passive controls [mean difference (MD) = −0.74, 95% confidence interval (CI): −1.04 to −0.44; MD = −0.43, 95% CI: −0.64 to −0.23; MD = −11.05, 95% CI = −14.22 to −7.88]. One SR (33) considered exercise and passive controls separately, showing no significant differences when comparing yoga intervention with the exercise control (MD = −0.78; 95% CI = −1.62 to 0.06; GRADE: very low) but showing a significant difference when comparing yoga intervention with the passive control (MD = −0.74; 95% CI = −1.04 to −0.44; GRADE: moderate). However, this difference only exists in the short term, as evidenced by a 12-month follow-up with no significant difference observed (MD = −0.58; 95% CI = −0.94 to 0.22; GRADE: moderate). Additionally, two SRs (34, 36) showed unclear results regarding whether yoga was more effective than non-exercise controls in the context of long-term efficacy at 12 months, with MD = −0.52, 95% CI = −1.64 to 0.59 (GRADE: very low) and MD = −5.87, 95% CI = −12.25 to 0.50 (GRADE: very low), respectively. Further details are presented in Table 6.

3.6.2. Effects of yoga on disability or back-specific functions

MAs were performed on six SRs (32–34, 36, 38, 42) on the effects of yoga on disability or back-specific functions, which were analyzed using the Oswestry Disability Index or Roland Morris Disability Questionnaire. A total of 25 pieces of evidence were obtained, comprising 11 moderate-, 13 low-, and one very low-quality pieces of evidence. One SR (34) compared the efficacy of yoga and physical exercise for improving functional disability associated with low back pain, and the results showed no statistically significant differences between the efficacy of yoga and physical therapy, with the quality of evidence ranging from moderate to very low. This finding indicated that the efficacy of yoga was not significantly greater than that of physical therapy for improving lumbar functional disability. One SR (36) examined the effect of yoga on back-specific function. Five pieces of evidence showed no significant difference between the efficacy of yoga and conventional exercise (GRADE: from moderate to low). Seven pieces of evidence from two studies (34, 36) suggest that yoga can improve back function and disability compared with non-exercise, and further details are presented in Table 7.

3.6.3. Effects of yoga on the quality of life

Four SRs (33, 34, 36, 42) analyzed the effect of yoga on the quality of life of patients with CLBP, generating a total of 38 pieces of evidence, which comprised 11 moderate-, 17 low-, and 10 very low-quality pieces of evidence. Factors such as physical and mental health were included in the assessment of the quality of life. One SR (42) showed that compared with controls, yoga improved the quality of life in the short and long terms. Furthermore, three SRs (33, 34, 36) showed that compared with no exercise, yoga positively affected physical function and mental health in the short- to long-term course of pain. However, most pieces of evidence showed no statistically significant differences (with the certainty of evidence ranging from moderate to very low) and showed large CIs. Thus, the efficacy of yoga in improving the physical and psychological quality of life remains unclear. Further details are presented in Table 8.

TABLE 5 Degree and number of literature reports.

Degree of literature reporting	Number of volumes	SRs
Relatively complete	2	(34, 36)
Certain defects	2	(33, 42)
Serious flaws	9	(31, 32, 35, 37–41, 43)

Completeness of 80% or more (33–42 points) is considered "relatively complete" and high quality; completeness of 60% or more (25–32 points) is considered "certain defects" and medium quality; completeness of <60% (<25 points) is considered a "relatively serious lack of information" and low quality.

3.7. Safety of yoga for low back pain

Six SRs (33, 34, 36, 37, 42, 43) showed adverse events associated with yoga for treating low back pain. Most adverse events were the mild-to-moderate exacerbation of low back pain. More severe adverse events included herniated disks and intense pain. MAs were performed on two SRs (33, 36) that focused on these adverse events. One SR (33) showed no significant difference in the incidence of adverse events between the yoga and active control groups [RR (risk ratio) = 0.58; 95% CI = 0.28–1.19; GRADE: low]. The other SR (36) showed that yoga and conventional exercise exhibited comparable safety profiles. Overall, yoga was not associated with serious adverse events; however, more studies are warranted to further investigate the safety of these interventions. Additional details are presented in Table 9.

3.8. Overlap

Graphical representation of overlap for overviews computes the overall CCA and provides a new graphical representation of the overlap between each pair of possible SRs/MAs. A total of 13 SRs comprised 172 RCTs. Of these, 52 RCTs overlapped, showing a calculated CCA of 19.23%. A total of 78 nodes between the reviews were observed, of which two were moderately overlapping, nine were highly overlapping, and 67 were very highly overlapping. Further details are presented in Figure 2.

TABLE 6 Quality of evidence on pain relief with GRADE.

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95%CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Pain											
Pain at short term (1 week)	Wieland et al. (36)	Yoga vs. exercise	1/80	MD = −14.50, 95% CI = −22.92 to −6.08	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
Pain at short term (4–6 weeks)	Dennis et al. (33)	Yoga vs. passive control	15/1,311	MD = −0.74; 95% CI = −1.04 to −0.44	I^2 = 34%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	10/1,167	MD = −0.78; 95% CI = −1.62 to 0.06	I^2 = 80%	−1	−1	0	−1	−1	⨁◯◯◯[a,b,c,d]
	Zhu et al. (34)	Yoga vs. non-exercise	6/381	MD = −0.83, 95% CI −1.19 to −0.48	I^2 = 0%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
		Yoga vs. physical exercise	5/350	MD = −0.37, 95% CI = −1.16 to 0.42	I^2 = 81%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	5/258	MD = −11.05, 95% CI = −14.22 to −7.88	I^2 = 0%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
		Yoga vs. exercises	3/201	MD = −12.47, 95% CI = −18.28, −6.66	I^2 = 36%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Holger et al. (42)	Yoga vs. control	6/584	SMD = −0.48; 95% CI = −0.65 to −0.31	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
Pain at short-intermediate term (3–4 months)	Zhu et al. (34)	Yoga vs. non-exercise	10/1,031	MD = −0.43, 95% CI = −0.64 to −0.23	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	4/564	MD = 0.19, 95% CI = −0.63 to 1.01	I^2 = 64%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	9/946	MD = −4.53, 95% CI = −6.61 to– 2.46	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	2/326	MD = 2.68, 95%CI = −2.01 to 7.36	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
		Yoga plus exercise vs. exercise	1/24	MD = −3.20, 95%CI = −13.76 to 7.36	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]

(Continued)

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TABLE 6 (Continued)

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95%CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Pain at intermediate term (6 months)	Zhu et al. (34)	Yoga vs. non-exercise	8/823	MD = −0.56, 95% CI = −1.02 to −0.11	I^2 = 50%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
		Yoga vs. physical exercise	4/392	MD = −0.73, 95% CI = −2.13 to 0.67	I^2 = 85%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	9/940	MD = −5.40, 95% CI = −8.58 to −2.22	I^2 = 40%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	3/331	MD = −6.41, 95%CI = −21.66 to 8.83	I^2 = 93%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
Pain at long term (12 months)	Dennis et al. (33)	Yoga vs. passive control	10/1,146	MD = −0.58; 95% CI = −0.94 to 0.22	I^2 = 33%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	5/663	MD = −0.62; 95% CI = −3.10 to 1.86	I^2 = 91%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Zhu et al. (34)	Yoga vs. non-exercise	2/355	MD = −0.52, 95% CI = −1.64 to 0.59	I^2 = 87%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	3/521	MD = −5.87, 95% CI = −12.25 to 0.50	I^2 = 68%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. exercise	1/199	MD = 3.00, 95% CI = −4.25 to 10.25	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Holger et al. (42)	Yoga vs. control	5/564	SMD = – 0.33; 95% CI = −0.59 to −0.07	I^2 = 48%	−1	0	0	0	0	⨁⨁⨁◯[a]
Pain at no staging	Sang (35)	Yoga vs. control	6/522	SMD = −0.41, 95% CI = −0.58 to−0.23	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
	Susan and Beggs (38)	Yoga vs. control	5/381	*d* = 0.623, 95% CI = 0.377 to 0.868;	I^2 = 22%	−1	0	0	−1	0	⨁⨁◯◯[a,c]

Evidence quality: ⨁◯◯◯, very low; ⨁⨁◯◯, low; ⨁⨁⨁◯, moderate; ⨁⨁⨁⨁, high.

[a]Downgraded for limitations: studies with methodological flaws of blinding and allocation concealment.

[b]Downgraded for inconsistency: significant heterogeneity.

[c]Downgraded for imprecision: small-sample size, or wide confidence interval.

[d]Downgraded for publication bias:asymmetric funnel plots.

N/n, number of studies/number of participants; CI, confidence interval; I^2, I-squared; d, effect size across the number of studies; MD, mean difference; SMD, standardized mean difference.

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TABLE 7 Quality of evidence on disability or back-specific function with GRADE.

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Disability											
Disability at short term (4–6 weeks)	Dennis et al. (33)	Yoga vs. passive control	15/1,327	MD = −2.28, 95% CI = −3.30 to −1.26	I^2 = 38%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	10/1,179	MD = −2.04, 95% CI = −4.02 to −0.06	I^2 = 77%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
	Zhu et al. (34)	Yoga vs. non-exercise	7/397	SMD = −0.30, 95% CI = −0.51 to−0.10	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	3/272	MD = −0.34, 95%CI = −1.60 to 0.92	I^2 = 0%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Holger et al. (42)	Yoga vs. control	8/689	SMD = – 0.59, 95% CI = −0.87 to −0.30	I^2 = 59%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
Disability at short-intermediate term (3–4 months)	Zhu et al. (34)	Yoga vs. non-exercise	9/951	SMD = −0.31, 95% CI = −0.45 to −0.18	I^2 = 30%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	4/519	MD = −0.04, 95% CI = −1.76 to 1.67	$I^{2=}$ 67%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
Disability at intermediate term (6 months)	Zhu et al. (34)	Yoga vs. non-exercise	6/688	SMD = −0.38, 95% CI = −0.53 to −0.23	$I^{2=}$ 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	2/229	MD = −1.32, 95% CI = −2.78 to 0.13	I^2 = 0%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
Disability at long term (12 months)	Dennis et al. (33)	Yoga vs. passive control	11/1,225	MD = −2.34, 95% CI = −3.30 to −1.38	I^2 = 27%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	5/675	MD = −2.04, 95% CI = −4.02 to −0.06	I^2 = 77%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
	Zhu et al. (34)	Yoga vs. non-exercise	2/365	SMD = −0.33, 95% CI = −0.54 to −0.12	I^2 = 9%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Holger et al. (42)	Yoga vs. control	5/574	SMD = – 0.35, 95% CI = −0.55 to −0.15	I^2 = 20%	−1	0	0	0	0	⨁⨁⨁◯[a]

(Continued)

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Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Disability at no staging	Kang et al. (32)	Yoga vs. routine group	14/1,684	MD = −1.86, 95%CI = −2.39 to −1.33	I^2 = 17%	−1	0	0	0	−1	⨁⨁◯◯[a,d]
	Susan and Beggs (38)	Yoga vs. control	8/743	*d* = 0.645, 95% CI = 0.496 to 0.795	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
Back-specific function											
At very short term (1 week)	Wieland et al. (36)	Yoga vs. exercise	1/80	MD = −1.25, 95%CI = −1.73 to −0.77	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At short term (4 to 8 weeks)	Wieland et al. (36)	Yoga vs. non-exercise	8/474	MD = −0.41, 95% CI = −0.61 to −0.21	I^2 = 6%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	4/395	MD = −0.04, 95%CI = −0.32 to 0.23	I^2 = 42%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At short-intermediate term (3 months)	Wieland et al. (36)	Yoga vs. non-exercise	11/1,155	MD = −0.31, 95% CI = −0.50 to −0.12	I^2 = 55%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
		Yoga vs. exercise	4/575	MD = −0.08, 95%CI = −0.28to 0.13	I^2 = 31%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga plus exercise vs. exercise	1/24	MD = −3.68, 95%CI = −8.44, 1.08	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At intermediate term (6 months)	Wieland et al. (36)	Yoga vs. non-exercise	11/1,157	MD = −0.36, 95% CI = −0.52 to −0.21	I^2 = 38%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	3/333	MD = −0.08, 95%CI = −0.40 to 0.23	I^2 = 47%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At long term (12 months)	Wieland et al. (36)	Yoga vs. non-exercise	3/532	MD = −0.27, 95% CI = −0.45 to −0.10	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	1/200	MD = −0.02, 95% CI = −0.29 to 0.26	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]

Evidence quality: ⨁◯◯◯, very low; ⨁⨁◯◯, low; ⨁⨁⨁◯, moderate; ⨁⨁⨁⨁, high.

[a]Downgraded for limitations: studies with methodological flaws of blinding and allocation concealment.

[b]Downgraded for inconsistency: significant heterogeneity.

[c]Downgraded for imprecision: small-sample size, or wide confidence interval.

[d]Downgraded for publication bias: asymmetric funnel plots.

N/n, number of studies/number of participants; CI, confidence interval; I^2, I-squared; d, effect size across the number of studies; MD, mean difference; SMD, standardized mean difference.

TABLE 8 Quality of evidence on the quality of life with GRADE.

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Physical quality of life											
At short term	Zhu et al. (34)	Yoga vs. non-exercise	1/13	MD = 0.75, 95% CI = −11.45 to 12.95	None	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Dennis et al. (33)	Yoga vs. passive control	9/980	MD = 2.80, 95% CI = 1.00 to 4.70	I^2 = 24%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	8/1,039	MD = 5.10, 95% CI = −0.30 to 10.50	I^2 = 88%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	2/81	MD = 0.50, 95% CI = 0.05 to 0.95	I^2 = 0%	−1	0	0	−1	0	⨁⨁◯◯[a,c]
		Yoga vs. exercise	3/219	MD = 1.03, 95% CI = 0.36 to 1.71	I^2 = 82%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
At short to intermediate term	Zhu et al. (34)	Yoga vs. non-exercise	5/617	SMD = 0.06, 95% CI = −0.10 to 0.22	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	2/348	MD = 0.18, 95% CI = −1.97 to 2.32	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
	Wieland et al. (36)	Yoga vs. non-exercise	6/686	MD = 0.20, 95% CI = 0.03 to 0.37	I^2 = 10%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	1/237	MD = 0.15, 95% CI = −0.11to 0.40	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At intermediate term	Zhu et al. (34)	Yoga vs. non-exercise	2/366	SMD = 0.08, 95% CI = −0.13 to 0.28	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	1/107	MD = −0.34, 95% CI = −12.77 to 12.09	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Wieland et al. (36)	Yoga vs. non-exercise	3/434	MD = 0.16, 95% CI = −0.13 to 0.46	I^2 = 52%	−1	−1	0	0	0	⨁⨁◯◯[a,b]
		Yoga vs. exercise	1/54	MD = 1.34, 95% CI = 0.75 to 1.94	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At long term	Zhu et al. (34)	Yoga vs. non-exercise	1/264	MD = 0.79, 95% CI = −1.52 to 3.10	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Dennis et al. (33)	Yoga vs. passive control	6/725	MD = 2.20, 95% CI = 0.30 to 4.10	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	3/283	MD = 3.10, 95% CI = −19.50 to 25.60	I^2 = 93%	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]

(Continued)

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TABLE 8 (Continued)

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
	Wieland et al. (36)	Yoga vs. non-exercise	1/264	MD = 0.17, 95% CI = −0.07 to 0.41	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
		Yoga vs. exercise	1/80	MD = 1.06, 95% CI = 0.59 to 1.53	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
Mental quality of life											
At short term	Dennis et al. (33)	Yoga vs. passive control	7/845	MD = 1.70, 95% CI = 0.20 to 3.20	$I^2 = 0\%$	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. active control	7/929	MD = 5.70, 95% CI = −2.50 to 14.00	$I^2 = 92\%$	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Zhu et al. (34)	Yoga vs. non-exercise	1/13	MD = −4.71, 95% CI = −21.66 to 12.24	None	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
	Wieland et al. (36)	Yoga vs. non-exercise	2/81	MD = −0.15, 95% CI = −1.24 to 0.93	$I^2 = 67\%$	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
		Yoga vs. exercise	3/219	MD = 1.03, 95% CI = −0.44 to 2.51	$I^2 = 96\%$	−1	−1	0	−1	0	⨁◯◯◯[a,b,c]
At short to intermediate term	Zhu et al. (34)	Yoga vs. non-exercise	5/617	SMD = 0.15, 95% CI = −0.01 to 0.31	$I^2 = 0\%$	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	2/348	MD = 0.07, 95% CI = −2.74 to 2.89	$I^2 = 0\%$	−1	0	0	0	0	⨁⨁⨁◯[a]
	Wieland et al. (36)	Yoga vs. non-exercise	6/686	MD = 0.20, 95% CI = 0.05 to 0.35	$I^2 = 0\%$	−1	0	0	0	0	⨁⨁◯◯[a,c]
		Yoga vs. exercise	1/237	MD = 0.16, 95% CI = −0.10 to 0.41	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At intermediate term	Zhu et al. (34)	Yoga vs. non-exercise	2/366	SMD = 0.18, 95% CI = −0.03 to −0.39	$I^2 = 0\%$	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. physical exercise	1/107	MD = 1.53, 95% CI = −6.43 to −9.49	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
	Wieland et al. (36)	Yoga vs. non-exercise	3/434	MD = 0.21, 95% CI = 0.00 to 0.41	$I^2 = 9\%$	−1	0	0	0	0	⨁⨁⨁◯[a]
		Yoga vs. exercise	1/54	MD = 1.33, 95% CI = 0.74 to1.92	None	−1	0	0	−1	0	⨁⨁◯◯[a,c]
At long term	Dennis et al. (33)	Yoga vs. passive control	4/595	MD = 1.30, 95% CI = −2.30 to 4.80	$I^2 = 39\%$	−1	0	0	−1	0	⨁⨁◯◯[a,c]

(Continued)

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TABLE 8 (Continued)

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
		Yoga vs. active control	2/173	MD = 6.40, 95% CI = −78.10 to 91.00	I^2 = 93%	−1	−1	0	−1	0	⨁○○○[a,b,c]
	Zhu et al. (34)	Yoga vs. non-exercise	1/264	MD = 0.42, 95% CI = −2.16 to 3.00	None	−1	0	0	−1	0	⨁⨁○○[a,c]
	Wieland et al. (36)	Yoga vs. non-exercise	1/264	MD = 0.07, 95% CI = −0.17 to 0.31	None	−1	0	0	−1	0	⨁⨁○○[a,c]
		Yoga vs. exercise	1/80	MD = 0.87, 95% CI = 0.41 to 1.33	None	−1	0	0	−1	0	⨁⨁○○[a,c]
Quality of life											
At short term	Holger et al. (42)	Yoga vs. control	4/388	SMD = 0.41; 95% CI = 0.11 to 0.93	I^2 = 72%	−1	−1	0	−1	0	⨁○○○[a,b,c]
At long term	Holger et al. (42)	Yoga vs. control	2/287	SMD = 0.18; 95% CI = 0.05 to 0.41	I^2 = 0%	−1	0	0	−1	0	⨁⨁○○[a,c]

Evidence quality: ⨁○○○, very low; ⨁⨁○○, low; ⨁⨁⨁○, moderate; ⨁⨁⨁⨁, high.

[a]Downgraded for limitations: studies with methodological flaws of blinding and allocation concealment.

[b]Downgraded for inconsistency: significant heterogeneity.

[c]Downgraded for imprecision: small-sample size, or wide confidence interval.

N/n, number of studies/number of participants; CI, confidence interval; I^2, I-squared; MD, mean difference; SMD, standardized mean difference.

TABLE 9 Quality of evidence on adverse events with GRADE.

Outcomes	Systematic review	Interventions vs. comparisons	*N/n*	MD (95% CI)	I^2	Risk of bias	Inconsistency	Indirection	Imprecision	Publication bias	Quality of evidence
Adverse events	Dennis et al. (33)	Yoga vs. passive control	9/949	RR = 3.78; 95% CI = 1.79 to 7.98	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁○[a]
		Yoga vs. active control	7/775	RR = 0.58; 95% CI = 0.28 to 1.19	I^2 = 69%	−1	−1	0	0	0	⨁⨁○○[a,b]
	Wieland et al. (36)	Yoga vs. non-exercise	8/1,037	RR = 4.76; 95% CI = 2.08 to 10.89	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁○[a]
		Yoga vs. exercise	5/6,40	RR = 0.93; 95% CI = 0.56 to 1.53	I^2 = 0%	−1	0	0	0	0	⨁⨁⨁○[a]

Evidence quality: ⨁○○○, very low; ⨁⨁○○, low; ⨁⨁⨁○, moderate; ⨁⨁⨁⨁, high.

[a]Downgraded for limitations: studies with methodological flaws of blinding and allocation concealment.

[b]Downgraded for inconsistency: significant heterogeneity.

N/n, number of studies/number of participants; CI, confidence interval; I^2, I-squared; RR, risk ratio.

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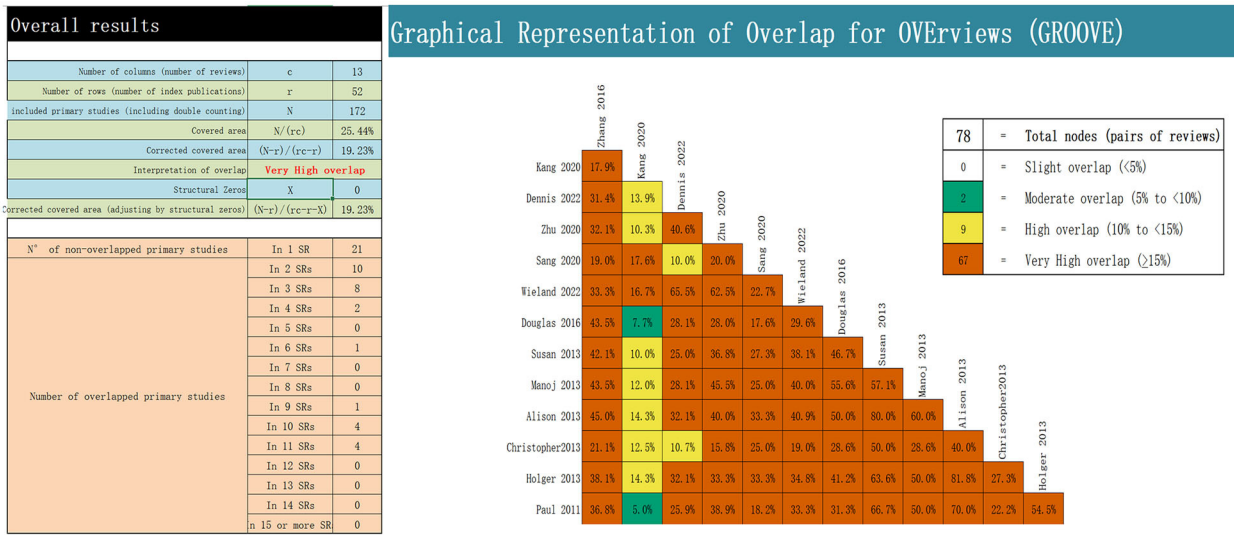
4. Discussion

The vast majority of patients with CLBP, a common MSK, complain of lumbosacral pain that lasts for an extended period. Moreover, the onset of the disease is insidious and not easily noticed by patients; thus, the disease puts a great burden on the mental and financial conditions of patients. The way a clinician approaches a patient with CBLP profoundly affects CLBP treatment because the patient may specifically remember negative inhibitory information and develop avoidance behavior and panic beliefs (21). Owing to the difficulty in determining CLBP pathogenesis, a clear pathological basis is unavailable for clinically available laboratory measures, and the subjective analysis of pain caused by the disease is common. Therefore, in the context of the modern biopsychosocial model of medicine, the American College of Physicians Guidelines for CLBP recommend a combination of physical and psychological treatments (12), and yoga meets this need.

Yoga, which originated in ancient India, is a form of physical and mental exercise that comprises meditative relaxation, breathing, and asanas. Meditation practice helps focus the mind and allows the practitioner to direct their awareness to breathing. Moreover, modern scientific research has shown that meditation can increase the levels of neurotransmitters, including melatonin and gamma-aminobutyric acid, and endorphins, thus playing a positive role in reducing mental stress and its effects in humans (44). Additionally, yoga asana practice can improve muscle strength, joint flexibility, and balance in patients with CLBP. Tilbrook et al. (45) found that after a 12-week yoga program, the back muscle function of adults with CLBP improved over 12 months, suggesting that yoga strengthened muscle stability and reduced low back pain by increasing hip and spinal flexibility. Thus, we searched for the published literature related to the SR of yoga in CLBP treatment to evaluate the effectiveness of yoga for managing CLBP and verify whether it is a supplementary and alternative treatment strategy for patients with CLBP.

We systematically evaluated the included studies using the AMSTAR-2 scale, PRISMA-2020 statement, and GRADE system. In terms of methodology, most critical factors were reported poorly because most studies lacked a presentation and description of the used preliminary research protocol and literature search, excluded reference lists, and failed to address sources of heterogeneity and risk of bias such as publication bias. Emphasizing the abovementioned factors can improve the methodological quality of SRs/MAs. In terms of reporting quality, the included SRs were generally of low reporting quality, primarily because of methodological flaws in reporting, especially regarding data processing and presentation. In terms of evidence quality, most SRs were characterized by inadequate or unreasonable randomization, blinding, and allocation concealment. Simultaneously, a significant risk of heterogeneity and homogeneity, mainly related to the small number of trials and the number of participants, as well as indicators observed in a single body of evidence, was present. Additionally, the repetition rate of the original RCT results extracted using the GROVE tool was very high, which might have resulted in some bias. Therefore, the careful handling and discussion of all aspects of a research design and its implementation are necessary. Moreover, higher-quality, large-sample, multi-center RCTs should be conducted to improve the homogeneity of evidence sources (46).

The present study showed that yoga exerted a certain therapeutic effect to improve pain and functional disability; however, the low-quality results reduced the credibility of the evidence. With respect to pain scores, most evidence pieces supported the efficacy of yoga in managing CLBP. Compared with non-exercise measures, yoga interventions significantly improved pain scores in patients with low back pain. Wieland et al. (36) showed a large pooled effect for yoga compared with non-exercise measures on pain scores, especially in the short term of 4–6 weeks (MD = −11.05, 95% CI = −14.22 to −7.88). However, this effect gradually decreased after 3 months (MD = −4.53, 95% CI = −6.61 to −2.46). Zhu et al. (34) showed no statistical significance regarding the long-term efficacy of yoga (MD = −0.52, 95% CI = −1.64 to 0.59). These results indicate that yoga probably exhibits better short-term efficacy than a non-exercise measure. Additionally, we found that compared with physical and exercise therapies, yoga did not exert remarkable effects, even though many results were statistically significant. Moreover, many MD values were less than the clinical minimum important difference. In this comparison, the pain improvement due to yoga was not considerable. Dennis et al. (33) distinguished passive exercises from active exercises. Compared with active exercises, yoga did not show statistical significance (MD = −0.78; 95% CI = −1.62 to 0.06), whereas compared with passive exercises, yoga showed significant results (MD = −0.74; 95% CI = −1.04 to −0.44) for CLBP management. Nevertheless, this difference decreased in follow-ups longer than 12 months (no statistical significance), suggesting a minor long-term pain improvement with yoga. In terms of improving functional disabilities, the study showed that yoga was advantageous in improving functional disability, which was more pronounced in a follow-up study by Dennis et al. (33), and Kang et al. (32) also found a significant advantage. However, Zhu et al. (34) found that compared with physical therapy, yoga showed no statistically significant results, suggesting that yoga might not be advantageous over physical therapy. Because the mentioned results have been pooled from a small number of studies, publication bias cannot be ruled out. In terms of improving the quality of life, yoga may not be effective compared with other controls, as evidenced by many non-significant results. With respect to a short- or long-term improvement in the quality of life, most evidence pieces (GRADE evidence from very low to moderate) showed that yoga had no significant advantage. These findings suggest that yoga may not have a noticeable therapeutic effect on improving the quality of life of patients with low back pain. However, we think that this inference may also be related to publication bias because these results are pooled from small-sample studies, and large-sample RCTs have not been conducted yet. Thus, future studies should verify this inference. Next, two studies (33, 36) assessed the safety of yoga for patients with low back pain using adverse events as the outcome. Wieland et al. (36) found that yoga was associated with a significantly increased risk of adverse events compared to non-exercise controls (RR = 4.76; 95% CI = 2.08–10.89); however, no statistical difference was observed when yoga intervention was compared with other exercises. Dennis et al. (33) showed no statistical difference in the incidence of adverse events



Overall results

Number of columns (number of reviews)	c	13
Number of rows (number of index publications)	r	52
included primary studies (including double counting)	N	172
Covered area	N/(rc)	25.44%
Corrected covered area	(N−r)/(rc−r)	19.23%
Interpretation of overlap	Very High overlap	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N−r)/(rc−r−X)	19.23%
N° of non-overlapped primary studies	In 1 SR	21
Number of overlapped primary studies	In 2 SRs	10
	In 3 SRs	8
	In 4 SRs	2
	In 5 SRs	0
	In 6 SRs	1
	In 7 SRs	0
	In 8 SRs	0
	In 9 SRs	1
	In 10 SRs	4
	In 11 SRs	4
	In 12 SRs	0
	In 13 SRs	0
	In 14 SRs	0
	In 15 or more SR	0

FIGURE 2
Overlapping of the included reviews.

between yoga and other conventional exercise groups, consistent with the Wieland et al. results. Therefore, we believe that yoga has the same safety profile as other exercise therapies; thus, it can be recommended as a supplementary exercise therapy for treating low back pain.

4.1. Strengths and limitations

To the best of our knowledge, this is the first study to assess the quality of methodologies and evidence pieces gathered from studies on yoga for CLBP and provide a specific evidence-based medical basis for formulating clinical guidelines. However, the study has certain objective limitations. First, evaluating the quality of methodologies and evidence pieces is subjective. Even if we evaluated each item of the evaluation system in detail and objectively, the overall confidence of most SRs was low, which led to a considerable risk of bias and uncertainty. Second, although we drafted a plan (Appendix 2) before implementing this review, it was not officially registered on PROSPERO (International Prospective Registration for System Review), and a reporting bias may exist. Finally, as the main outcome indicator of interest is the effect of yoga on pain, further research is necessary to clarify the potential benefits of yoga in improving balance, reducing the risk of falls, and increasing musculoskeletal strength.

4.2. Implications

This SR offers implications at several levels as follows: (a) From the perspective of the evidence obtained and its systematic evaluation: similar to the results of the SRs, the overview by Roberta pointed out that yoga significantly improved pain, especially low back pain (47). Furthermore, the small-sample size and lack of appropriate methods reduced the quality of evidence, leading to unclarity regarding the benefits of yoga. Additionally, compared with recent clinical guidelines (12), which recommend incorporating yoga as a non-pharmacological treatment option for CLBP, the present findings support this recommendation by showing that yoga can help improve pain and dysfunction in patients and is a relatively safe physical and mental exercise. (b) From the perspective of the clinical treatment mode for patients experiencing pain: while treating chronic musculoskeletal pain, the concept of comprehensive guidance through a person-centered approach (including biological, psychological, and social factors) is crucial and determines the effectiveness of interventions; thus, finding low-cost treatment options to treat chronic non-specific pain will offer greater benefits to patients (48), and yoga is a proactive intervention method that meets the characteristics of low cost and high patient acceptance. Additionally, clinicians are recommended to appropriately shift their attention to biomechanics and anatomical pathology to humanistic factors such as the social psychology of patients. Thus, by creating a positive and autonomous medical and health environment, the avoidance behavior and panic beliefs of patients caused by negative inhibitory information can be avoided and active physical activity can be promoted (49).

5. Conclusion

In conclusion, yoga appears to be an effective and safe non-pharmacological strategy for treating CLBP. Currently, it may exhibit better efficacy in improving pain and functional disability associated with CLBP. However, owing to the generally low quality and certainty of the evidence pooled from the included SRs, the present results should be interpreted cautiously. In addition, we found numerous non-significant results and low-quality evidence regarding yoga practice to improve the quality of life in patients with CLBP. Therefore,

whether yoga is different from other exercise or non-exercise therapies in improving the quality of life remains unclear. Nevertheless, the evidence presented herein is mostly obtained from small-sample studies without verification and validation from large-sample MAs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

XZ: Conceptualization, Formal analysis, Methodology, Writing—original draft. TC: Conceptualization, Formal analysis, Methodology, Supervision, Writing—original draft. WH: Conceptualization, Data curation, Supervision, Validation. MS: Conceptualization, Formal analysis, Methodology, Supervision. YC: Conceptualization, Data curation, Supervision, Validation. SW: Data curation, Formal analysis. GZ: Data curation, Formal analysis, Methodology. MH: Data curation, Formal analysis, Methodology. MZ: Conceptualization, Data curation, Formal analysis. JY: Conceptualization, Data curation, Formal analysis. HY: Conceptualization, Data curation, Formal analysis. LZ: Data curation, Formal analysis. CZ: Data curation, Formal analysis. ZL: Funding acquisition, Writing—review & editing. XL: Funding acquisition, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1273473/full#supplementary-material

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Short-term and long-term effectiveness of acupuncture and Tuina on knee osteoarthritis: study protocol for a randomized controlled trial

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Background: The effectiveness of acupuncture and tuina in treating knee osteoarthritis (KOA) is still controversial, which limits their clinical application in practice. This study aims to evaluate the short-term and long-term effectiveness of acupuncture and tuina on KOA.

Methods/design: This parallel-group, multicenter randomized clinical trial (RCT) will be conducted at the outpatient clinic of five traditional Chinese medicine hospitals in China. Three hundred and thirty participants with KOA will be randomly assigned to acupuncture, tuina, or home-based exercise group with a ratio of 1:1:1. The primary outcome is the proportion of participants achieving a minimal clinically important improvement defined as a ≥12% reduction on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain dimension on short term (week 8) and long term (week 26) compared with baseline. Secondary outcomes are knee joint conditions (pain, function, and stiffness), self-efficacy of arthritis, quality of life, and psychological conditions, which will be evaluated by the WOMAC score and the Patient Global Assessment (PGA), and in addition, the respondents index of OMERACT-OARSI, Short Form 12 Health Survey (SF-12), arthritis self-efficacy scale, and European five-dimensional health scale (EQ-5D). Adverse events will be collected by self-reported questionnaires predefined.

Clinical trial registration: https://www.chictr.org.cn

KEYWORDS

knee osteoarthritis, acupuncture, tuina, exercise, randomized controlled trial, telehealth

1 Introduction

Knee osteoarthritis (KOA) is the most common type of osteoarthritis, characterized by chronic pain and impaired activity function that significantly impacts the activities of daily living and quality of life of patients (1). In 2019, the global age-standardized prevalence rate (ASR) of OA was 6348.25 per 100,000, with KOA accounting for approximately 60.6% (2). In China, the number of prevalent cases of KOA has increased from approximately 110 million in 2016 (3) to 132.81 million in 2019 (2), with 75% of patients aged 45–74 years (2). From a public health point of view, KOA imposes an increasing economic burden on individuals and society (4).

Acupuncture is increasingly being used as a complementary alternative therapy during medical interventions, and substantial patients are willing to use it for disease treatment and prevention (5, 6). Analgesia is one of the primary effects of this therapy (7). Although studies have found that acupuncture benefits function, pain, and knee stiffness (8–10), its effectiveness in treating KOA is still equivocal (11), and most studies have only focused on its short-term benefits. A meta-analysis showed that acupuncture can alleviate pain and improve function in both the short term and long-term (12) but more rigorously designed studies are needed to investigate its medium-term or long-term effectiveness (13, 14). As another non-invasive and non-pharmaceutical therapy (15), tuina is widely accepted as a medical intervention in Asia. Some previous studies have shown that it is effective in relieving pain and improving function for some musculoskeletal diseases such as neck pain, back pain, and KOA (16). However, evidence of its effectiveness on KOA is lacking, and well-designed studies estimating its medium-term and long-term effectiveness are rare so far (16). Thus, considering the chronic and degenerative characteristics of KOA (17), it is of utmost importance to assess the long-term effectiveness of acupuncture and tuina for patients with KOA. Additionally, exercise programs are currently adopted among KOA patients and predisposing effectiveness has been observed (18, 19). Consistent with this, most guidelines recommended health education and management, weight loss, and exercise therapy as the core treatments for KOA (20, 21). However, the application of exercise and physicians capable of directing appropriate exercise therapy are limited (22, 23), and continuous practitioner involvement may be impractical due to cost and/or work time. Based on the increasing popularity of mobile video in daily life, it is possible to design a convenient platform to support online exercise programs to guide patients' exercise.

Therefore, the primary aim of our randomized controlled trial (RCT) is to assess the short-term and long-term effectiveness of acupuncture or tuina, respectively, compared with home-based exercise with an online program in treating KOA.

Abbreviations: KOA, knee osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ASR, age-standardized prevalence rate; RCT, randomized controlled trial; KL, Kellgren–Lawrence; NRS, numerical rating scale; HIS, Hospital Information System; APP, application; SOP, Standardized Operating Procedures; PGA, Patient Global Assessment; OARSI, Osteoarthritis Research Society International; OMERACT, Outcome Measures in Rheumatology; Sf-12, Short Form 12 Health Survey; ASES-8, Arthritis Self Efficacy Scale; EQ-5D, European Five-Dimensional Health Scale; DOMS, delayed onset muscle soreness; ITT, intention-to-treat; TCM, Traditional Chinese Medicine.

2 Methods

2.1 Study design and setting

This is a parallel multicenter, pragmatic, randomized controlled study that will be performed at five centers in China between October 2021 and December 2025. These centers were selected as they are representative of TCM of these hospitals and the distribution of patients with KOA in the local communities: (1) Dongzhimen Hospital of Beijing University of Chinese Medicine, (2) Guang'anmen Hospital (Southern District), China Academy of Chinese Medical Sciences, (3) Shunyi Hospital of Beijing Traditional Chinese Medicine Hospital, (4) Weifang Hospital of Traditional Chinese Medicine, (5) The Affiliated TCM Hospital of Guangzhou Medical University.

The trial has been approved by the Ethics Committee of Beijing University of Chinese Medicine (2023BZYLL0708), completing the ethical process per sub-center, and it has been registered on the Chinese Clinical Trial Registry (ChiCTR2200058089). This study will report following the guidelines of SPIRIT (24). Figure 1 shows the flowchart of the study design.

2.2 Participants

The diagnosis (1. of Supplementary material) criteria of KOA was made based on the criteria of the Chinese Orthopaedic Association (25) and the American College of Rheumatology (26). Eligible participants should: (1) be aged 45–75 years; (2) Kellgren–Lawrence (KL) grade (27) II or III; (3) have average knee pain over 1 week of the numerical rating scale (NRS) $\geq$ 4; (4) be suffered from pain in the last 3 months; (5) sign the informed consent form. The exclusion criteria are as follows: (1) knee pain caused by other diseases (such as infectious arthritis) or comorbid contusion or other trauma; foot deformity, pain, and other diseases affecting walking; serious osteoporosis; the skin around the knee joint broken or suffered from dermatosis that affect manipulation; (2) history of knee surgery or waiting for knee surgery; arthroscopy within 12 months; intra-articular injection within 6 months; medication for treating KOA within 1 week; (3) history of knee exercise program within 6 months or comorbidities that affect lower limb motor ability, balance ability, or strength training, such as stroke, myocardial infarction, peripheral neuropathy, Parkinson's disease, and multiple sclerosis; (4) history of receiving acupuncture or tuina therapy within 3 months or participating in another clinical study in the previous 3 months; (5) history of fainting during acupuncture; (6) comorbidities such as serious cardiovascular and cerebrovascular diseases, mental disorders, malignant tumors, coagulation disorders, liver and kidney dysfunction, and severe gastrointestinal diseases; (7) pregnant or breastfeeding or with a pregnancy plan; (8) not familiar with using smartphones. Participants who meet any of the above exclusion criteria will be excluded.

2.3 Sample size

According to the previous studies (28), the baseline value of the WOMAC pain subscale in Chinese KOA patients was obtained as a mean difference of 6.5 (SD = 2.8) on the Likert scale, scored on a range

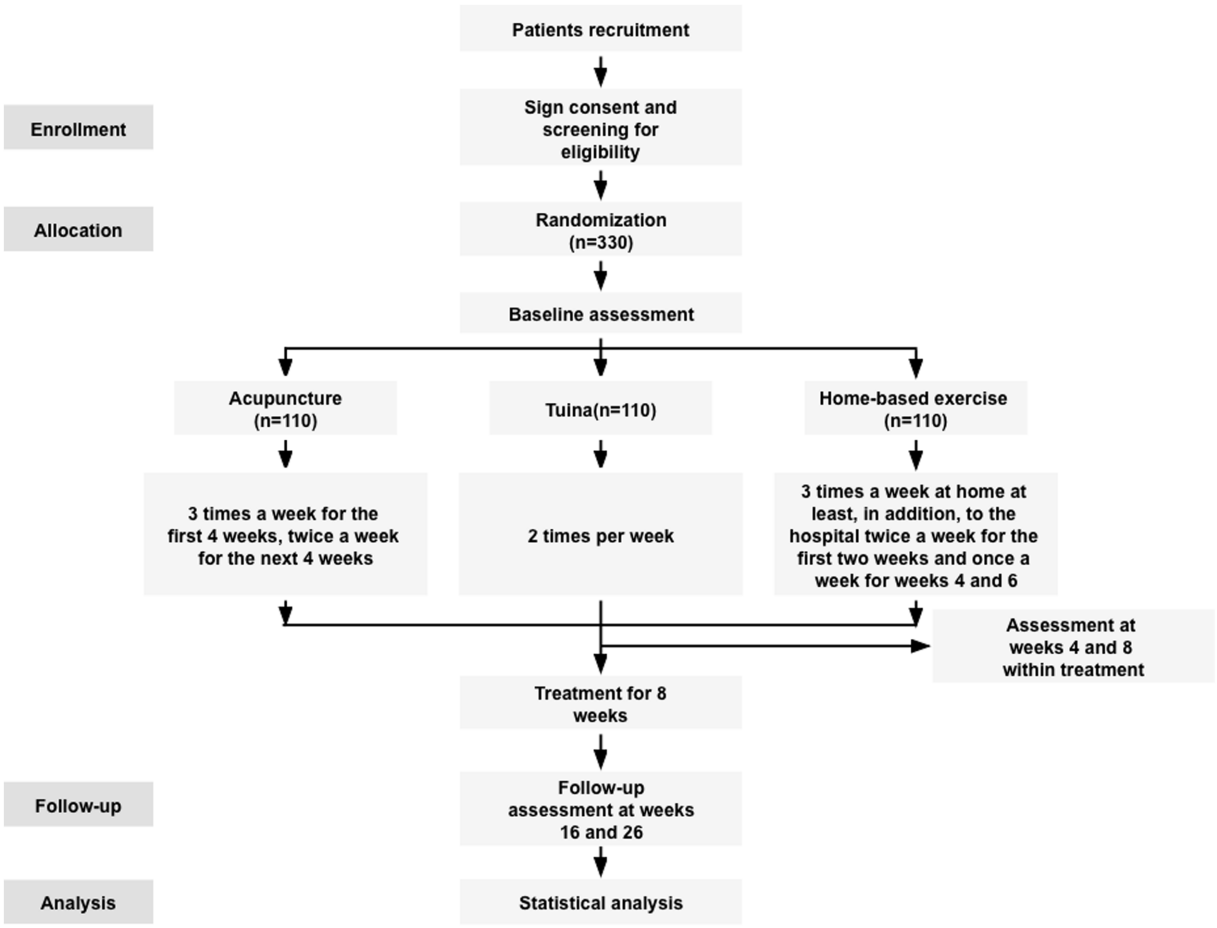

FIGURE 1
Flow diagram of the study participants enrollment and follow-up.

of 0–4 points. Using which the pain subscale value was transformed to 16.25 (standard deviation [SD] = 7) on the 0–10 points NRS scale. The Minimum Clinically Important Difference (MCID) of the WOMAC pain subscale is a reduction of at least 12% (29). We estimate that there will be a difference of at least 12% between acupuncture and home-based exercise groups, or tuina and home-based exercise groups, in the WOMAC pain subscale after 8 weeks of treatment. Furthermore, we anticipate this difference to be maintained at the 26-week follow-up, with a value of 1.95 (SD = 7). Using a Bonferroni correction method to avoid the inflation of type I errors, a two-sided significance level of 0.025 was set for two independent test hypotheses, namely, acupuncture vs. home-based exercise and tuina vs. home-based exercise. To achieving a power of 80%, 82 participants will be needed in each group. Assuming a drop-out rate of 25%, a total of 330 eligible participants with 110 participants per group will be needed.

2.4 Recruitment, randomization, and blinding

Participants will be recruited from the outpatient departments at each center as well as through various strategies that involve the use of a hospital information system (HIS). These methods may include posting posters in the clinics and distributing e-posters on social media platforms, such as WeChat.

Prior to any study procedures, potential participants will be recruited sequentially from each center. Written informed consent will be obtained from potential participants during the screening and eligibility assessment phase. Those who meet the eligibility criteria will be randomly assigned in a 1:1:1 ratio to either acupuncture or tuina or home-based exercise groups, stratified by a study center. The randomization sequence will be generated using the PROC PLAN process in SAS (version 9.3). The central randomization system developed by the Institute of Basic Research in Clinical Medicine at the China Academy of Chinese Medical Sciences will implement the group assignment. An independent statistician, who will not conduct the evaluation or statistical analysis of the trial, will ensure adequate randomization.

While the participants and physicians will not be blinded to interventions, the outcome evaluators and biostatisticians will be blinded to group details.

2.5 Interventions

Each participant will receive a usual care education package for KOA, excluding the corresponding treatment. This package will

	Study period						
	Enrollment	Allocation	Intervention			Follow-up	
TIME POINT(week)			W0	W4	W8	W16	W26
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization	X						
Allocation		X					
INTERVENTIONS:							
Acupuncture			◆	—	◆		
Tuina			◆	—	◆		
Home-based exercise			◆	—	◆		
ASSESSMENTS:							
WOMAC function		X		X	X	X	X
WOMAC pain		X		X	X	X	X
WOMAC stiffness		X		X	X	X	X
PGA				X	X	X	X
SF-12		X			X	X	X
ASES-8		X			X	X	X
EQ-5D		X			X	X	X
Credibility and Expectancy Questionnaire		X					
Adherence				X	X		
Rescue medicine				X	X	X	X
Adverse events				X	X	X	X

FIGURE 2
Schedule of enrollment, intervention, and assessments of this study protocol. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PGA, Patient Global Assessment; SF-12, 12-item Short Form Health Survey; ASES, Arthritis Self Efficacy Scale; EQ-5D, European Five-Dimensional Health Scale. "X" projects that must be completed.

provide basic knowledge of osteoarthritis, pain management, treatment recommendations, physical activity administration, the benefits of exercise, and health notes for KOA. Our study team has integrated these educational materials into a mobile phone application (APP) called *Knee for long*, which is specially designed for patients with KOA by our team. The APP includes various modules for health records, self-management, and clinical research. Through the APP, participants will receive the same educational information via tweets, recordings, and videos regarding the causes, symptoms, and main treatment measures of KOA. To ensure consistent treatment time across all three groups, practitioners will only treat the worse knee if participants with bilateral KOA. The schedule of enrollment, interventions, assessments, and participant visits are shown in Figure 2.

2.5.1 Acupuncture group

The acupuncture prescription was developed based on previous clinical research (8) and expert consensus (2.0 of Supplementary material and Figure 3). It is semi-standardized, incorporating six essential acupoints and three adjunct acupoints. The essential acupoints are *Dubi* (ST35), *Neixiyan* (EX-LE5), *Zusanli* (ST36), *Yinlingquan* (SP9), *Yanglingquan* (GB34), and an *Ashi* point (where the participant feels the worst pain). Selection of the adjunct acupoints will be based on the location of pain according to meridians. All acupoints will be localized according to the Nomenclature and Location of Acupuncture Points in the People's Republic of China in 2021 (GB/T 12346–2021) (30) (2.0 of Supplementary material). If the pain is located in the anterior aspect of the affected knee joint, three YangMing acupoints will be chosen from *Futu* (ST32), *Liangqiu* (ST34), *Heding* (EX-LE2), and *Fenglong* (ST40). For lateral pain, indicative of ShaoYang syndrome, three adjunct acupoints will be selected from *Waiqiu* (GB36), *Xuanzhong* (GB39), *Zulinqi* (GB41), and *Xiyangguan* (GB33). For posterior pain, associated with TaiYang syndrome, adjunct acupoints will be *Weizhong* (BL40), *Chengshan* (BL57), and *Kunlun* (BL60). For medial pain, indicative of three-yin syndrome, three adjunct acupoints will be chosen from *Xuehai* (SP10), *Yingu* (KI10), *Xiguan* (LR7), *Sanyinjiao* (SP6), *Taixi* (KI3), *Taichong* (LR3), and *Gongsun* (SP4). If more than two meridians are affected, three relevant adjunct acupoints will be selected from those for the corresponding syndromes.

The treatment will be performed by licensed acupuncturists or tuina practitioners who have a minimum of 5 years of experience in treating KOA. Prior to the study, they will be trained in the implementation of standardized operating procedures (SOP) at each center. To ensure consistency, a detailed instruction manual and video will be provided to them.

Uniform disposable sterile filiform needles (0.25 mm in diameter, 40–50 mm in depth) from Tianjin Yipeng Medical Device Co., Ltd. in China will be used in each center. After skin disinfection, acupuncturists will insert needles into the predetermined acupoints to induce the deqi sensation, characterized by soreness, numbness, distention, and

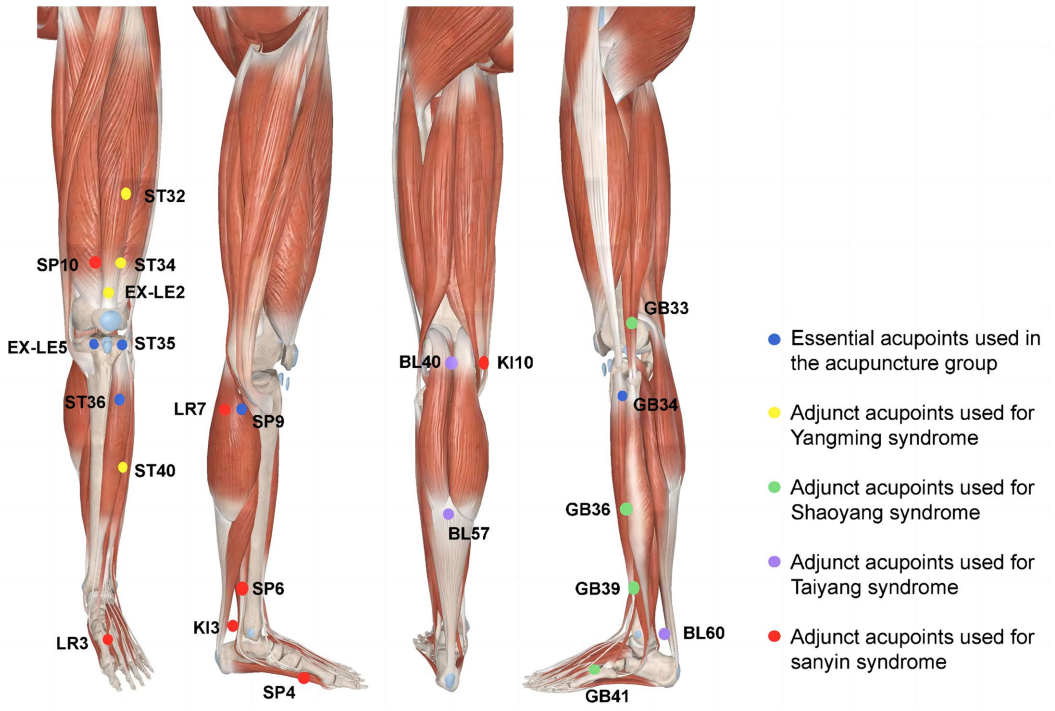

FIGURE 3
Locations of acupoints. Blue dots: essential acupoints used in the acupuncture group. Yellow dots: adjunct acupoints used for YangMing syndrome. Green dots: Adjunct acupoints used for ShaoYang syndrome. Purple dots: Adjunct acupoints used for TaiYang syndrome. Red dots: Adjunct acupoints used for three-yin syndrome (Note: Modified based on 3D body).

heaviness. During the 30 min retention, a small amplitude of uniform lifting and thrusting twirling lasting 10–15 s will be performed every 10 min to sustain the deqi sensation. The acupuncture treatment will consist of 20 sessions over 8 weeks (3 sessions per week for the first 4 weeks, 2 sessions per week for the subsequent 4 weeks).

2.5.2 Tuina group

Tuina therapy consists of six standardized steps based on the expert nation-wide consensus on the manipulation of tuina for KOA (31) and clinical experts' suggestions. The procedure will be precisely defined in terms of actions, duration, frequency, and intensity to ensure consistency (Table 1). The manipulation intensity should be tolerated to the participant's tolerance and violent manipulation will be prohibited. The tuina therapy will comprise 16 sessions of 25 min in duration, held over 8 weeks with two sessions per week.

2.5.3 Home-based exercise group

The home-based exercise program, based on previous clinical research and self-management mode (19, 32), will be incorporated into the APP. Participants will receive the same educational materials as the other two groups, along with an online home-based stepped exercise program accessible through the APP. Only participants allocated to the home-based exercise group will have access to the exercise module, which contains instructions, prerecorded exercise videos, time consumption, and assessments of difficulty level. During the first 2 weeks, participants will be required to receive guidance on exercise in hospitals twice a week, while in the 4th and 6th weeks once a week, there is a need to assess and guide the accuracy of their movements. Based on guidance in hospital, participants will be informed to carry out the exercise program at home at least three times per week according to the videos provided. Each training and the duration of the exercise will be recorded by the APP. The exercise program includes three parts: preparation activity, formal exercise program (comprising five subsections), and the ending stage. Each program has various subsections, and the formal exercise program will also have three intensity levels. The APP will distribute different levels to participants based on their post-exercise evaluations. If any subsection evaluated fulfills the easy level (three levels: easy, moderate, and difficult), the exercise intensity level will be increased by adding ankle weights and/or changing body position. If the entire program is evaluated as moderate in level four or less for at least three days on a modified Borg Rating of Perceived Exertion scale (33), the next stage will be unlocked. Additional detailed exercise sessions and videos can be found in 3.0 of Supplementary material, providing detailed instructions for the program.

During the trial, other therapies and any analgesic medications relevant to KOA will be prohibited. All participants will be provided with acetaminophen (tylenol) after enrollment. If their symptoms worsen and become unbearable, participants may take acetaminophen (325 mg.qd, with a maximum dose of 2,600 mg.qd). Each use of acetaminophen should be recorded promptly. Participants should be questioned about any other medications for other diseases in detail during the first and last two visits.

2.6 Outcomes

The efficacy of the intervention will be evaluated based on knee joint conditions (pain, function, and stiffness), self-efficacy of arthritis,

TABLE 1 Detailed manipulation of tuina.

Relaxation	Prone position: relaxing the bladder meridian of foot-TaiYang (from the hip's horizontal grain to the Achilles tendon) on the affected limb's back. Performing rolling manipulation, poking manipulation, and pushing manipulation with palm root, respectively, for five times, a total of 3.5 min.	
Press the acupoints	Supine position: acupressure will be applied to specific acupoints: *Xuehai* (SP10) - *Liangqiu* (ST34), *Dubi* (ST35) *Neixiyan* (EX-LE5), *Zusanli* (ST36), *Yinlingquan* (SP9), *Yanglingquan* (GB34) will be pressed using the belly of the thumb and index finger, with gradual and continuous from light to heavy. Each acupoint pair will be pressed for 30 s, a total of five times.	
	The medial and lateral collateral ligaments will be plucked with the thumb or four fingers for five times, approximately 1 min.	
Adjust muscles and tendons	Plucking the head of the gastrocnemius muscle and the hamstring muscle from the top to the bottom using the four-finger pulp of both hands back and forth for five times, approximately 1 min.	
Settle patella	Grabbing patella	Pushing the patella to the medial side with one thumb, and slowly grabbing the patella from bottom to top along the inner edge of the patella with the other four fingers. This action will be repeated once, with two hands and the direction reversed, approximately 1 min.
	Kneading patella	Kneading on the affected patella by using the palm with clockwise or counterclockwise direction, for 2 min.
Move knee joint	Flexion-extension-distraction manipulation of the knee	Supine position: the hip and knee joints will be flexed at a 90° angle. The four fingers will hold the lower part of the knee joint in the popliteal fossa while the two thumbs face upwards. Then swinging up and down the knee joint for 10 times and stretched out once. The procedure will be repeated five times, approximately 2 min.
	Hamstring stretch	Making the ankle dorsiflexed with one hand using a steady force, while the other hand is placed on the knee joint. The ankle will be extended as far as the participant can tolerate. The operation will be held for 10–15 s with five times, approximately 1 min.
Ending manipulation	Pushing the stomach meridian of foot-YangMing, using the palm root or thenar apply pressure on the front thigh, for 10 times, approximately 1 min.	
After the manipulation, lying down and resting for 3 min.		

quality of life, and psychological conditions. Endpoints will be recorded and assessed on the 8th week and 26th week after initial treatment.

2.6.1 Primary outcomes

The primary outcomes of the intervention will be measured by the improvement of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale after 8 and 26 weeks as compared with baseline levels. The WOMAC (34) is a disease-specific measure used to evaluate pain, stiffness, and joint function for KOA. Each of the 24 items is rated on a 0–10 numeric rating scale, with total scores ranging from 0 to 240 points. The subscales consist of 5, 2, and 17 items for pain, stiffness, and functional assessment, respectively. Lower scores indicate a milder symptom for each subscale.

2.6.2 Secondary outcomes

2.6.2.1 WOMAC

Changes in total scores, stiffness, and function subscales of WOMAC will be assessed at the baseline and weeks 4, 8, 16, and 26. The WOMAC pain subscale will be assessed at the baseline and weeks 4 and 16.

2.6.2.2 Patient global assessment

This scale will assess the overall degree of improvement at weeks 4, 8, 16, and 26 by inquiring how participants feel about their knee. PGA consists of seven options: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse (35).

2.6.2.3 The respondents index of OMERACT-OARSI

This study measures clinical outcomes for osteoarthritis, co-developed by Osteoarthritis Research Society International (OARSI) and the Outcome Measures in Rheumatology (OMERACT). OMERACT-OARSI response criteria will be calculated based on pain and functional subscales of WOMAC and PGA at weeks 4, 8, 16, and 26. The pain and function subscales of WOMAC scores will be converted to a 0–100 point scale by multiplying (100/50) and (100/170), respectively. The PGA score will be multiplied by 10 and converted to a 0–100 point scale. Scores meeting the following criteria will be considered clinically relevant: (1) improvement of ≥50% in WOMAC pain or function subscales and an absolute change of ≥20 points; (2) improvement of ≥20% in WOMAC pain or function subscales and an absolute change of ≥10 points or PGA improvement of ≥20% with an absolute change of ≥10 points.

The following scales will be assessed at weeks 8, 16, and 26 (36).

2.6.2.4 Short form 12 health survey

SF-12 is a tool that measures the quality of life in both physical and mental health, using a 12-item questionnaire that evaluates eight dimensions: general health, physical functioning, role physical, bodily pain and energy, social functioning, role emotional, and mental health. Higher scores on the questionnaire correspond to a better quality of life (37).

2.6.2.5 Arthritis self-efficacy scale

The ASES-8 scale is a shorter version of the tool that measures three dimensions of pain, function, and other symptoms in just eight items. Each item is scored from 1 to 10, and the final score is the mean of the 8 items. A higher score indicates a stronger sense of self-efficacy (38).

2.6.2.6 European five-dimensional health scale

This scale consists of the EQ-5D-5L and the EQ-VAS. The EQ-5D-5L evaluates five dimensions: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Each dimension corresponds to a question, with five answer levels. The EQ-VAS is a vertical visual scale that ranges from 0 (worst) to 100 (best) health. The utility value scoring system converts the results into a final quality of life (39).

2.6.2.7 Proportion of rescue medication

During each visit, participants will be asked if they have used emergency medications in order to evaluate the proportion of taking emergency medication during the study period.

2.6.2.8 Credibility and expectancy questionnaire

The efficacy expectation scale will only be evaluated at baseline (40).

2.6.3 Adverse events

Any adverse events and related information, such as occurrence time, symptoms, severity, and duration will be inquired and recorded at weeks 4, 8, 16, and 26 by the outcome assessor. Specific adverse events related to acupuncture, tuina, and home-based exercise will be predefined due to the unique characteristics of each intervention. Acupuncture-related adverse events include unbearable acupuncture pain, severe pain lasting more than 1 h (VAS $\geq$ 4 on a 10-point scale), local hematoma, metal allergy, bent, stuck, or broken needle, fainting, pneumothorax, nerve injury, visceral injury, and others. Tuina-related adverse events include swelling of the treated area, subcutaneous damage, subcutaneous bleeding, delayed onset muscle soreness (DOMS) (41), fracture, and others. Adverse events associated with home-based exercise include falls, sprain, muscle and ligament strains, DOMS, and others. Generic adverse events that occur during the study will also be recorded.

2.7 Data management

We will apply an Electronic Data Capture system to collect the data (eCRF). Independent evaluators at each site, who are not involved in allocation or treatment, will enter the data generated in this trial. The database will be locked upon completion, preventing modifications by researchers. Any changes needed in the data must be approved by the project leader and documented by the data management unit. Both paper and electronic documents will be retained for 5 years after publication. To ensure participant confidentiality and prevent information leakage, participant information will remain anonymous.

2.8 Quality control

In the process of design, the expert in acupuncture, orthopedics, methodology, and statistics demonstration meeting will be conducted to guarantee the scientificity and rationale of the trial design. A pre-specified SOP will be used in each procedure. Online monitoring and on-site monitoring will be applied in the study. All modifications of the data and the reasons for modifications can be found through the eCRF.

2.9 Statistical analysis

The intention-to-treat (ITT) analysis including all randomized participants from the three groups will be used. The primary outcomes will be analyzed using a mixed-effects model of repeated measures to compare the changes in the WOMAC pain subscale between the acupuncture or tuina group and the home-based exercise group at weeks 8 and 26 as compared to baseline. Similarly, changes in the WOMAC function subscale and stiffness subscale will also be analyzed using the same methodology. The response rate of OMERACT-OARSI will be assessed using the chi-square test. For SF-12 and ASES-8, analysis of covariance will be employed to evaluate differences in the total score improvements between groups compared to baseline. Differences in the PGA between groups will be evaluated using the Kruskal–Wallis test. Multiple imputations will be used for missing data. The chi-square or Fisher's exact test will be used to compare the incidence of adverse events.

3 Discussion

This study aims to assess the short-term and long-term effectiveness of acupuncture and tuina in treating KOA as compared to home-based exercise using telehealth programs. This study will prompt to lay a more evidential foundation for the selection of KOA treatments.

Acupuncture and tuina are among the most widely used traditional Chinese medicine (TCM) therapies for treating KOA in clinical practices (42, 43). However, there is a relative lack of supportive high-quality evidence in the literature, and only limited studies with low quality have shown that acupuncture and tuina were effective in reducing pain and improving function in individuals with chronic degenerative osteoarthritis (44, 45). Meanwhile, these studies have primarily focused on the immediate and short-term effectiveness of acupuncture and tuina (12, 46), and the evidence regarding long-term outcomes is equivocal. For example, studies comparing acupuncture versus sham acupuncture for KOA have shown inconsistent results after 26 weeks of treatment (46). Therefore, this study is designed to further explore the effectiveness of acupuncture and tuina for both short-term and long-term outcomes in a well-designed, large-scale trial. Self-management with physical exercise will serve as the standard control, as recommended in current various international guidelines (21, 22, 47).

An 8-week acupuncture prescription is adapted based on a previous study conducted by our team (8), which is a combination of adjacent, local, and distant points to achieve acupuncture analgesia and promote knee function recovery (48, 49). While the previous trial validated the regimen's short-term effectiveness, a rigorous RCT is needed to establish its long-term effectiveness. For our tuina regimen, we mainly adapted the Institution Standardized Regimen of Tuina for KOA, which is based on an expert consensus (31). The regimen aims to eliminate neutrophils caused by the injured muscle tissue and inhibit the release of inflammatory factors, thereby relieving pain, promoting muscle recovery (50), and relieving local or even lower limb dysfunction (51, 52). Prior to the implementation of the sub-center, we trained all the researchers to ensure the consistency of every operation. To guarantee the quality of the study, only those who passed the SOP examination could be eligible to conduct the trial.

We designed a stepped-exercise program for our study, which is highly beneficial for participants' self-management. These videos focus on strength and function training of lower limbs to improve core strength, adjust the structural mechanics of the knee joint, and reduce pain (53). To optimize acceptability, we have designed prerecorded exercise videos to vary in difficulty, allowing participants to choose their intensity level and progress at their own pace. The videos will be integrated into the APP for the home-based group, providing participants with the flexibility to customize their exercise intensity according to their individual tolerance level. Besides providing exercise guidance, this APP also offers a reminder function to enhance adherence. To enhance the degree of completion and exercise accuracy of participants in the home-based exercise group, they will be invited to our sub-center for face-to-face guidance twice a week for the first two weeks and once a week for week 4 and week 6.

Our study has a few limitations. First, considering the distinct intervention characteristics of acupuncture, tuina, and home-based exercise, blinding participants and physicians is impossible. However, we will take the following measures so as to avoid the crossover between the three groups. We will train all the physicians before implementing the trial of the first participant, and the physicians for each group will be fixed and treated independently. For participants, it is not allowed to change groups after randomization. If a participant changes group, he/she will discontinue the study, and just the data before group changing will be analyzed. Nevertheless, a study demonstrated that blinding may be of lower importance than is commonly believed in randomized controlled trials (54). To minimize the risk of potential bias, evaluators and statisticians were blinded to the group assignments for this study. Secondly, since we only enrolled patients with mild-to-moderate level KOA symptoms, the effectiveness of severe symptoms might not be observed in our study, thereby potentially limiting the generalization of the findings.

To summarize, this study is expected to produce valuable evidence regarding the short-term and long-term effectiveness of acupuncture or tuina as complementary alternative therapies for KOA. Meanwhile, the findings of this study may help to enhance the clinical application of these therapies in the treatment of KOA.

Ethics statement

The studies involving humans were approved by the Clinical Research Ethics Committee of Beijing University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

R-lZ: Writing - original draft, Project administration. P-hM: Writing - original draft, Project administration. B-yL: Methodology. C-hY: Methodology. H-rZ: Data curation. QL: Investigation. D-wY: Investigation. Y-pY: Investigation. H-yL: Investigation. F-yW: Investigation. C-sY: Investigation. S-gS: Investigation. H-cW: Investigation. X-yW: Conceptualization. S-yY: Conceptualization, Methodology.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fneur.2023.1301217/full#supplementary-material

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Effectiveness and safety of auricular acupuncture on adjuvant analgesia in patients with total knee arthroplasty: a randomized sham-controlled trial

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Objective: This study aimed to evaluate the effectiveness and safety of auricular acupuncture (AA) on postoperative analgesia, the degree of postoperative nausea, and the effect of inflammation after total knee arthroplasty (TKA).

Methods: This was a single-center, placebo-controlled, randomized clinical trial. In total, 96 patients were randomly divided into an AA group with an indwelling intradermal needle ($n = 48$) and a sham auricular acupuncture (SAA) group with a non-penetrating placebo needle ($n = 48$). Intra-spinal anesthesia was adopted in both groups during surgery, and an epidural analgesic pump was implanted after surgery for 48 h. The primary outcome was the post-surgery visual analog score (VAS) of resting and movement states (at 6, 12 h and 1, 2, 3, 5, and 7 days). The secondary outcomes included additional doses of analgesic injection during the treatment, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count on the 1st, 3rd, and 7th day after the operation, nausea on the 1st, 2nd, and 3rd day after the operation, the Hospital for Special Surgery Knee Score (HSS) on the 2nd and 12th week after the operation, and adverse events.

Results: The VAS in the AA group at 6 h, 12 h, 2, 3, and 5 days after surgery were lower than those of the SAA group ($p < 0.05$). Among the secondary outcomes, the total dose of additional analgesic injection after surgery in the AA group was lower than that in the SAA group ($p < 0.05$). The serum CRP on the 1st day after operation in the AA group was lower than that in the SAA group ($p < 0.05$). The degree of nausea on 2nd day after surgery in the AA group was lower than that in the SAA group ($p < 0.05$). There was no significant difference in other outcomes ($p > 0.05$).

Conclusion: In this study, AA was shown to be an effective and safe complementary and alternative therapy for pain relief after TKA, which was able to reduce the total postoperative dose of additional painkillers, decrease serum CRP 1 day after surgery, and improve the degree of postoperative nausea.

Clinical trial registration: www.chictr.org.cn, ChiCTR2100054403.

KEYWORDS

total knee arthroplasty, adjuvant analgesia, auricular acupuncture, randomized clinical trial, pain management

Introduction

Knee osteoarthritis (KOA) is a chronic degenerative disease characterized by articular cartilage damage and involves the whole joint tissue (1). KOA is very common in elderly patients. Knee deformity and swelling can directly affect the function of the lower limbs, cause a series of complications, and seriously affect the quality of life of elderly patients (2).

Patients suffering from KOA are mainly treated by surgery and analgesic drugs, while total knee arthroplasty (TKA) is mostly used for patients with advanced KOA. However, TKA is often accompanied by varying degrees of persistent pain, which causes physiological and psychological adverse effects, reducing the efficacy of surgery to a certain extent (3, 4). The use of analgesics during and after surgery is associated with numerous side effects, including nausea and vomiting, respiratory depression (5), liver and kidney injury, depression (6), and adverse cardiovascular events (7). Therefore, it is particularly important to explore a method that can effectively control pain and reduce the use of analgesics.

Previous studies have found that acupuncture is primarily used to treat pain, and acupuncture has significant effects on pain relief, with high safety and few side effects (8, 9). A previous meta-analysis demonstrated that auricular point pressing, a traditional acupuncture therapy, combined with conventional analgesia can effectively relieve postoperative pain and reduce the consumption of different types of analgesic drugs (10). According to the theory of biohology, the auricle forms a holographic reflex path from the homologically connected neurons in the brain and acts through the holographic connection of neurons in the brain (11). Therefore, abnormalities in various parts of the body cause corresponding changes in the ear through the holographic reflex path. Similarly, in the case of pain, the stimulation of ear points will also be transmitted to the corresponding organs of the body through the holographic reflex path to achieve the purpose of analgesia, while intervention away from the surgical incision site can avoid infection.

Two non-TKA randomized controlled trials (RCTs) (12, 13) have compared the use of indwelling intradermal needles in postoperative analgesia, with the results demonstrating that indwelling intradermal needles are effective in postoperative analgesia. The needles (14–17) used in previous postoperative analgesia studies were 0.2–0.22 mm in diameter and 1.2–1.5 mm in length, but the needle used in this study was 0.4 mm in diameter and 2.1 mm in length, which is larger in diameter and longer in the body than the conventional needles; thus, it is hoped that the needle will also provide better analgesia. However, there has been no previous RCT to evaluate the analgesic effect of an indwelling intradermal needle after TKA.

The underlying cause of postoperative pain is the stimulation of inflammatory factors. Serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count are routine blood indicators used to assess postoperative infection as they represent inflammatory and anti-inflammatory factors in the serum of postoperative trauma (18). When an infection occurs after surgery, these indicators rise significantly. However, due to factors such as their short half-life, these indicators alone cannot be used as inflammation indicators to determine postoperative infection. Therefore, a combination of more than two indicators should be used to improve the accuracy of predicting postoperative infection after TKA (19). Additionally, numerous studies have demonstrated a positive correlation between CRP and postoperative visual analog score (VAS), suggesting that CRP may serve as an objective indicator for evaluating the postoperative analgesic effect of TKA (20–22).

Therefore, we designed a prospective sham-RCT to provide a clinical basis for the efficacy and safety of auricular indwelling intradermal needles as adjuvant analgesia to reduce the use of analgesic drugs.

Materials and methods

Study design and participants

This study was a single-center placebo-controlled RCT. The patients in the AA group received an indwelling intradermal needle and were covered by a disposable opaque circular Band-Aid, whereas the patients in the SAA group only received the Band-Aid to cover five auricular acupoints. All eligible participants provided written informed consent before the trial. This study strictly followed the Declaration of Helsinki and SPIRIT guidelines. The study was approved by the Ethics Committee of Shijiazhuang West Medical Center (No. JXXYYLL006) and registered in the Chinese Clinical Trial Registry (ChiCTR2100054403). Patients who underwent TKA in the Department of Joint Surgery of the center from November 2021 to October 2022 were recruited by conversation.

This trial was based on the Guidelines for the Diagnosis and Treatment of Osteoarthritis (2018 edition) (23) issued by the Orthopaedic Branch of the Chinese Medical Association as the criteria for the diagnosis of KOA, including (1) recurrent knee pain within the last month; (2) X-ray films (standing or weight-bearing position) showed narrowing of the joint space, sclerosis and/or cystic degeneration of the subchondral bone, and osteophyte formation at the joint edge; (3) age $\geq$ 50 years old; (4) morning stiffness time $\leq$ 30 min; and (5) a bone rub (feeling) during activity.

The inclusion criteria were as follows: patients diagnosed with KOA; conservative treatment was ineffective and met the surgical indications of TKA (24); patients undergoing primary TKA; patients and their families were fully informed, and informed consent was obtained; and patients with clear consciousness who possessed the capacity to communicate.

The exclusion criteria were as follows: strong resistance to acupuncture therapy or a history of seasickness; accompanied by pain in other parts of the body; serious medical diseases such as severe cardiovascular and cerebrovascular diseases or liver and kidney dysfunction; and dependent on or allergic to narcotic drugs.

Interventions

The patients were anesthetized by spinal anesthesia during surgery and implanted with an epidural analgesia pump after surgery. The specific equation of the analgesia pump included sufentanil citrate injection (No. H20054171, Yichang Renfu Pharmaceutical Co., Ltd.), ketorolac tropanol injection (No. H20052634, Shandong New Times Pharmaceutical Co., Ltd.), and granisetron hydrochloride injection (No. H20093415, Hebei Yipin Pharmaceutical Co., Ltd.) in 96 mL of 0.9% sodium chloride solution (the specific content of the injections

was determined according to the patient's weight, age, sex, and other factors). The conventional drug administration rate was 2 mL/h, the patient-controlled dose was 0.5 mL/15 min, and the analgesia time after operation was 48 h. Celecoxib capsules (No. H20203297, Shiyao Group Ouyi Pharmaceutical Co., Ltd.) were taken orally for 7 days after surgery at a dosage of 200 mg/capsule twice a day, 1 capsule once after breakfast and dinner.

In the AA group, on the basis of the conventional treatments, the indwelling intradermal needles (type C, specification: 0.4 mm, 2.1 mm; Yushang Zhuzhun 20,202,200,203, Henan Kangjiulai Medical Technology Co., Ltd.; Figure 1) were inserted into five auricular acupoints, including those at the shenmen (TF_4), adrenal gland (TG_{2p}), knee (AH_4), subcortex (AT_4), and stomach (CO_4) (25) (Figure 2, this right ear in the figure was provided by the first author). The needles were used on the operated side 1 day before the operation and on the contralateral side 3 days after the operation, lasting for 5 days. The treatment was performed under strict aseptic conditions by the same acupuncturist who had obtained the doctor's certificate. After the needle was directly pricked into the selected auricular acupoints, a disposable opaque round Band-Aid was applied to cover the site. In the SAA group, a disposable opaque circular Band-Aid was applied to patch these acupoints (26, 27).

Outcome measures

Primary outcome

The primary outcome was the VAS (28, 29) of resting and movement states at 6 h, 12 h, and 1, 2, 3, 5, and 7 days after surgery. The evaluation was conducted face to face by the evaluator and the patient using a VAS of 0–10 points. At the time of evaluation, the patient was shown a ruler with a scale of 10 cm, where 0 cm on one end indicated no pain, and 10 cm on the other end indicated the most pain. At each time point of the evaluation, the patient outlined the point that best represented the degree of pain, and this point was taken as the patient's score.

FIGURE 1
Indwelling intradermal needles.

Secondary outcomes

Additional analgesic injections

Parecoxib sodium for injection (No. H20193217, Hunan Cylon Pharmaceutical Co., Ltd., 40 mg/dose) was added when the pain score was greater than 6, and the total additional dose during the treatment period was recorded.

Hospital for special surgery knee score

The hospital for special surgery knee score (HSS) (30) was recorded when the patients were followed up by telephone or outpatient visits at 2 and 12 weeks postoperatively.

Serum examination

The CRP level, ESR, and WBC count in the two groups were detected at 1, 3, and 7 days after the operation. CRP was detected by immunoturbidimetry, ESR by Wei's method, and WBC by semiconductor laser flow cytometry.

Degree of postoperative nausea

The VAS was used to record nausea at 1, 2, and 3 days after surgery (31, 32) when the evaluator was face to face with the patient. The VAS scale ranged from 0 to 10 points. At each time point of the evaluation, the point that best represented the degree of nausea was outlined by the patient, and this point was recorded as the patient's score.

Safety assessments

The adverse reactions of the two groups during the treatment were observed and recorded; these included whether skin allergy, subcutaneous hematoma, local infection, and fainting occurred during acupuncture in the AA group and whether skin allergy occurred in the SAA group.

Sample size calculation

Sample size calculations were determined from known literature (33, 34). The ratio between the two groups was 1:1 according to the following equation:

$$n = \left[\left(Z_\alpha + Z_\beta \right)^2 \times \left(1 + 1/k \right) \times P\left(1 - P \right) \right] / \left(P_1 - P_2 \right)^2 \quad (1)$$

where n is the required number of cases in each group, P_1 and P_2 represent the estimated values of the AA group and SAA group, respectively (represented by decimal points), and P is the combined rate. If the number of the two groups is equal (i.e., $k = 1$), $P = (P_1 + P_2)/2$. Type I error probability was set to $\alpha = 0.05$, and type II error probability was set to $\beta = 0.10$; therefore, according to our clinical experience and the literature, $Z_\beta = 1.645$, $Z_\alpha = 1.282$, $P_1 = 95.18\%$, and $P_2 = 70.22\%$. $n \approx 40$ can be calculated using Equation 1. As the patient required two treatments

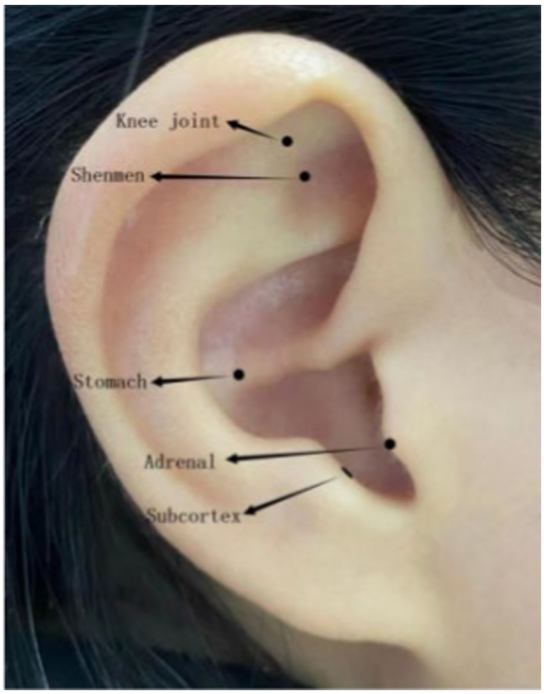

FIGURE 2
Selected auricular acupoints.

and a follow-up after discharge, we considered a dropout rate of 20%. A total of 96 patients were needed, 48 patients in each group.

Randomization, allocation concealment, and blinding

The enrolled patients were randomly assigned at a 1:1 ratio to the AA or SAA group using a random number table method generated by IBM SPSS 25.0 software, with treatments fixed in sequentially numbered opaque envelopes. When a patient was admitted for elective surgery, a physician who was not involved in the assessment opened the envelope to identify the patient group and informed the nurse to arrange the corresponding ward. The day before surgery, the patients were informed that they would receive auricular acupuncture at specific acupoints in addition to standard postoperative analgesia. After obtaining informed consent from the patient, the acupuncturist began the intervention. The acupuncturist had no further personal contact with the included patients at the end of each intervention. A professional orthopedics clinician, who had received training before the trial, was selected as the evaluator. The evaluators did not intervene and were unaware of the grouping of the patients. Similarly, the patients were also unaware of their grouping. Case collectors, acupuncturists, and data analysts were kept separate.

Statistical analysis

Data were analyzed using IBM SPSS 25.0 software analysis. Measurement data were first analyzed to determine whether they followed a normal distribution using a Shapiro–Wilk normality test. If the data had a normal distribution, they were expressed as the mean ± standard deviation ($\bar{x} \pm s$), and if they did not, then they were expressed as the median (upper quartile, lower quartile) [M (P25, P75)]. Comparisons between the two groups were performed using the Kruskal–Wallis test; intra-group comparisons were conducted using the Wilcoxon signed-rank test or Friedman test; and different time points were compared through repeated-measures analysis of variance between groups. Count data are described by the number of cases and percentage, and the chi-square test was used to compare the differences between the two groups. Two-sided p-values <0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 112 patients were recruited, and 16 were excluded due to meeting the exclusion criteria. The flow chart of the study is shown in Figure 3. Because the patients were hospitalized during the treatment period and the later follow-up was in the form of re-consultation, there were no cases of dropout. The two groups were comparable, with no significant differences at baseline. All baseline demographic characteristics are shown in Table 1.

Primary outcome

The VAS values of the resting and movement states were significantly different between the two groups at 6 h, 12 h, 2 days, 3 days, and 5 days after the operation. The VAS values of patients who received AA were lower than those of the SAA group ($p < 0.05$, Figure 4), but there was no significant difference between the two groups at 1 day and 7 days after the operation ($p > 0.05$, Table 2).

Secondary outcomes

The total dosage of analgesic requirement after the operation in the AA group was lower than that in the SAA group ($p < 0.05$), and the additional dosage at each time point in the AA group was also lower than that in the SAA group postoperative days 1 and 2 ($p < 0.05$) as shown in Table 3.

The level of CRP in the AA group was lower than that in the SAA group on the 1st day after the operation ($P < 0.05$), while there was no significant difference in CRP between the two groups on the 3rd and 7th days after the operation ($P > 0.05$). In addition, there was no significant difference in ESR and WBC between the two groups at 1, 3, and 7 days after the operation ($p > 0.05$, Table 4).

The degree of nausea in the AA group was lower than that in the SAA group on the 2nd day after the operation ($p < 0.05$), but there was no significant difference on the 1st and 3rd days after the operation ($p > 0.05$, Table 5).

The HSS was not significantly different between the two groups ($p > 0.05$, Table 6).

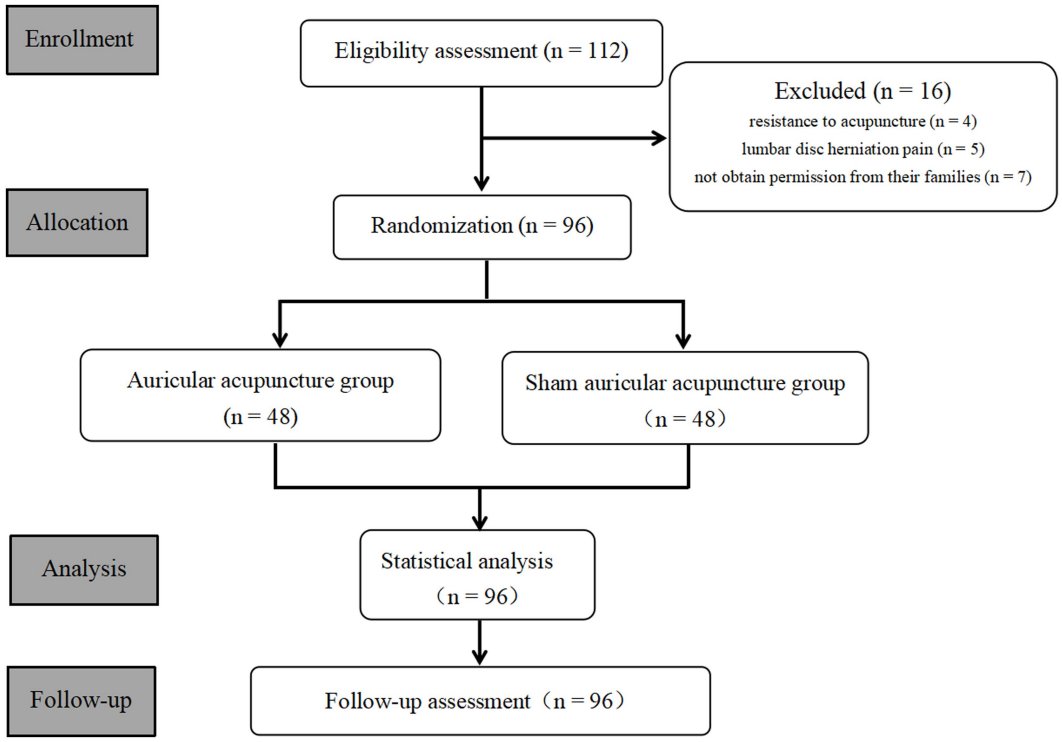

FIGURE 3
Flow chart of this trial.

Adverse events

During the treatment, none of the patients suffered any adverse events (e.g., infection). The safety was not significantly different between the two groups ($p > 0.05$).

Discussion

Approximately 10–34% of patients with TKA have poor acute pain control, leading to chronic pain (35), which seriously affects the postoperative rehabilitation and quality of life of the patients and increases their reliance on analgesics. However, the drug-related side effects of analgesics limit their application in daily clinical practice (36). Therefore, it is particularly important to explore an analgesic method with the characteristics of green therapy (37).

As a kind of green complementary and alternative therapy, auricular acupuncture therapy has a good analgesic effect during the perioperative period and has been widely used in gynecology, orthopedics, anorectal, and other fields (10). According to the theory of biohology, the close association between auricular acupoints and zangfu-meridians is the basis for the clinical treatment of pain (11).

The pain mechanism of TKA can be attributed to peripheral sensitization and central sensitization (38). Peripheral sensitization is caused by injury to the body, resulting in inflammation and local organ pain. On the other hand, central sensitization occurs due to pain stimulation, leading to increased neuronal excitability in the dorsal horn of the spinal cord and resulting in pain. Research has demonstrated that the application of auricular acupuncture can activate the descending pain inhibition pathway along the dorsal side of the spinal cord, specifically where the dorsal horn cells are located. This activation plays an analgesic role and effectively relieves pain after TKA (39). In addition, the analgesic effect of auricular acupuncture also works by

TABLE 1 Baseline characteristics of the population.

Characteristics	Auricular acupuncture group (n = 48)	Sham auricular acupuncture group (n=48)
Age, year	67.9 ± 6.6	66.5 ± 7.5
Sex (male/female)	20/28	9/39
Weight, kg	71.69 ± 12.02	71.89 ± 12.12
Height, cm	163.02 ± 7.24	160.13 ± 5.54
Course of disease, year	10.5 (6.58, 15)	10.75 (7.25, 16)
Hypertension	19 (19.8%)	14 (14.6%)
Type 2 diabetes	4 (4%)	3 (3%)
Hypertension and type 2 diabetes	3 (3%)	2 (2%)
None	21 (21.9%)	29 (30.2%)
Initial pain, visual analog scale score	6.36 ± 1.77	6.50 ± 1.60
Left	29 (30%)	25 (26%)
Right	19 (20%)	23 (24%)
C-reactive protein, mg/L	1.82 (0.98, 2.66)	2.14 (0.88, 4.23)
Erythrocyte sedimentation rate, mm/h	17 (10, 26.75)	16.5 (11, 34.5)
White blood cell count, cell/μL	5.70 ± 1.65	5.95 ± 1.72

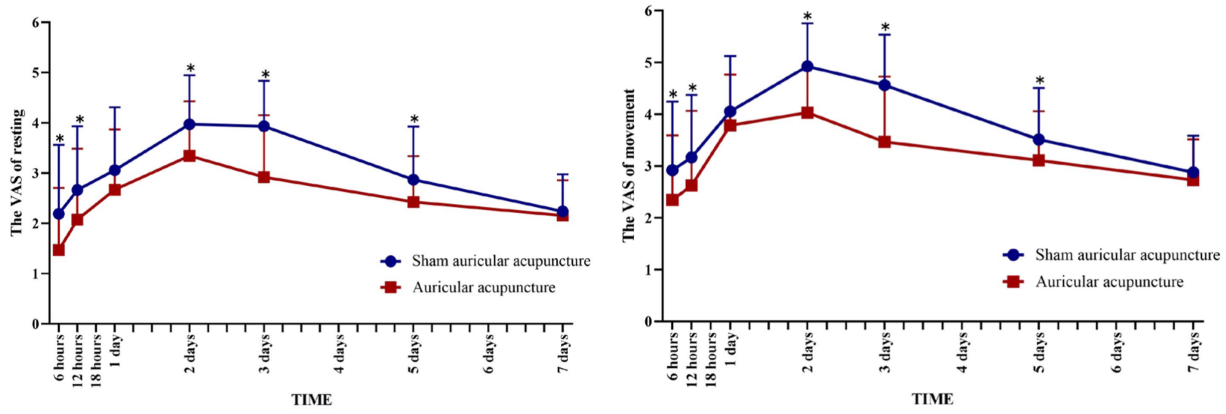

FIGURE 4
Visual analog scale scores over time in the AA and SAA groups. *Compared with sham auricular acupuncture, *$P < 0.05$.

TABLE 2 Comparison of the postoperative VAS values during resting and movement states at each time point between the two groups.

	Auricular acupuncture group ($n = 48$)	Sham auricular acupuncture group ($n = 48$)	*p-value*
Post-operative VAS value at resting state, score			
6 h	1.47 ± 1.24	2.19 ± 1.37	0.008
12 h	2.08 ± 1.41	2.67 ± 1.27	0.034
1 day	2.68 ± 1.20	3.06 ± 1.26	0.125
2 days	3.34 ± 1.09	3.98 ± 0.98	0.004
3 days	2.92 ± 1.23	3.94 ± 0.90	0.000
5 days	2.43 ± 0.91	2.87 ± 1.06	0.030
7 days	2.16 ± 0.70	2.24 ± 0.74	0.581
Post-operative VAS value at movement state, score			
6 h	2.35 ± 1.24	2.92 ± 1.32	0.031
12 h	2.63 ± 1.44	3.17 ± 1.20	0.048
1 day	3.79 ± 0.98	4.05 ± 1.07	0.203
2 days	4.03 ± 0.90	4.93 ± 0.83	0.000
3 days	3.47 ± 1.26	4.56 ± 0.98	0.000
5 days	3.11 ± 0.95	3.51 ± 0.99	0.045
7 days	2.73 ± 0.78	2.89 ± 0.70	0.326

TABLE 3 Comparison of the postoperative dose of additional analgesic injections between the two groups.

Additional dosage at each time point	Auricular acupuncture group ($n = 48$)	Sham auricular acupuncture group ($n = 48$)	*P-value*
6 h	1 (0, 1)	1 (1, 1)	0.348
12 h	0 (0, 1)	0 (0, 1)	0.943
1 day	0 (0, 1)	0 (0, 1)	0.044
2 days	0 (0, 0)	0 (0, 1)	0.019
3 days	0 (0, 0)	0 (0, 0)	0.103
5 days	0 (0, 0)	0 (0, 0)	0.313
7 days	0 (0, 0)	0 (0, 0)	0.058
Total additional injections	3 (1, 4)	1 (1, 2.5)	0.004

stimulating specific acupoints on the ear to activate the nociceptin receptors, which release endogenous morphine-like substances such as endorphins and enkephalins, thereby enhancing the pain threshold and reducing the degree of pain (40). Our results demonstrated that an indwelling intradermal needle, as an auricular acupuncture device, could provide effective postoperative analgesia after TKA. The best analgesic effect was achieved 2 days after the operation, which reduced moderate pain (VAS score 4–6 points) to mild pain (VAS score 0–3 points), as well as the dose of analgesic needling.

Based on previous literature, textbooks, and clinical practice experience of acupuncture, the auricular acupoints stimulated in this study included the TF_4, TG_{2p}, AH_4, AT_4, and CO_4. First, according to the results of literature data mining (41, 42), TF_4 and AT_4 were the two most commonly used in perioperative analgesia. The TG_{2p} can effectively regulate the patient's autonomic nerve with sedative and analgesic effects (43). Second, after the operation, the vital qi of the body is consumed and the qi of the spleen and stomach is gradually weakened, causing the stomach qi to be out of balance. At the same time, the usage of analgesics stimulates the stomach organ, which leads to nausea and vomiting. The CO_4 was selected to control nausea and vomiting based on clinical experience. Third, according to the location of the lesion, the AH_4 was directly stimulated to relieve the pain, which is a type of acupoint selection method based on traditional Chinese medicine. All in all, the combination of five acupoints can regulate the meridians and collateralis to reduce pain.

It is found that CRP, ESR, and WBC are the primary inflammatory and anti-inflammatory factors in the serum of patients who have suffered postoperative trauma. Those blood indicators may be an objective index for the evaluation of postoperative analgesia after TKA. Our results showed that AA could reduce the CRP level over a certain period of time, which showed that the analgesic effect of intradermal needling may be the result of an anti-inflammation effect; however, ESR and WBC did not decrease significantly. The reason for this could be that the diagnostic advantage of CRP is significantly higher than that of the ESR and WBC count (44). The ESR and WBC are often used as monitoring indices to evaluate postoperative infection; however, as the specificity of these indices is relatively low and easily affected by many factors (45), this result still needs to be verified by a larger sample size.

TABLE 4 Comparison of the postoperative serum CRP, ESR, and WBC between the two groups.

C-reactive protein	Auricular acupuncture group ($n = 48$)	Sham auricular acupuncture group ($n = 48$)	*P-value*
1 day	67.25 ± 32.20	80.79 ± 34.43	0.049
3 days	147.53 ± 52.95	155.36 ± 52.95	0.446
7 days	64.39 ± 33.18	62.08 ± 28.38	0.715
Erythrocyte sedimentation rate			
1 day	25 (15, 35.75)	20 (15.25, 30)	0.359
3 days	93.50 ± 29.28	92.56 ± 24.07	0.864
7 days	93.38 ± 26.53	99.29 ± 30.60	0.314
White blood cell count			
1 day	11.47 ± 3.33	11.98 ± 3.38	0.459
3 days	9.30 ± 2.73	9.34 ± 2.30	0.955
7 days	7.38 ± 1.87	7.74 ± 2.17	0.381

TABLE 5 Comparison of postoperative nausea between the two groups.

Degree of postoperative nausea	Auricular acupuncture group ($n = 48$)	Sham auricular acupuncture group ($n = 48$)	*P-value*
1 day	1 (0, 2.5)	2.3 (0, 4.08)	0.062
2 days	1.25 (0, 2.3)	1.7 (0.08, 3.38)	0.046
3 days	0 (0, 1)	1 (0, 1.73)	0.081

TABLE 6 Follow-up results of HSS scores in the two groups.

Postoperative HSS score	Auricular acupuncture group ($n = 48$)	Sham auricular acupuncture group ($n = 48$)	*P-value*
2 weeks	95.5 (88, 100)	98 (90, 100)	0.348
12 weeks	100 (100, 100)	100 (100, 100)	0.095

The degree of postoperative nausea in the AA group was lower than that in the SAA group at 2 days after the operation, partly because fewer analgesic needles were added in the AA group, especially at 2 days after the operation. According to the perspective of Chinese medicine, the pathogenesis of vomiting is a "stomach disorder causing qi inverse to the upper." Patients with TKA have a deficiency of both qi and blood of the body, which impairs the function of the spleen and stomach qi and the occurrence and aggravation of nausea induced by qi inverse (46). In addition, the risk of nausea is increased due to the aggravation of postoperative pain in patients. Simultaneously, the use of analgesics stimulates the vomiting center of the brain, which will also induce the generation and aggravation of nausea (47). Modern research has proved that auricular acupoint therapy can effectively alleviate the degree of postoperative nausea (47). Moreover, it has been verified that CO_4, one of the five acupoints selected in this study, can reduce regurgitation and stop vomiting.

Limitations

First, the population of this trial was taken from a single center, which may cause population bias. In future, our research team will conduct a multicenter RCT with a large sample size. Second, this pilot study only examined the visual analog score as the primary outcome measure of postoperative pain but did not consider the possible influencing factors such as perioperative patients' emotional state and cognitive function on pain assessment. The effect of these factors on the results is unknown. Third, this study was invasive and may not have been double-blind. Despite the implementation of the principle of three separations, the effect of blind implementation was not assessed, which is an important point for future consideration of sham control settings. Fourth, the study should be conducted in experienced institutions to obtain more rigorous data. Fifth, the research team will consider how to assess the analgesia-related effects of indwelling intradermal needles independently of the use of analgesics. In parallel, we will seek to provide more reliable and effective clinical methods for postoperative analgesia in TKA based on this study in the future.

Conclusion

Auricular acupuncture is effective for adjuvant analgesia after TKA and functions by reducing CRP on the first day after the operation, the use of analgesic needles, and the occurrence of postoperative nausea.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Shijiazhuang West Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XZ: Writing – original draft. HC: Writing – original draft. JQL: Data curation, Visualization, Writing – review & editing. XL: Funding acquisition, Resources, Writing – review & editing. PX: Conceptualization, Methodology, Writing – review & editing. ML: Formal analysis, Writing – review & editing. JDL: Funding acquisition, Resources, Supervision, Writing – review & editing. YS: Conceptualization, Funding acquisition, Methodology, Resources, Visualization, Writing – review & editing. XW: Methodology, Software.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1275192/full#supplementary-material

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Combining various acupuncture therapies with multimodal analgesia to enhance postoperative pain management following total knee arthroplasty: a network meta-analysis of randomized controlled trials

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Objective: This study aims to evaluate the efficacy and safety of various acupuncture treatments in conjunction with multimodal analgesia (MA) for managing postoperative pain and improving knee function in patients undergoing total knee arthroplasty (TKA), based on the findings from clinical research indicating the potential benefits of acupuncture-related therapies in this context.

Methods: We searched Web of Science, PubMed, SCI-hub, Embase, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese Scientific Journal Database (VIP) to collect randomized controlled trials of acupuncture-related therapies for post-TKA pain. After independent screening and data extraction, the quality of the included literature was evaluated. The potential for bias in the studies incorporated in the analysis was assessed according to the guidelines outlined in the Cochrane Handbook 5.1. Network meta-analysis (NMA) was conducted using RevMan 5.4 and Stata 16.0 software, with primary outcome measures including visual analog scale (VAS), pain pressure threshold (PPT), hospital for special surgery knee score (HSS), and knee joint range of motion (ROM). Furthermore, the interventions were ranked based on the SUCRA value.

Results: We conducted an analysis of 41 qualifying studies encompassing 3,003 patients, examining the efficacy of four acupuncture therapies (acupuncture ACU, electroacupuncture EA, transcutaneous electrical acupoint stimulation TEAS, and auricular acupoint therapy AAT) in conjunction with multimodal analgesia (MA) and MA alone. The VAS results showed no significant difference in efficacy among the five interventions for VAS-3 score. However, TEAS+MA (SMD: 0.67; 95%CI: 0.01, 1.32) was more effective than MA alone for VAS-7 score. There was no significant difference in PPT score among the three interventions. ACU + MA (SMD: 6.45; 95%CI: 3.30, 9.60), EA + MA (SMD: 4.89; 95%CI: 1.46, 8.32), and TEAS+MA (SMD: 5.31; 95%CI: 0.85, 9.78) were found to be more effective than MA alone for HSS score. For ROM score, ACU + MA was more efficacious than EA + MA, TEAS+MA, and AAT + MA, MA. Regarding the incidence

of postoperative adverse reactions, nausea and vomiting were more prevalent after using only MA. Additionally, the incidence of postoperative dizziness and drowsiness following ACU + MA (OR = 4.98; 95%CI: 1.01, 24.42) was observed to be higher compared to that after AAT + MA intervention. Similarly, the occurrence of dizziness and drowsiness after MA was found to be significantly higher compared to the following interventions: TEAS+MA (OR = 0.36; 95%CI: 0.18, 0.70) and AAT + MA (OR = 0.20; 95%CI: 0.08, 0.50). The SUCRA ranking indicated that ACU + MA, EA + MA, TEAS+MA, and AAT + MA displayed superior SUCRA scores for each outcome index, respectively.

Conclusion: For the clinical treatment of post-TKA pain, acupuncture-related therapies can be selected as a complementary and alternative therapy. EA + MA and TEAS+MA demonstrate superior efficacy in alleviating postoperative pain among TKA patients. ACU + MA is the optimal choice for promoting postoperative knee joint function recovery in TKA patients. AAT + MA is recommended for preventing postoperative adverse reactions.

Systematic review registration: https://www.crd.york.ac.uk/, identifier (CRD42023492859).

KEYWORDS

acupuncture therapy, total knee arthroplasty (TKA), pain management, alternative therapies, network meta-analysis (NMA), randomized controlled trials

1 Background

The incidence of knee osteoarthritis (KOA) has significantly risen due to the acceleration of population aging and the increasing prevalence of obesity and overweight individuals. Data from the China Health and Retirement Longitudinal Study (CHARLS) database indicate that symptomatic knee osteoarthritis now affects 13.7 and 10.8% of individuals in southwest and northwest China, respectively (1). TKA, a well-established and effective reconstructive treatment, has demonstrated long-term efficacy in managing severe multi-compartmental knee osteoarthritis with deformity. When compared to basic treatment, pharmacological intervention, and reparative approaches for KOA, TKA demonstrates significant improvements in pain relief and joint function (2), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, hospital for special surgery knee score (HSS), and overall quality of life during long-term follow-up.

The presence of pain after TKA is a significant factor that affects the outcomes of patient rehabilitation. According to the International Association for the Study of Pain (IASP) (3), pain is defined as an unpleasant sensory and emotional experience that is linked to actual or potential tissue damage and is influenced by biological, psychological, and social factors to varying extents. Pain can easily result in the development of depression, anger, and anxiety, which is why it is considered as the fifth vital sign (4). In contrast to total hip arthroplasty, it is imperative to incorporate high-intensity knee flexion and extension training after TKA to enhance functional activity and prevent complications such as postoperative knee stiffness. However, it is important to note that early functional exercise may potentially worsen postoperative pain. The relationship between postoperative pain and knee joint rehabilitation is reciprocal (5). The implementation of enhanced recovery after surgery (ERAS) in perioperative management has made it essential to effectively manage postoperative pain and knee swelling as an integral aspect of early rehabilitation (6).

Previous research has established that high levels of sedentary behavior put people with musculoskeletal conditions (such as osteoarthritis) at elevated risk for reduced physical function, increased physical frailty and blood pressure, and may increase mortality (7). However, physical activity provides a multitude of health advantages, encompassing the prevention and management of various ailments, such as hypertension, stroke, obesity, diabetes, and mental health disorders, such as anxiety and depression (8). Consequently, the World Health Organization has initiated the Global Action Plan on Physical Activity 2018–2030, with the objective of augmenting physical activity levels by 15% before 2030 (9). Regrettably, a concerning observation is that individuals undergoing total knee arthroplasty (TKA) often exhibit limited engagement in physical activity post-surgery (10), primarily due to their obesity that was present preoperatively. Merely, 5% of TKA patients adhere to national physical activity guidelines (11), which put them at increased risk of cardiovascular disease and cancer (12). The studies (13) have demonstrated that augmenting physical activity can effectively enhance gait function following TKA, with a realistic and appropriate target of approximately 3,000 steps per day for postoperative TKA patients. This suggests the attainability of heightened postoperative gait function. Additionally, another study (14) has revealed that initiating ambulation and engaging in 15–30 min of walking twice daily, commencing on the initial day after surgery, can significantly diminish the occurrence of thromboembolic complications subsequent to TKA. Consequently, it is imperative to augment physical activity following TKA.

The implementation of multimodal analgesia in the perioperative pain management of TKA has gradually gained traction (15). Within the ERAS framework, multimodal analgesia not only plays a central role but also demonstrates a strong interconnection with other rehabilitation measures. The primary goal of perioperative pain management has evolved beyond solely providing pain relief to encompass facilitating the prompt recovery of patients as a whole (16). Moreover, when incorporating multimodal analgesia, careful attention must be paid to its effects on the entire ERAS system (17). Multimodal analgesia encompasses a range of interventions, both non-pharmacological and pharmacological, that aim to manage pain. Non-pharmacological interventions include acupuncture, moxibustion, massage, and psychological guidance. Pharmacological interventions involve the use of various drugs and delivery routes, such as traditional Chinese medicine, patient-controlled analgesia (PCA), regional nerve block, intravenous/oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, as well as periarticular multimodal drug injection (PMI) (18).

The administration of femoral nerve block, iliac fascia nerve block, adductor canal block, and sciatic nerve block to alleviate postoperative pain in TKA patients may lead to varying degrees of muscle strength decline in the quadriceps femoris, biceps femoris, gastrocnemius (19), and other related muscles. This decline in muscle strength is not beneficial for the isometric contraction rehabilitation exercise of these muscles following TKA. In multimodal analgesia, analgesics are commonly administered in a stepwise manner. For the management of mild pain, oral non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids, such as celecoxib, flurbiprofen axetil, and nalbuphine (20), are commonly prescribed. On the other hand, for moderate-to-severe pain, strong opioids or narcotic analgesics, such as morphine, butorphanol, and fentanyl (21), are typically utilized. It is important to note that traditional NSAIDs function as non-selective inhibitors of both COX−1 and COX-2 enzymes. However, the presence of COX−1 in the stomach, kidney, and platelets can result in an increased risk of adverse reactions, including gastrointestinal damage and bleeding (22). Selective COX-2 inhibitors, in contrast, specifically target COX-2 activity while exerting minimal influence on COX−1; however, apprehensions have arisen regarding their cardiovascular safety profile and nephrotoxicity. Similarly, opioids employed for the management of moderate-to-severe pain are accompanied by notable adverse effects such as nausea, vomiting, constipation, respiratory depression, and cognitive impairment (23). These untoward effects have the potential to protract hospitalization duration, escalate hospitalization expenses, and induce anxiety among patients.

In the context of TKA surgery, there exist two primary categories: those in which the posterior cruciate ligament (PCL) is preserved and those in which it is not. A randomized controlled study (24) was conducted to investigate the effects of PCL preservation on patients who received a prosthesis. The hypothesis was that by maintaining the PCL, mechanical stress would stimulate PCL proprioceptors, leading to the activation of nerve reflexes and subsequent tightening of relevant muscles and ligaments. However, due to the loss of normal function in most patients, the formation of nerve reflexes proved challenging. Conversely, the prosthesis that replaces the posterior cruciate ligament does not maintain the integrity of the ligament itself. Instead, it utilizes a post and cassette structure to facilitate the rolling back mechanism and enhance knee joint flexion. Comparisons between TKA procedures with and without preservation of the PCL revealed no significant differences in VAS pain scores and HSS scores. The potential retention of proprioceptive sensation during knee flexion in patients with preserved PCL prostheses warrants further investigation to determine its potential benefits for subsequent knee rehabilitation (25). Danilo De Oliveira Silva's findings (26) indicate that most of the patients (85%) who had undergone TKA using a posterior-stabilized (PS) prosthesis with routine patellar resurfacing reported absence of anterior knee pain at 12 months following surgery. The study conducted by White et al. (27) revealed that undergoing TKA, the Attune PS prosthesis exhibited a significantly lower overall occurrence of anterior knee pain (AKP) and knee crepitation in comparison with the PFC Sigma prosthesis (12.5% vs. 25.8%, $p < 0.05$). The occurrence of painful tremor was lower in both groups (1.0% vs. 4.1%), with no statistically significant difference, and there were no significant disparities observed in the four postoperative indices, namely, the HSS score, WOMAC score, ROM, and patient satisfaction. Both prostheses are extensively utilized in clinical practice, and the prevalence of residual knee pain was minimal after a 2-year follow-up period. A group of 47 TKA prostheses applied to 39 patients (32 women) were analyzed retrospectively. All the prostheses had been implanted by the same team of orthopedic surgeons using the same surgical method (cemented, with patella prosthesis and posterior stabilization with the sacrifice of the posterior cruciate ligament). It was found that male sex were considered good outcome predictors, underlying the importance of considering sex in understanding postoperative pain course; meanwhile, old preoperative age was considered as unfavorable underlying (28).

Due to the limitations of pharmacological therapy, a number of patients have turned to acupuncture as a supplementary and alternative treatment. Traditional Chinese Medicine (TCM) analgesia holds a crucial position in clinical practice for managing perioperative pain and should not be disregarded. Extensive research has consistently focused on acupuncture analgesia, with multiple clinical studies documenting its effectiveness in alleviating postoperative pain following TKA (29). Clinical reports on the utilization of acupuncture anesthesia in thyroid surgery and thoracic surgery have been documented as early as the 1980s. By integrating traditional Chinese medicine's meridian and acupoint theory with nerve electrical stimulation technology, electroacupuncture and transcutaneous electrical acupoint stimulation present notable alternative therapeutic options (30). These methods not only exhibit clinical effectiveness but also mitigate labor costs and technical challenges associated with acupuncture treatment, while concurrently minimizing adverse reactions such as needle bending, bleeding, and infection. Research studies have demonstrated that the integration of transcutaneous electrical acupoint stimulation and electroacupuncture in the perioperative management of patients undergoing total knee arthroplasty (TKA) effectively mitigates pain, diminishes limb edema, expedites recovery (31), and aligns with the principles of ERAS. This incorporation of acupuncture techniques broadens the scope of clinical applications and garners acceptance from a growing cohort of surgeons. The ear is intricately linked to the body's meridians, and auricular therapy represents a unique modality within the realm of acupuncture and moxibustion. This therapy involves the stimulation of specific areas on the auricle, known as auricular points, through the application of acupuncture or other methods, with the aim of diagnosing and treating various

diseases (32). Numerous clinical studies have demonstrated the effectiveness of auricular point therapy in alleviating conditions such as traumatic pain (33), headache (34), postoperative wound pain, and neuropathic pain (35).

The study of the analgesic properties of acupuncture serves as a connection between traditional Chinese medicine and modern Western medicine. Through fundamental research, new insights have been gained regarding the mechanisms underlying acupuncture-induced pain relief, including the involvement of peripheral purine signaling (36) and TRPV channels (37), which expand upon the established central opioid peptide analgesia paradigm (38). Simultaneously, acupuncture therapies have been shown to modulate pain sensation, emotion, and memory (39), thereby enhancing the understanding of its analgesic mechanisms. The field of acupuncture research has long grappled with the challenge of bridging the gap between basic research and clinical practice, but there is growing anticipation that the analgesic mechanisms of acupuncture therapy will be increasingly validated through clinical trials. The four commonly utilized acupuncture-related therapies in clinical practice are traditional acupuncture, electroacupuncture, transcutaneous electrical acupoint stimulation, and auricular point therapy. Previous studies on postoperative pain following total knee arthroplasty have primarily compared various acupuncture-related therapies collectively against other interventions, emphasizing pairwise comparisons. Despite the widespread utilization of acupuncture, the existing evidence on its efficacy appears to be inconclusive. Various studies have yielded divergent findings. One systematic review demonstrated that acupuncture may improve postoperative pain management after total knee arthroplasty (TKA) (40), while a clinical trial suggested that acupuncture was not superior to pharmacological treatments (41). This study employed a network meta-analysis (NMA) approach to evaluate and rank four distinct types of acupuncture-related interventions in conjunction with multimodal analgesia for post-TKA pain relief. This study seeks to utilize the benefits of combining traditional Chinese and Western medicine to offer evidence-based recommendations for selecting the most optimal treatment approach in clinical settings.

2 Materials and methods

Our study was conducted based on the checklist of the preferred reporting items for systematic reviews and meta-analyses for network meta-analysis (PRISMA-NMA) guidelines (42) (Supplementary Appendix 1) and reporting items of systematic reviews and meta-analyses involving acupuncture (43). The PRISMA-NMA and PRISMA for acupuncture checklists are both updates to PRISMA. Based on the 27 items from the PRISMA checklist, the PRISMA-NMA checklist revised 11 items related to NMA and added 5 new items to guide and improve the writing and reporting for NMA, while PRISMA for acupuncture checklist revised 6 items related to acupuncture operations and added 5 new items to be better used for the systematic review about acupuncture therapies. The research has been registered in PROSPERO, with the registration website https://crd.york.ac.uk/PROSPERO/#recordDetails and registration number CRD42023492859.

2.1 Literature retrieval strategy

A computer search was conducted in five English databases (Web of Science, PubMed, SCI-hub, Embase, and Cochrane Library) and four Chinese databases [China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese Scientific Journal Database (VIP)] to collect all randomized controlled trials (RCTs) on acupuncture therapy for pain after TKA from the establishment of the database until November 1, 2023 (Supplementary Appendix 2). The retrieval strategy employed a combination of subject headings and free words which were adjusted based on different retrieval systems. Retrieval terms included acupuncture, electroacupuncture, auricular acupuncture, transcutaneous electrical acupoint stimulation, total knee arthroplasty, multimodal analgesia, and pain (Figure 1).

2.2 The literature inclusion criteria

(1) The literature utilized in this study was a prospective randomized controlled trial (RCT). The inclusion criteria for the cases involved a diagnosis of knee osteoarthritis (44) based on the established diagnostic criteria for knee osteoarthritis (refer to Table 1). The cases were required to meet the first criterion and any two of the second, third, fourth, and fifth criteria. Additionally, the severity of knee osteoarthritis was assessed through the grading of knee X-ray films using the Kellgren-Lawrence method (45) (refer to Table 2). Subjects with Kellgren-Lawrence grades III and IV, necessitating TKA surgical intervention (46), will be encompassed. No limitations will be imposed on the patients' age, gender, or race.

(2) The treatment group was administered various interventions, including acupuncture, transcutaneous electrical acupoint stimulation, electroacupuncture, and auricular acupuncture, in conjunction with multimodal analgesia (including one or more of analgesics, nervous block, and patient-controlled analgesia pump), while the control group solely received multimodal analgesia.

(3) The literature should contain original data pertaining to postoperative VAS score, preoperative and postoperative HSS score, preoperative and postoperative ROM measurements, preoperative and postoperative PPT score, and postoperative adverse events.

(4) The language of the literature could be either Chinese or English.

2.3 Exclusion criteria for literature

(1) The subjects in this study were diagnosed with knee arthritis, as indicated in Table 1. However, their Kellgren-Lawrence classification ranged from 0 to II, as shown in Table 2. Consequently, non-surgical therapy was chosen over TKA. The objective of this research was to conduct a randomized controlled trial to evaluate the efficacy of various acupuncture therapies in alleviating pain associated with knee arthritis.

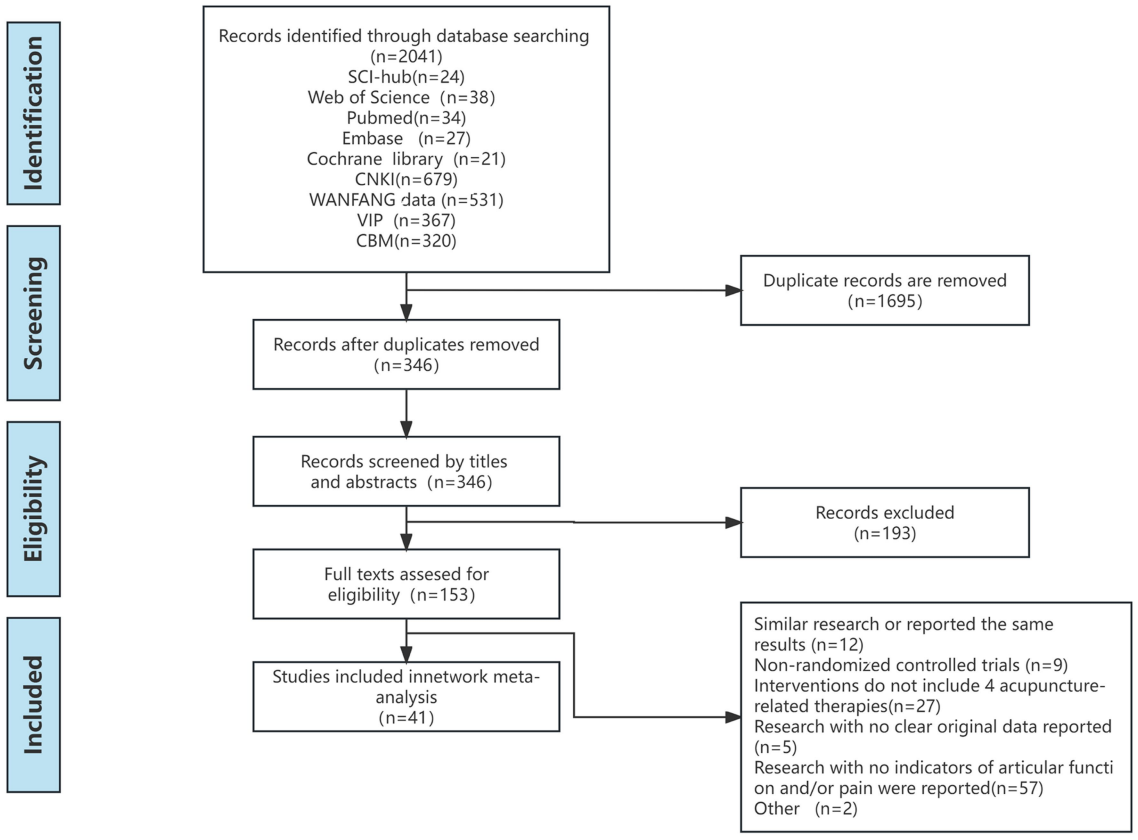

FIGURE 1
Study flow diagram.

TABLE 1 Diagnostic criteria utilized for identifying osteoarthritis of the knee.

Serial number	Symptoms or signs
1	Recurrent knee pain in the past month
2	The X-ray film, taken in a standing or weight-bearing position, revealed the presence of joint space narrowing, subchondral sclerosis and/or cystic degeneration, as well as osteophytes at the articular edge
3	Individuals aged over 50 years
4	Morning stiffness duration of less than 30 min
5	Audible bone friction sound (or sensation) experienced during physical activity

(2) Non-randomized studies (NRSs) include non-randomized controlled clinical trials, self-control studies, historical control studies, cohort studies, case–control studies, and cross-sectional survey studies.
(3) Other non-penetrating stimuli (such as point ion penetration, laser irradiation, and magnetic therapy), other penetrating stimuli (such as head acupuncture, point injection, and point embedding), and special acupuncture methods (such as triangle needle, fire needle, and acupotomy).
(4) The control group received additional interventions, including psychological counseling and massage therapy.
(5) There was no original data in the literature, and the author could not be contacted.
(6) The authors of the literature were the same or showed the similar data results.

2.4 Primary and secondary outcomes

2.4.1 Primary outcome indicators

The primary outcome measures encompass two dimensions: first, the pain intensity experienced by the participants following TKA; second, the functional status of the knee joint in the participants prior to and post-TKA.

(1) Visual analog scale (VAS) score (47): A 10 cm long straight line is drawn on a blank sheet of paper, with "no pain" and "most severe pain" labeled at each end. The patient is instructed to indicate their pain level and psychological perception by marking a point on the line. The distance from the starting point to the marked point represents the intensity of pain. The study aims to assess the disparities in the VAS score between the third and seventh day after surgery, as well as the baseline value.
(2) The pain pressure threshold (PPT) (48) will be measured by applying pressure to the medial side of the knee joint, within a

TABLE 2 Kellgren-Lawrence grading system for osteoarthritis.

Grade	Radiologic findings of knee osteoarthritis
0	No radiological findings of knee osteoarthritis
I	Doubtful narrowing of joint space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of joint space
III	Moderate multiple osteophytes, definite narrowing of joint space, small pseudocystic areas with sclerotic walls and possible deformity of bone contour
IV	Large osteophytes, marked narrowing of joint space, severe IV sclerosis, and definite deformity of bone contour

3 cm range from the midpoint of the medial edge of the patella, using a digital pressure tester. The pressure will be gradually increased until the patient experiences pain, at which point it will be immediately ceased and the corresponding value recorded. The discrepancy between the PPT and the baseline value will then be calculated.

(3) The evaluation of the knee joint's performance at hospital for special surgery (HSS) (49) encompasses various aspects, including pain, function, activity, muscle strength, flexion deformity, stability, and other relevant factors. A higher score on the HSS scale indicates better knee function. Additionally, the disparity between the HSS score and the initial value is computed to determine the improvement.

(4) The range of motion (ROM) (49) of the knee joint is assessed by measuring the extent of movement before and after TKA using a joint ruler. The discrepancy between ROM and the baseline value is then calculated.

2.4.2 Secondary outcome indicators

To further assess the effectiveness and safety of various acupuncture therapies, secondary outcome measures including the occurrence of postoperative nausea and vomiting, dizziness, and drowsiness were employed.

2.5 Literature screening and data extraction

Two researchers (YH and YX) independently conducted a comprehensive literature review and meticulously extracted relevant data. In concrete terms, the title and abstract were read and checked to exclude literature that did not meet the inclusion criteria. Then, the full texts of the potentially eligible studies were read to identify studies that could be included in this quantitative analysis. The results were cross-checked for accuracy, and in the event of any disagreement, a third researcher was consulted to reach a consensus.

Regarding data extraction, Excel 2016 was utilized to construct a systematic table encompassing pertinent information from eligible studies. This included: (1) general information: first author's name, journal title, publication date, grouping details, and sample sizes in each group; (2) baseline characteristics: age distribution, disease duration, and pre-treatment measurements for each outcome indicator within every group; (3) intervention measures: type of acupuncture therapy administered, treatment frequency, and duration of treatment cycles; and (4) outcome indicators' data along with post-treatment adverse reactions.

2.6 Assessment of risk bias in included studies

The Cochrane Handbook 5.1 was utilized for the assessment of risk bias in the included studies, encompassing randomization, assignment concealment, blinding of patients and staff, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias (50, 51). In RevMan 5.4 software, we categorized the levels of risk as "high," "low," or "unclear," respectively.

2.7 Statistical analysis

Software programs RevMan (Version 5.4) and Stata (Version16.0) were used to do statistical analysis. The study utilized odds ratios (ORs) and 95% confidence intervals (95% CIs) for dichotomous variables and mean differences ± standardized mean differences (SMD) and 95% CI for continuous variables.

Bias risk assessment was conducted using RevMan 5.4 software, and frequency science network meta-analysis was performed using Stata16.0. Data processing, network evidence graph drawing, network league table creation, and calculation of the surface under the cumulative ranking curve (SUCRA) were performed using the network and mvmeta package commands. The study was divided and restructured into all-paired two-arm trials if it had been a three-arm trial (52). In instances where closed loops were observed in the network evidence graph, indicating discrepancies among research findings, the ifplot command was employed to identify inconsistencies. The inconsistency factor (IF) value and its corresponding 95% confidence interval were computed for each closed loop to evaluate the consistency of direct and indirect comparison results. The fitting inconsistency test was performed on the closed loops formed in the network meta-analysis. If $p > 0.05$, the inconsistencies in direct and indirect comparisons were not statistically significant, and a consistency model could be used for meta-analysis. If there was no closed loop, the consistency model could be used directly. The SUCRA was generated with Stata16.0, which shows the SUCRA scores for all interventions, with higher SUCRA values denoting a higher treatment class. The closer the value was to 100%, the better the efficacy of the intervention (53). A funnel plot was constructed using Stata16.0 to examine potential publication bias within the included studies (54).

3 Results

3.1 Literature retrieval

After primary retrieval, a total of 2041 relevant literature were identified, comprising 1897 Chinese and 144 English publications. Following the removal of 1,695 duplicate articles, the remaining literature underwent screening based on titles and abstracts, resulting in the exclusion of 193 studies. Subsequently, after full-text evaluation, an additional 112 literature were excluded. Finally, a total of 41

literature (55–94) were included in this review (Figure 1 illustrates the specific inclusion process).

3.2 Basic characteristics of the included studies

In these selected studies (n = 41), four types of acupuncture therapy interventions were investigated: acupuncture alone, electroacupuncture, transcutaneous electrical acupoint stimulation (TEAS), and auricular therapy. These interventions were combined with perioperative multimodal analgesia. Among them, one study employed a three-arm trial design (57), while the rest utilized two-arm trials. Tables 3, 4 present detailed information regarding baseline characteristics and acupuncture methods used in the included studies.

3.3 Quality evaluation of the included literature

The risk bias assessment was independently conducted by two researchers (DZ and LW). The evaluation criteria consisted of seven items including randomization method, allocation concealment method, and blinding procedures for participants or outcome assessment. Of all the trials reviewed (n = 41), 41 (100%) described their random sequence generation process, while only 17 (42%) reported their allocation concealment method. None of the studies implemented blinding techniques for participants or outcome evaluation. Twenty-seven trials (65%) provided complete outcome data. It should be noted that due to the nature of acupuncture treatment involving active participation from both practitioners and patients during administration, implementing blind methods is challenging. The results of risk assessment are shown in Figure 2.

The quality of evidence of the included studies was evaluated according to the GRADE assessment method, and seven outcome indicators were analyzed. Evidence for VAS-3, HSS, ROM, incidence of PODS, and incidence of PONV was of medium quality. The quality of evidence for VAS-7 and PPT was low. The decline in quality was mainly caused by the limitations of randomization method and the blinding method as well as the imprecision due to the small sample size. The detailed quality assessment is shown in Table 5.

3.4 Results of network meta-analysis

3.4.1 Evidence network diagram of intervention measures

Stata16.0 was utilized to analyze the evidence network diagram of five intervention measures, where the size of each circle represents the sample size and the thickness of connecting lines indicates the number of RCTs using two intervention measures (Figure 3).

3.4.2 Conflict detection

The evidence network diagram presented in Figure 3 indicated the absence of closed-loop formation for both primary and secondary outcome indicators, thereby precluding the need for an inconsistency test.

3.4.3 Primary outcome indexes VAS-3, VAS-7, PPT, HSS, and ROM scores

(1) As shown in Figure 3A, a total of 29 RCTs mentioned VAS score on the third day after TKA, involving 2039 patients and 5 interventions including ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. There was no significant difference in the efficacy of the five interventions in improving VAS score on the third day after TKA (Table 6).

(2) As shown in Figure 3B, a total of 21 RCTs mentioned VAS score on the seventh day after TKA, involving 1,447 patients and 5 interventions including ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. In improving VAS score on the seventh day after TKA, TEAS+MA (SMD: 0.67; 95% CI: 0.01, 1.32) was superior to MA (Table 6).

(3) As shown in Figure 3C, a total of four RCTs mentioned postoperative PPT scores, involving 408 patients and 3 interventions: EA + MA, TEAS+MA, and MA. In terms of improving PPT scores after TKA, there was no significant difference in the efficacy of EA + MA, TEAS+MA, and MA interventions (Table 6).

(4) As shown in Figure 3D, a total of 15 RCTs mentioned postoperative HSS scores, involving 1,397 patients and 5 interventions including ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. In terms of improving postoperative HSS scores after TKA, the three interventions including ACU + MA (SMD: 6.45; 95%CI: 3.30, 9.60), EA + MA (SMD: 4.89; 95%CI: 1.46, 8.32), and TEAS+MA (SMD: 5.31; 95%CI: 0.85, 9.78) were more effective than MA, which helped to promote early knee joint function recovery after TKA (Table 6).

(5) As shown in Figure 3E, a total of 18 RCTs mentioned postoperative ROM, involving 1,150 patients and 5 interventions including ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. In terms of improving postoperative ROM scores after TKA, the efficacy of ACU + MA (SMD:7.43; 95%CI: 2.51, 12.36) was better than EA + MA, the efficacy of ACU + MA (SMD:10.12; 95%CI: 2.79, 17.45) was better than TEAS+MA, the efficacy of ACU + MA (SMD: 7.82; 95%CI: 2.21, 13.43) was better than AAT + MA, and the efficacy of ACU + MA (SMD: 9.74; 95%CI: 6.12, 13.37) was better than MA. It can be seen that ACU + MA has a significant advantage in improving postoperative ROM compared with other interventions (Table 6).

3.4.4 Secondary outcome indicators: incidence of adverse reactions

(1) As shown in Figure 3F, a total of 21 RCTs mentioned the incidence of postoperative nausea and vomiting, involving 1,389 patients and 5 interventions: ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. The occurrence of postoperative nausea and vomiting was significantly lower with ACU + MA (OR = 0.30; 95%CI: 0.11, 0.85), EA + MA (OR = 0.44; 95%CI: 0.22, 0.87), TEAS+MA (OR = 0.30; 95%CI: 0.17, 0.53), and AAT + MA (OR = 0.20; 95%CI: 0.11, 0.36) compared to MA (Table 6).

(2) As shown in Figure 3G, a total of 16 RCTs mentioned the incidence of postoperative dizziness and drowsiness, involving

TABLE 3 Baseline characteristics of the included studies.

References	Country	Intervention			Control			Course	Type of outcomes	Adverse reaction
		Treatment	n	Years ($\bar{\chi} \pm s$)	Treatment	n	Years ($\bar{\chi} \pm s$)			
Yang et al.	China	EA + MA	30	67.30 ± 0.00	MA	30	68.50 ± 0.00	1 W	VAS, ROM	NR
Chen et al.	China	EA + MA	20	67.10 ± 7.00	MA	20	66.70 ± 6.30	1 W	VAS	NR
Kang et al.	China	EA + MA	63	70.19 ± 5.42	MA	63	70.46 ± 4.90	1 W	PPT	NR
Zhu	China	EA + MA	16	69.29 ± 6.43	MA	16	66.56 ± 6.69	2 W	VAS, ROM	NR
Ling et al.	China	ACU + MA	30	65.73 ± 7.29	MA	30	64.27 ± 6.13	1 W	VAS, HSS	NR
Zheng et al.	China	ACU + MA	30	67.80 ± 8.12	MA	30	70.70 ± 8.47	1 W	VAS	NR
Zhen et al.	China	TEAS+MA	25	65.92 ± 7.60	MA	25	65.64 ± 7.15	1 W	VAS, HSS	Reported
Wei et al.	China	TEAS+MA	49	66.26 ± 7.35	MA	49	67.90 ± 7.69	2 W	VAS, HSS	Reported
Xiang et al.	China	EA + MA	41	63.00 ± 5.00	MA	61	63.00 ± 6.00	2 W	VAS, ROM	Reported
Zhang	China	ACU + MA	43	63.12 ± 8.31	MA	43	62.75 ± 8.19	2 W	VAS, HSS	NR
Ma et al.	China	EA + MA	41	69.63 ± 7.60	MA	41	70.92 ± 6.55	5D	VAS, HSS	NR
Zhang et al.	China	ACU + MA	30	67.00 ± 7.00	MA	30	67.00 ± 9.00	2 W	VAS, ROM, HSS	Reported
Zhu et al.	China	ACU + MA	45	49.23 ± 5.61	MA	45	48.23 ± 5.41	1 W	VAS	Reported
Liao et al.	China	ACU + MA	30	70.00 ± 4.67	MA	30	71.37 ± 3.15	2 W	VAS	NR
Liu et al.	China	ACU + MA	20	65.26 ± 7.23	MA	20	67.32 ± 6.54	1 W	VAS	Reported
Li et al.	China	ACU + MA	20	67.90 ± 7.50	MA	20	66.8 ± 6.3	2 W	VAS, ROM	NR
Wang	China	ACU + MA	54	53.29 ± 4.52	MA	51	54.13 ± 6.24	2 W	VAS, HSS, ROM	NR
Wu et al.	China	TEAS+MA	60	70.75 ± 8.23	MA	60	70.55 ± 7.44	4 W	VAS, HSS	NR
Zhang et al.	China	TEAS+MA	40	69.20 ± 3.00	MA	40	68.60 ± 3.20	3D	VAS	NR
Chen et al.	China	TEAS+MA	30	63.37 ± 5.81	MA	30	65.17 ± 5.78	1 W	VAS	Reported
Bai et al.	China	TEAS+MA	71	65.61 ± 5.73	MA	69	65.07 ± 5.98	1 W	VAS, HSS	Reported
Xu et al.	China	TEAS+MA	46	67.00 ± 7.00	MA	45	67.70 ± 7.30	2 W	VAS, ROM	NR
Wang et al.	China	TEAS+MA	45	70.00 ± 4.00	MA	45	71.00 ± 6.00	3D	VAS	Reported
Tsang et al.	Hong Kong, China	ACU + MA	12	70.60 ± 5.80	MA	12	66.10 ± 7.50	1 W	VAS, ROM	NR
Tzeng et al.	Taiwan, China	EA + MA	16	69.60 ± 5.60	MA	17	70.10 ± 6.90	2D	VAS	Reported
		no-point group	14	71.40 ± 7.30						
Chen et al.	China	EA + MA	30	68.90 ± 9.00	MA	30	69.00 ± 8.60	1 W	VAS	Reported
Lan	China	EA + MA	20	61.72 ± 9.94	MA	20	64.45 ± 8.43	1 W	VAS + ROM	Reported
Sheng	China	EA + MA	20	67.05 ± 7.04	MA	20	66.70 ± 6.28	1 W	VAS + ROM	Reported
Guo	China	EA + MA	25	64.72 ± 7.28	MA	25	62.64 ± 6.16	1 W	VAS + ROM+HSS	Reported
Chen et al.	China	EA + MA	35	64.70 ± 5.10	MA	35	65.60 ± 5.10	2 W	ROM+HSS	NR
Zhong	China	EA + MA	55	69.33 ± 5.66	MA	55	68.42 ± 5.35	3D	HSS	NR
Tong et al.	China	AAT + MA	30	70.00 ± 4.79	MA	30	71.37 ± 3.18	1 W	VAS + ROM+HSS	Reported
Yan	China	AAT + MA	30	70.00 ± 4.78	MA	30	71.37 ± 3.18	3D	VAS	NR
Zhang	China	AAT + MA	23	62.00 ± 8.00	MA	23	61.00 ± 9.00	2D	VAS	Reported
Kong et al.	China	AAT + MA	40	59.16 ± 6.42	MA	40	61.28 ± 5.63	1 W	VAS + ROM	NR
Du et al.	China	AAT + MA	30	65.02 ± 3.00	MA	30	64.38 ± 2.77	3D	VAS	Reported
Yan et al.	China	AAT + MA	102	62.20 ± 9.10	MA	102	64.10 ± 8.20	1 W	VAS + HSS	NR
Zhong et al.	China	AAT + MA	50	65.75 ± 1.41	MA	50	64.60 ± 0.70	3D	VAS + HSS	NR
Fu	China	AAT + MA	30	64.6 ± 7.29	MA	30	66.57 ± 6.96	3D	VAS + HSS	Reported
Wang et al.	China	AAT + MA	31	60.19 ± 6.33	MA	29	66.02 ± 7.76	3D	VAS	Reported
He	China	AAT + MA	45	62.56 ± 6.10	MA	45	61.58 ± 6.66	1 W	VAS + ROM+HSS	Reported

ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy; MA, multimodal analgesia; NR, No reported; W, week; D, day; VAS, visual analog scale; ROM, the range of motion; HSS, hospital for special surgery; PPT, pain pressure threshold.

TABLE 4 Descriptions of the included acupuncture and related therapies.

References	Study of acupuncture	Names of acupuncture points used	Retention time	Acupuncturist qualifications	Acupuncture reaction	Frequency and course of acupuncture
Yang et al.	EA	Qimen (SP11), Sanyinjiao (SP06), Biguan (ST31), Fenglong (ST40)	30 min	Reported	Deqi	Once a day for 1 week
Chen et al.	EA	Liangqiu (ST34), Xuehai (SP10), Yinlingquan (SP09), Zusanli (ST36), Fenglong (ST40), Qiuxu (GB40)	30 min	NR	Deqi	Once a day for 1 week
Kang et al.	EA	Futu (ST32), Zusanli (ST36), Yinlingquan (SP09), Yanglingquan (GB34)	20 min	NR	Deqi	Once a day, 5 times for 1 week
Zhu	EA	Liangqiu (ST34), Xuehai (SP10), Yinlingquan (SP09), Zusanli (ST36), Fenglong (ST40), Qiuxu (GB40)	30 min	Reported	NR	NR
Ling et al.	ACU	Jianzhong (GB21), Linggu (GV20), Taibai (SP03)	NR	NR	Deqi	Once a day for 1 week
Zheng et al.	ACU	Xuehai (SP10), Liangqiu (ST34), Zusanli (ST36), Yanglingquan (GB34), Sanyinjiao (SP06), Taixi (KI03), Taichong (LR03), Hegu (LI04)	30 min	Reported	Deqi	Once a day for 1 week
Zhen et al.	TEAS	Hegu (LI04), Neiguan (PC06), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09), Zusanli (ST36)	30 min	NR	Deqi	Once a day for 1 week
Wei et al.	TEAS	Zusanli (ST36), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09), Taichong (LR03), Weizhong (BL40)	30 min	Reported	Deqi	3 times 1 day for 2 weeks
Xiang et al.	EA	Zusanli (ST36), Yinlingquan (SP09), Yanglingquan (GB34)	30 min	Reported	Deqi	Once a day for 1 week
Zhang	ACU	Xuehai (SP10), Yinmen (BL37), Yinlingquan (SP09), Yanglingquan (GB34), Chengfu (BL36)	NR	Reported	Deqi	Once a day for 2 weeks
Ma et al.	EA	Shousanli (LI10), Quchi (LI11), Zhouliao (LI12), Binao (LI14), Chize (LU05), Sidu (SJ09)	20 min	Reported	Deqi	Once a day for 5 days
Zhang et al.	ACU	Taichong (LR03), Kunlun (BL60), Shousanli (LI10), Quchi (LI11), Chize (LU05), Houxi (SI03), Shenmai (BL62), Sanyinjiao (SP06)	30 min	NR	Deqi	Once a day for 2 weeks
Zhu et al.	ACU	Chengfu (BL36), Taichong (LR03), Yinlingquan (SP09)	NR	NR	Deqi	Once a day for 1 week
Liao et al.	ACU	Taichong (LR03), Hegu (LI04)	30 min	NR	Deqi	Once a day for 2 weeks
Liu et al.	ACU	Taichong (LR03), Hegu (LI04), Liangqiu (ST34), Zhongdu (LR06)	30 min	NR	Deqi	Once a day for 3 days
Li et al.	ACU	Taichong (LR03), Kunlun (BL60), Yanglingquan (GB34), Zusanli (ST36), Hegu (LI04), Sanyinjiao (SP06)	30 min	Reported	Deqi	Once a day for 2 weeks
Wang	ACU	Chengfu (BL56), Yinmen (BL37), Xuehai (SP10), Yinlingquan (SP09), Yanglingquan (GB34), Taichong (LR03)	NR	NR	Deqi	Once a day for 2 weeks
Wu et al.	TEAS	Liangqiu (ST34), Zusanli (ST36), Yinlingquan (SP09), Yanglingquan (GB34), Xuehai (SP10), Yinshi (ST33)	30 min	NR	Deqi	Once a day for 4 weeks
Zhang et al.	TEAS	Hegu (LI04), Neiguan (PC06)	30 min	NR	Deqi	Once a day for 3 days

(Continued)

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TABLE 4 (Continued)

References	Study of acupuncture	Names of acupuncture points used	Retention time	Acupuncturist qualifications	Acupuncture reaction	Frequency and course of acupuncture
Chen et al.	TEAS	Zusanli (ST36), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09), Yanglingquan, (GB34), Weizhong (BL40), Hegu (LI04), Neiguan (PC06)	30 min	NR	Deqi	3 times 1 day for 1 week
Bai et al.	TEAS	Zusanli (ST36), Weizhong (BL40), Yanglingquan (GB34), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09)	30 min	NR	Deqi	3 times 1 day for 1 week
Xu et al.	TEAS	Zusanli (ST36), Weizhong (BL40), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09), Yanglingquan (GB34)	30 min	Reported	Deqi	Twice a day for 1 week
Wang et al.	TEAS	Hegu (LI04), Neiguan (PC06), Zusanli (ST36)	30 min	NR	Deqi	NR
Tsang et al.	ACU	Futu (ST32), Yinshi (ST33), Fengshi (GB31), Yangjiao (GB35), Yanglingquan (GB34), Zusanli (ST36)	20 min	Reported	Deqi	NR
Tzeng et al.	EA	Zusanli (ST36), Yanglingiquan (GB34)	30 min	Reported	Deqi	Once a day for 2 days
Chen et al.	EA	Zusanli (ST36), Xuehai (SP10), Liangqiu (ST34), Weizhong (BL40), Xiguan (LR07)	30 min	Reported	Deqi	Before the start of surgery
Lan	AAT	Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP09), Yanglingquan (GB34)	30 min	NR	Deqi	Once a day for 1 week
Sheng	AAT	Liangqiu (ST34), Xuehai (SP10), Yinlingquan (SP09), Zusanli (ST36), Fenglong (ST40), Qiuxu (GB40)	30 min	Reported	Deqi	Once a day for 1 week
Guo	AAT	Hegu (LI04), Zusanli (ST36), Taichong (LR03), Taixi (KI03), Yinlingquan (SP09), Yanglingquan (GB34)	30 min	Reported	Deqi	Once a day for 1 week
Chen et al.	AAT	Xuehai (SP10), Liangqiu (ST34), Dubi (ST35), Neixiyan (EX-LE4), Yanglingquan (GB34), Zusanli (ST36), Kunlun (BL60)	30 min	NR	Deqi	Once a day for 2 weeks
Zhong	AAT	Futu (ST32), Zusanli (ST36), Yanglingquan (GB34), Yinlingquan (SP09)	20 min	Reported	Deqi	Once a day for 3 days
Tong et al.	AAT	Shenmen (TF4), Subcortex (AT4), Sympathetic (AT1), Knee (TG1)	5 min	NR	Deqi	Once every 30 min for 1 week
Yan	AAT	Shenmen (TF4), Knee (TG1), Kidney (TG2), Small occipital nerve point, Large auricular nerve point	5 min	NR	Deqi	Once every 2 h for 3 days
Zhang	AAT	Shenmen (TF4), Subcortex (AT4), Knee (TG1)	10 min	NR	Deqi	3 to 5 times 1 day for 3 days
Kong et al.	AAT	Shenmen (TF4), Subcortex (AT4), Sympathetic (AT1), Endocrine (AT2), Knee (TG1)	3 min	Reported	Deqi	Twice 1 day for 1 week
Du et al.	AAT	Shenmen (TF4), Subcortex (AT4), Sympathetic (AT1), Knee (TG1), Kidney (TG2), Spleen (AT5), Stomach (AT6)	2 min	Reported	Deqi	4 times 1 day for 3 days
Yan et al.	AAT	Shenmen (TF4), Subcortex (AT4), Sympathetic (AT1), Knee (TG1)	5 min	Reported	Deqi	3 times 1 day for 2 week
Zhong et al.	AAT	Shenmen (TF4), Subcortex (AT4), Knee (TG1), Kidney (TG2)	3 min	Reported	Deqi	4 times 1 day for 3 days
Fu	AAT	Shenmen (TF4), Subcortex (AT4), Knee (TG1), Kidney (TG2)	2 min	Reported	Deqi	4 times 1 day for 3 days
Wang et al.	AAT	Shenmen (TF4), Subcortex (AT4), Knee (TG1), Lung (AT3)	5 min	Reported	Deqi	Operation when feeling the pain
He	AAT	Shenmen (TF4), Subcortex (AT4), Sympathetic (AT1), Knee (TG1)	3 min	Reported	Deqi	4 times 1 day for 1 week

ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy; MA, multimodal analgesia; NR, no reported.

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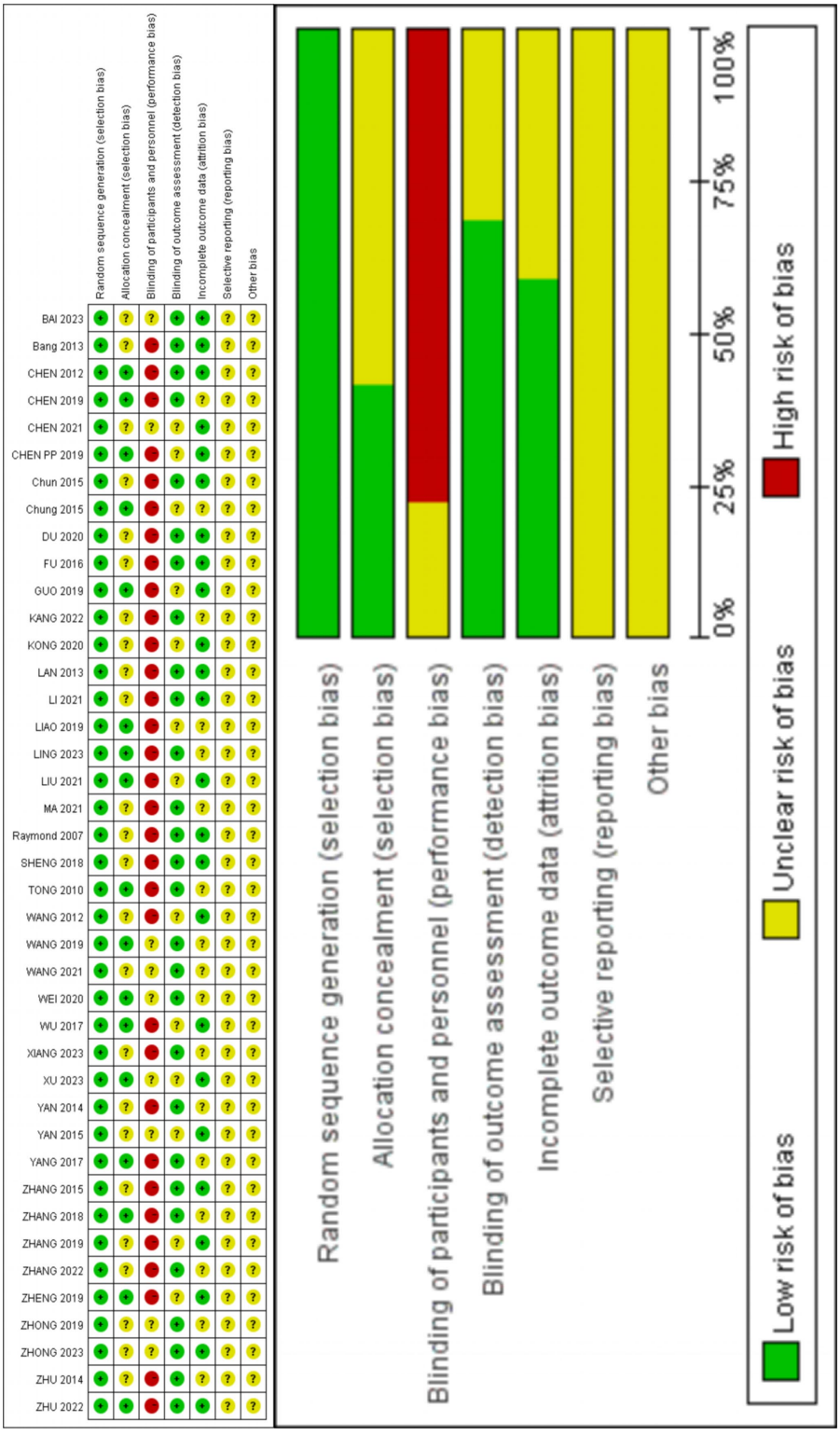

FIGURE 2
Quality assessment of included studies.

1,076 patients and 5 interventions: ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA. The occurrence of postoperative dizziness and drowsiness was higher with ACU + MA (OR = 4.98; 95%CI: 1.01, 24.42) than with AAT + MA; the incidence of postoperative dizziness and drowsiness was lower with TEAS+MA (OR = 0.36; 95%CI: 0.18, 0.70) and AAT + MA (OR = 0.20; 95%CI: 0.08, 0.50) than with MA (Table 6).

TABLE 5 GRADE assessment of outcome indicators.

Outcome indicator	Downgrading factors					Quality grade
	Boundedness	Inconsistency	Not directly	Inaccuracy	Publication bias	
VAS-3	−1	0	0	0	0	Middle rank
VAS-7	−1	0	0	0	−1	Low rank
PPT	−1	0	0	0	−1	Low rank
HSS	−1	0	0	0	0	Middle rank
ROM	−1	0	0	0	0	Middle rank
Incidence of PONV	−1	0	0	0	0	Middle rank
Incidence of PODS	−1	0	0	0	0	Middle rank

VAS, visual analog scale;VAS-3, VAS score assessed on the third postoperative day; VAS-7, VAS score assessed on the seventh postoperative day; ROM, the range of motion; HSS, hospital for special surgery; PPT, pain pressure threshold; incidence of PONV, incidence of postoperative nausea and vomiting; incidence of PODS, incidence of postoperative dizziness and sleepiness.

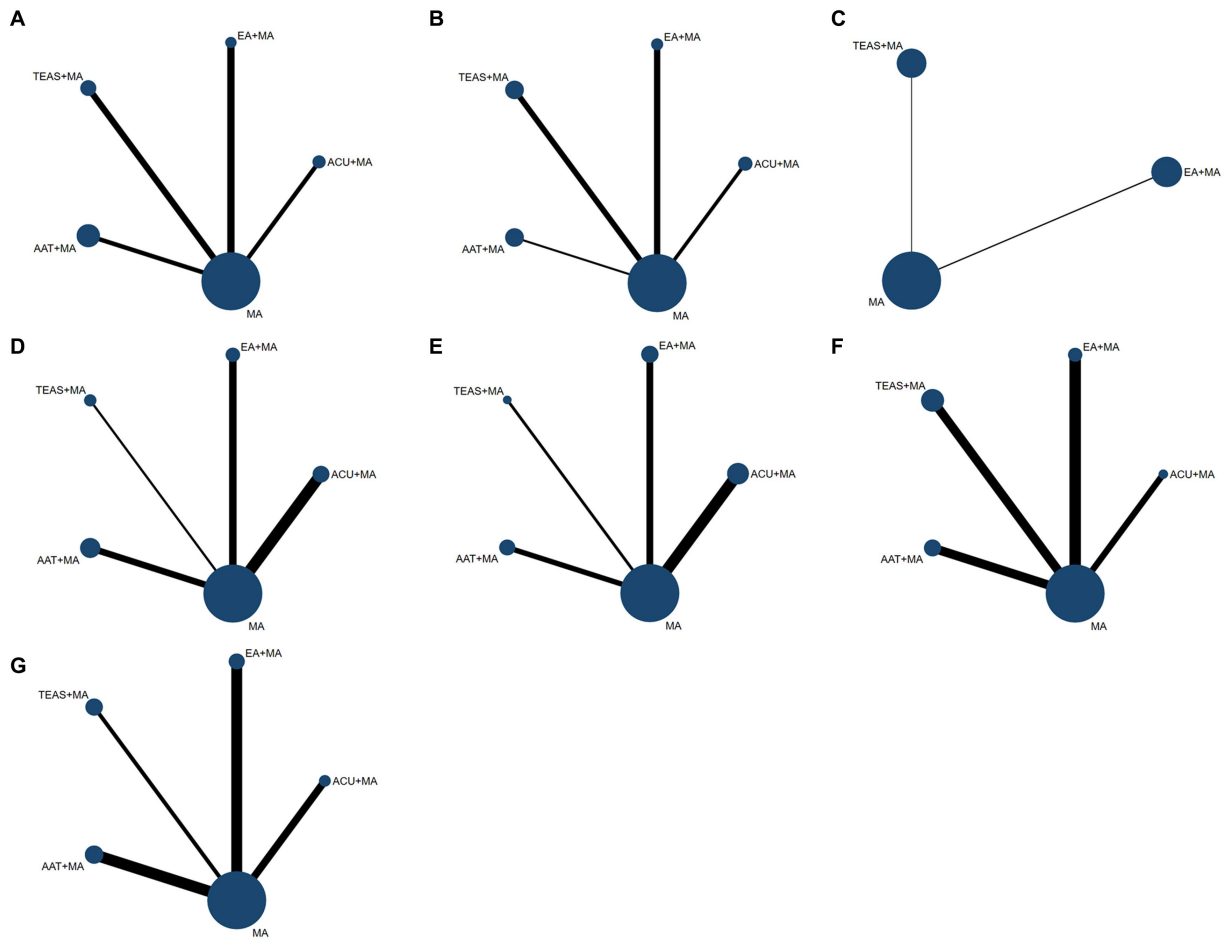

FIGURE 3
Network structure for treatment comparisons. **(A)** VAS-3 scores; **(B)** VAS-7 scores; **(C)** PPT scores; **(D)** HSS scores; **(E)** ROM scores; **(F)** incidence of postoperative nausea and vomiting; **(G)** incidence of postoperative dizziness and sleepiness. ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy: MA, multimodal analgesia.

The incidence of adverse reactions in the study utilizing acupuncture-related therapy as an intervention measure was generally lower compared to that of the simple multimodal analgesia scheme, thereby indicating the safety and efficacy of applying acupuncture-related therapy during the perioperative period of TKA.

3.4.5 SUCRA probability ranking

(1) As shown in Table 7 and Figure 4A, in terms of improving VAS score on the third day after surgery, the SUCRA probability ranking results showed that EA + MA (SUCRA = 74.2%) > TEAS+MA (SUCRA = 73.3%) > MA

TABLE 6 Network meta-analysis results.

(A) VAS-3				
ACU + MA				
−0.33 (−1.21, 0.55)	EA + MA			
−0.33 (−1.25, 0.58)	−0.00 (−0.93, 0.93)	TEAS+MA		
0.28 (−0.53, 1.09)	0.62 (−0.21, 1.44)	0.62 (−0.25, 1.49)	AAT + MA	
−0.10 (−0.71, 0.51)	0.23 (−0.40, 0.86)	0.23 (−0.45, 0.92)	−0.38 (−0.92, 0.15)	MA
(B) VAS-7				
ACU + MA				
−0.46 (−1.27, 0.36)	EA + MA			
−0.80 (−1.66, 0.06)	−0.35 (−1.23, 0.54)	TEAS+MA		
0.01 (−0.87, 0.89)	0.47 (−0.44, 1.37)	0.81 (−0.13, 1.76)	AAT + MA	
−0.14 (−0.70, 0.42)	0.32 (−0.27, 0.91)	0.67 (0.01, 1.32)*	−0.15 (−0.83, 0.54)	MA
(C) PPT				
EA + MA				
−0.05 (−0.82, 0.73)	TEAS+MA			
0.37 (−0.20, 0.93)	0.41 (−0.12, 0.95)	MA		
(D) HSS				
ACU + MA				
1.56 (−3.08, 6.20)	EA + MA			
1.13 (−4.33, 6.60)	−0.42 (−6.05, 5.21)	TEAS+MA		
3.23 (−1.35, 7.81)	1.67 (−3.11, 6.46)	2.10 (−3.48, 7.67)	AAT + MA	
6.45 (3.30, 9.60)*	4.89 (1.46, 8.32)*	5.31 (0.85, 9.78)*	3.22 (−0.13, 6.56)	MA
(E) ROM				
ACU + MA				
7.43 (2.51, 12.36)*	EA + MA			
10.12 (2.79, 17.45)*	2.69 (−4.51, 9.89)	TEAS+MA		
7.82 (2.21, 13.43)*	0.39 (−5.05, 5.83)	−2.30 (−9.98, 5.38)	AAT + MA	
9.74 (6.12, 13.37)*	2.31 (−1.03, 5.65)	−0.38 (−6.75, 6.00)	1.92 (−2.37, 6.21)	MA
(F) Incidence of postoperative nausea and vomiting				
ACU + MA				
0.68 (0.20, 2.35)	EA + MA			
0.98 (0.30, 3.20)	1.45 (0.60, 3.47)	TEAS+MA		
1.47 (0.45, 4.82)	2.17 (0.89, 5.29)	1.50 (0.67, 3.36)	AAT + MA	
0.30 (0.11, 0.85)*	0.44 (0.22, 0.87)*	0.30 (0.17, 0.53)*	0.20 (0.11, 0.36)*	MA
(G) Incidence of postoperative dizziness and sleepiness				
ACU + MA				
1.84 (0.38, 8.85)	EA + MA			
2.81 (0.65, 12.26)	1.52 (0.51, 4.55)	TEAS+MA		
4.98 (1.01, 24.42)*	2.70 (0.77, 9.40)	1.77 (0.57, 5.45)	AAT + MA	
1.01 (0.27, 3.74)	0.55 (0.23, 1.30)	0.36 (0.18, 0.70)*	0.20 (0.08, 0.50)*	MA

ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy; MA, multimodal analgesia; VAS, visual analog scale;VAS-3, VAS score assessed on the third postoperative day; VAS-7, VAS score assessed on the seventh postoperative day; ROM, the range of motion; HSS, hospital for special surgery; PPT, pain pressure threshold; incidence of PONV, incidence of postoperative nausea and vomiting; incidence of PODS, incidence of postoperative dizziness and sleepiness.
*Represents positive results.

(SUCRA = 51.1%) > ACU + MA (SUCRA = 39.7%) > AAT + MA (SUCRA = 11.8%).

(2) As shown in Table 7 and Figure 4B, in terms of improving VAS score on the seventh day after surgery, the SUCRA probability ranking results showed that TEAS+MA (SUCRA = 92.0%) > EA + MA (SUCRA = 69.6%) > MA (SUCRA = 37.8%) > AAT + MA (SUCRA = 25.6%) > ACU + MA (SUCRA = 24.9%).

(3) As shown in Table 7 and Figure 4C, in terms of improving postoperative PPT score, the SUCRA probability ranking results showed that TEAS+MA (SUCRA = 74.4%) > EA + MA (SUCRA = 67.1%) > MA (SUCRA = 8.2%).
(4) As shown in Table 7 and Figure 4D, in terms of improving postoperative HSS score, the SUCRA probability ranking results showed that ACU + MA (SUCRA = 83.2%) > TEAS+MA (SUCRA = 66.5%) > EA + MA (SUCRA = 61.2%) > AAT + MA (SUCRA = 38.0%) > MA (SUCRA = 1.0%).
(5) As shown in Table 4 and Figure 4E, in terms of improving postoperative ROM score, the SUCRA probability ranking results showed that ACU + MA (SUCRA = 99.9%) > EA + MA (SUCRA = 55.9%) > AAT + MA (SUCRA = 49.6%) > TEAS+MA (SUCRA = 24.1%) > MA (SUCRA = 20.5%).
(6) As shown in Table 7 and Figure 4F, the SUCRA probability ranking results for the incidence of postoperative nausea and vomiting were as follows: MA (SUCRA = 99.5%) > EA + MA (SUCRA = 62.4%) > TEAS+MA (SUCRA = 39.0%) > ACU + MA (SUCRA = 37.4%) > AAT + MA (SUCRA = 11.7%).
(7) As indicated in Table 7 and Figure 4G, the SUCRA probability ranking results demonstrate that MA (SUCRA = 85.0%) exhibits a higher incidence of postoperative dizziness and drowsiness compared to ACU + MA (SUCRA = 79.6%), EA + MA (SUCRA = 50.8%), TEAS+MA (SUCRA = 28.7%), and AAT + MA (SUCRA = 5.9%).

3.4.6 Publication bias test

The adjustment-comparison funnel plots were constructed to assess publication bias for both primary and secondary outcome indicators. However, the asymmetry observed in the HSS score "comparison-adjustment" funnel plots suggests potential publication bias among the included studies. Additionally, some studies examining the primary outcome indicators deviated from the 95% confidence interval of the funnel plot, indicating a possible small sample effect (Figure 5).

4 Discussion

This network meta-analysis included 41 randomized controlled trials involving 3,003 patients who underwent TKA. It aimed to explore the effectiveness and safety of different acupuncture therapies in reducing postoperative pain after TKA, evaluating them based on four outcome indicators and the incidence of adverse reactions. The results revealed that EA + MA and TEAS+MA demonstrated superior efficacy in improving the postoperative VAS score of TKA patients. ACU + MA showed better efficacy in enhancing the postoperative ROM score and HSS score of TKA patients. In terms of adverse reactions, AAT + MA effectively reduced the occurrence of postoperative nausea, vomiting, dizziness, and drowsiness. Furthermore, EA + MA, TEAS+MA, and AAT + MA all exhibited better efficacy than MA alone while establishing the safety profile of acupuncture-related therapies for TKA.

The NMA method utilized in this study compared the effectiveness of various acupuncture therapies for postoperative pain and joint function recovery through indirect data analysis, compensating for the lack of direct evidence. These findings provide some support for acupuncture-related treatments to enhance postoperative pain management and facilitate early rehabilitation. In contrast to traditional meta-analyses (95), this study employed the NMA approach to comprehensively assess the included literature and rank different acupuncture therapies. Furthermore, our results confirmed the potential benefits of acupuncture-related interventions in improving postoperative pain and promoting early rehabilitation. Notably, common complications following TKA include nausea, vomiting, dizziness, and drowsiness that can cause significant discomfort for patients. Such symptoms may trigger a self-protective response that makes patients feel seriously ill and leads to reduced activity levels as well as negative attitudes toward early rehabilitation. Therefore, we also evaluated the incidence of adverse reactions after TKA.

The primary objective of TKA is to alleviate the pain associated with knee arthritis, enhance knee joint functionality, and enhance the overall quality of life for patients. However, the occurrence of severe postoperative pain following TKA is a prevalent adverse event that can impede the progress of rehabilitation training. In 1998, Wulf et al. (96) introduced the notion of external focus of attention (EFA), which has garnered significant attention within the realm of rehabilitation medicine (97). The concept of EFA pertains to the process of engaging in actions, specifically skill learning, by directing attention toward the surrounding environment of the action, including sports equipment, the intended goal, and the resultant effect. In contrast, the traditional approach known as Internal Focus of Attention (IFA) centers attention

TABLE 7 Ranking of SUCRA for each outcome index after TKA using different acupuncture therapy combined with multimodal analgesia.

Treatment	VAS-3		VAS-7		PPT		HSS		ROM		Incidence of PONV		Incidence of PODS	
	Rank (%)	Sort	Rank (%)	Sort	Rank (%)	Sort	Rank (%)	Sort	Rank (%)	Sort	Rank (%)	Sort	Rank (%)	Sort
ACU + MA	39.7	4	24.9	5	_	_	83.2	1	99.9	1	37.4	4	79.6	2
EA + MA	74.2	1	69.6	2	67.1	2	61.2	3	55.9	2	62.4	2	50.8	3
TEAS+MA	73.3	2	92.0	1	74.4	1	66.5	2	24.1	4	39.0	3	28.7	4
AAT + MA	11.8	5	25.6	4	_	_	38.0	4	49.6	3	11.7	5	5.9	5
MA	51.1	3	37.8	3	8.2	3	1.0	5	20.5	5	99.5	1	85.0	1

ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy; MA, multimodal analgesia; incidence of PONV, incidence of postoperative nausea and vomiting; incidence of PODS, incidence of postoperative dizziness and sleepiness; VAS, visual analog scale; VAS-3, VAS score assessed on the third postoperative day; VAS-7, VAS score assessed on the seventh postoperative day; ROM, the range of motion; HSS, hospital for special surgery; PPT, pain pressure threshold.

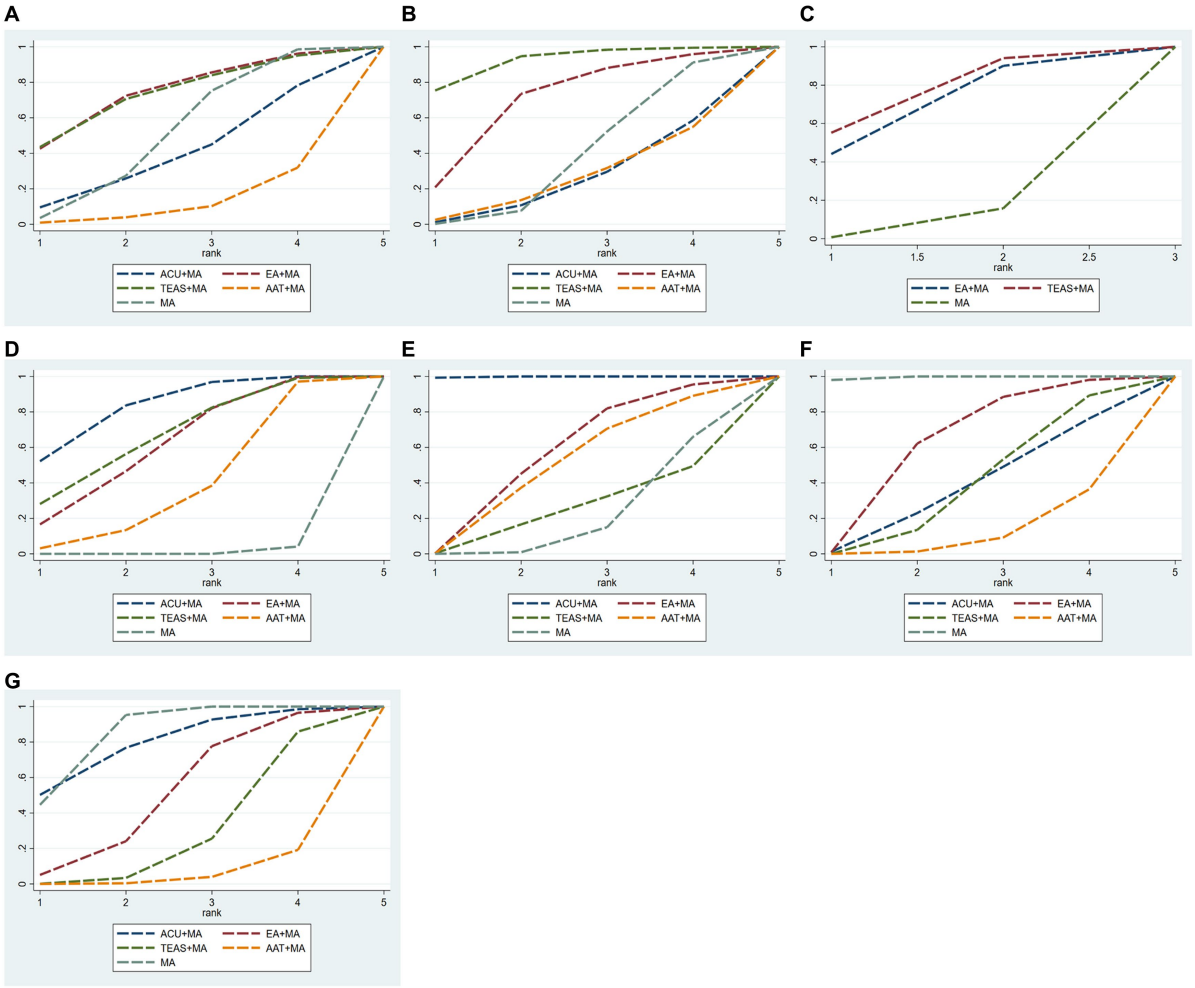

FIGURE 4
SUCRA probability ranking of interventions. **(A)** VAS-3 scores; **(B)** VAS-7 scores; **(C)** PPT scores; **(D)** HSS scores; **(E)** ROM scores; **(F)** incidence of postoperative nausea and vomiting; **(G)** incidence of postoperative dizziness and sleepiness. ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation; AAT, auricular acupoint therapy; MA, multimodal analgesia.

on the action itself, focusing on the involved joints and muscles. EFA aiming at the movement effect has been reported to have more efficacy than IFA aiming at movement characteristics in healthy subjects (98). Research findings have consistently demonstrated that the implementation of EFA, as opposed to IFA, significantly contributes to the restoration of motor function in patients afflicted with anterior cruciate ligament injury (99), ankle sprain (99), stroke (99), and Parkinson's disease (97). Giacomo Rossettini's research has revealed that the EFA strategy influences positively the motor performance more than IFA and control and is preferred by the subjects (98). Acupuncture therapy is commonly employed in the rehabilitation of musculoskeletal disorders, including post-total knee arthroplasty. In this study, the acupuncture practitioner primarily instructs patients to perform the EFA strategy, such as attempting to kick a training bat held by the practitioner, as part of the treatment. Postoperative rehabilitation exercise plays a crucial role in mitigating complications, such as knee stiffness and limited activity, for patients undergoing TKA. In clinical practice, it is commonly recommended that patients achieve a knee flexion of 90°and a knee extension of 0°after TKA, to fulfill the general activity requirements (100). The rehabilitation exercise regimen primarily encompasses active knee extension training, straight leg lifting training, and passive knee flexion and extension exercises, with a gradual increment in the angle of knee flexion exercise, while encouraging patients to get out of bed as soon as possible with crutches (101).

The postoperative pain experienced by patients undergoing TKA has detrimental effects on both their physical functioning during exercise and their mental wellbeing. If joint mobility remains restricted and deformities persist following the surgical procedure, it can easily trigger negative emotions. A study conducted by researchers (102) demonstrated a significant correlation ($r = 0.40$, $p < 0.001$) between the severity of depression and the intensity of pain experienced by patients 48 h after the surgery. Postoperative pain is a common adverse event following TKA, with multifaceted causes including mechanical pain resulting from surgical damage to the knee joint and surrounding tissues (103), spasm pain caused by vascular stenosis, tissue ischemia, and edema due to intraoperative tourniquet application (37), neuropathic pain caused by perioperative nerve compression, nerve ischemia, and hypoxia (such as anterolateral knee epidermal nerve injury) (104), and idiopathic pain caused by

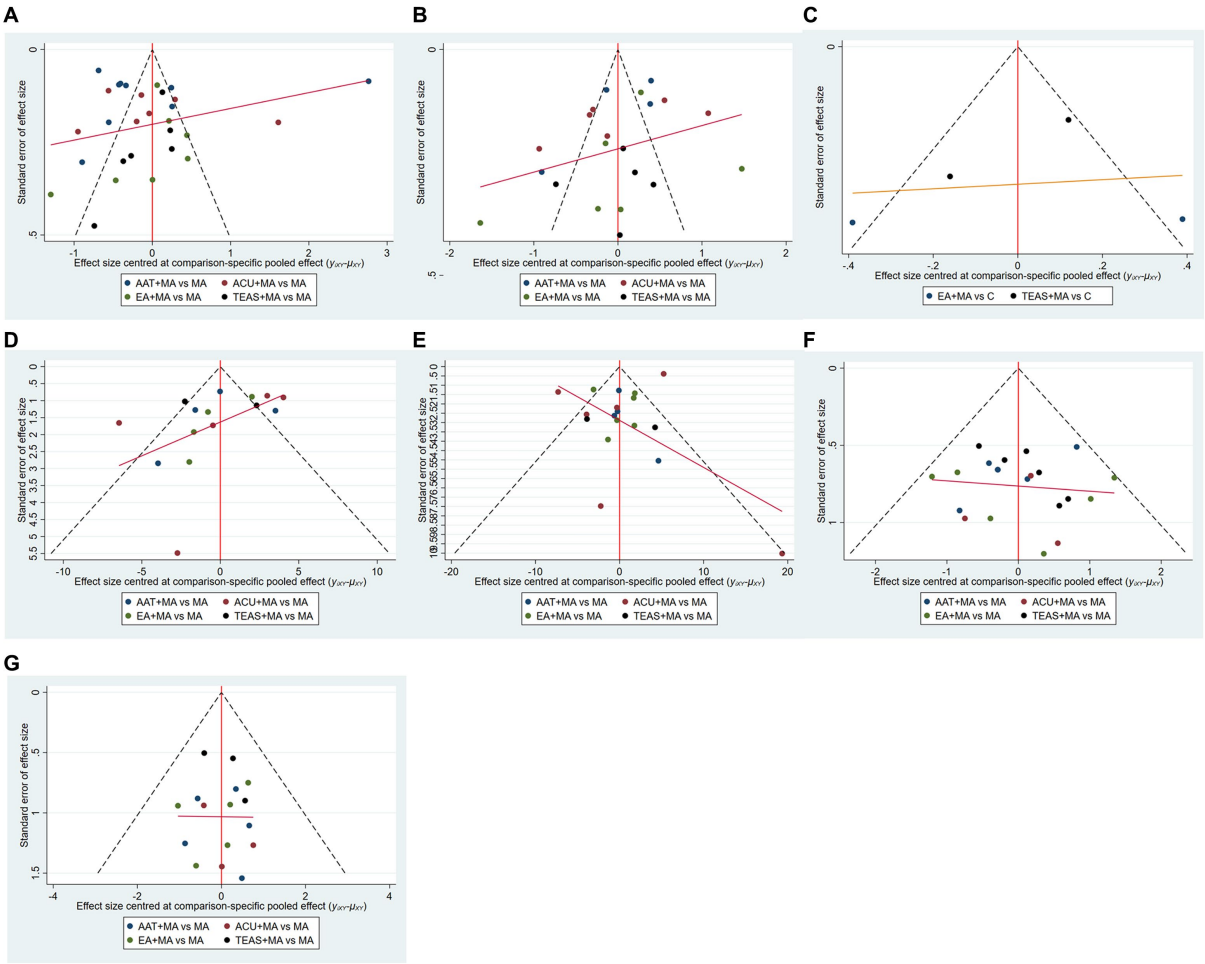

FIGURE 5
Funnel diagram. **(A)** VAS-3 scores; **(B)** VAS-7 scores; **(C)** PPT scores; **(D)** HSS scores; **(E)** ROM scores; **(F)** incidence of postoperative nausea and vomiting; **(G)** incidence of postoperative dizziness and sleepiness. ACU, acupuncture; EA, electroacupuncture; TEAS, transcutaneous electrical acupoint stimulation.

emotional factors. Although multimodal analgesia schemes have been used in clinical practice for over 20 years to treat post-TKA pain, reports indicate that 10–34% of patients still experience severe pain. Acupuncture has been found to exert peripheral analgesic effects through purinergic signals, the endocannabinoid system, peripheral endogenous opioid peptides, and transient receptor potential vanilloid subfamily (TRPV) channels (36, 105). The reward system and limbic system are related to the central loop of acupuncture-induced pain reduction; among these regions, the rostral anterior cingulate cortex (rACC) is a key brain region. Cannabinoid receptors and dopamine receptors in the brain are closely associated with acupuncture's ability to relieve pain (106). While different acupuncture therapies operate on floodgate theory mechanisms for their mechanism of action, their afferent effect mechanisms differ. Acupuncture and electroacupuncture regulate dorsal root nerves' transient potential receptor 1 and purinergic signal P2X3 for analgesic effects (107), while auricular therapy and TEAS may be related to the activation of subcutaneous class C afferent nerve fibers and class A nerve fibers (108). Which afferent effect mechanism is more effective is still unclear. Both acupuncture therapy and exercise therapy have been shown to have a significant therapeutic impact on the rehabilitation process following total knee arthroplasty. The combination of acupuncture therapy and exercise rehabilitation training specifically targets the affected knee joint. Acupuncture therapy effectively alleviates postoperative pain, while exercise therapy promotes active movement and strengthening of the knee joint. The application of acupuncture therapy has been found to enhance local blood circulation, mitigate inflammatory response, and effectively promote detumescence and analgesia. Concurrently, exercise therapy has been shown to enhance the flexion and extension movement function of the knee joint, as well as augment muscle strength (109). The integration of these two treatment modalities effectively addresses the limitations associated with relying solely on a single rehabilitation approach (110).

A meta-analysis study revealed a correlation between pain intensity in musculoskeletal disorders and somatoperception (SoP), space perception (SpP), and body ownership (BO). Following TKA procedures, there was an increase in SoP, SpP, and BO at 3 and 6 weeks post-surgery as pain intensity decreased. Patients with knee osteoarthritis exhibited higher levels of somatosensory dysfunction compared to healthy individuals, while those with fibromyalgia were more susceptible to experiencing bodily illusions. While the precise correlation between pain intensity and the three (SoP, SpP, BO)

remains uncertain, it is plausible to posit that the interplay between pain and sensory dysfunction may significantly influence clinical outcomes (111). Previous research (112) has indicated that a majority of individuals diagnosed with knee osteoarthritis (KOA) experience varying levels of proprioception impairments and diminished accuracy. Proprioception is a crucial factor in upholding knee posture and stability during both stationary and active movements as it collaborates with the vestibular and visual systems within a closed loop. Following TKA, patients may restrict their range of motion due to apprehension of pain or unsuitable environmental circumstances, consequently resulting in compromised sensorimotor control functionality. The sensorimotor control disorder of the knee joint, resulting from post-TKA pain, is regarded as a stress response mechanism aimed at reducing further stimulation of painful tissue (113). Over time, this disorder may lead to fatigue and tissue damage in the muscle groups adjacent to the knee joint, exacerbate pain by sensitizing both the peripheral and central nervous systems, and contribute to the disruption of movement patterns (114). Acupuncture is a complex somatosensory stimulation that triggers a wide range of effects in the body (115). Neuroimaging studies have suggested that acupuncture-induced cortical activation mainly reflects the somatosensory, affective, and cognitive processing of pain (116). Genuine acupuncture stimulated several networks of brain activation, including ACC (pregenual anterior, dorsal anterior, and middle), prefrontal cortex, and the parahippocampus (117). The anterior insula is well known for its integrative role in afferent and visceral information and representation of subjective feeling in diverse domains, including pain perception (118). The activation of the ACC also triggers the endogenous analgesia system and modulates sensory transmission at the level of the spinal cord via descending inhibitory modulation (119). The findings of a meta-analysis were that proprioceptive training seemed to alleviate pain and improve the walking speed of patients with knee OA (120). Nevertheless, acupuncture therapy can enhance proprioception of knee joints in patients with osteoarthritis. Simultaneously, acupuncture stimulation increases tactile sensitivity in the ACC and parahippocampus and also strongly influences pain perception in the two-point discrimination task. Acupuncture stimulation leads to the activation of brain regions such as the posterior frontal lobe and anterior cingulate cortex, but the involved interoceptive-autonomic neural network still needs further study (121). Another study concluded that acupuncture may offer analgesic effect that is not dependent on precisely where the needles are inserted so much as that the patient attends to where they are inserted. The mechanism is improvement in self-perception mediated through the sensory discrimination-like qualities of acupuncture (122).

Acupuncture has been found to elicit immune cell stimulation, particularly the activation of regulatory T cells (Treg cells), resulting in increased production of IL−10 (123). This process also aids in regulating the decrease of macrophages and neutrophils, thereby inhibiting the expression of pro-inflammatory mediators such as IL−1β, NLRP3, and TNF-α. Consequently, acupuncture demonstrates anti-inflammatory and analgesic effects. Additionally, acupuncture directly activates endogenous opioids, such as enkephalin and β-endorphin, in both the central and peripheral systems, thereby contributing to its analgesic effects (124). In addition to conventional analgesic methods, acupuncture has the potential to alleviate pain indirectly through various mechanisms, including the placebo effect (125), modulation of patients' negative emotions, and alteration of the contextual effect (CE) (126). The placebo effect (125) associated with sham acupuncture refers to the phenomenon wherein patients do not receive genuine acupuncture treatment, yet experience symptom relief due to their "psychological belief" in the efficacy of the ineffective therapy. The mechanism of the placebo analgesic effect and acupuncture analgesia exhibits similarities. Research employing μ opioid selective tracing and positron emission tomography (PET) to examine the analgesic impact of sham acupuncture demonstrated the presence of endogenous opioids being released in areas associated with pain regulation (127), such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (rACC), and periaqueductal gray (PAG). Functional magnetic resonance imaging (fMRI) investigations have additionally demonstrated a decrease in pseudo-needle-induced signals within pain-sensitive cerebral areas, namely, the thalamus and the insular cortex, potentially associated with the alleviation of pain through pseudo-needles (128). Moreover, the placebo response elicited by sham acupuncture involving skin penetration exhibits a greater magnitude of effect compared to sham acupuncture devoid of skin penetration (129). Placebo effect of sham acupuncture incarnates the psychosomatic co-governance of Chinese medicine and also conforms to modern biological–psychological–social–medical philosophy. The anterior cingulate cortex (ACC) serves as the regulatory hub for emotional activity within the limbic system, and it exhibits fiber connections with various brain regions (130). Within the ACC, there exists excitatory glutamate N-methyl-D-aspartate (NMDA), which has garnered considerable interest in the context of pain aversion. Specifically, the NR2 subtype of NMDA is implicated in the modulation of nociceptive perception within the central nervous system and assumes a pivotal role in the development of pain. Acupuncture has been shown to decrease the levels of NR2A and NR2B proteins in the ACC brain region, resulting in a reduction in the excitability of ACC neurons. This downregulation of phosphorylation levels in the ACC contributes to the alleviation of pain aversion and ultimately diminishes the pain experience in patients (131, 132). Contextual factors (CFs) are components of all therapeutic encounters and may constitute the entirety of the perceived effects of the intervention itself or be additive to effects of interventions such as pharmacological and non-pharmacological treatments (133). CFs are perceived cues that affect both the patient and practitioner. Different categories of CFs exist, encompassing patient characteristics, practitioner characteristics, treatment characteristics, the dynamics between the patient and practitioner, and the setting in which the encounter takes place. The size of the observed clinical effects related to CFs can vary significantly based on the patient's attributes, the practitioner involved, the specific condition being addressed, and the intervention employed. Notably, acupuncture treatment presents a unique challenge in blinding, resulting in a heightened expectation-related placebo effect compared to other placebos (134). For instance, the acupuncturist's expertise and effective communication foster positive treatment expectations, which frequently correlate with improved treatment outcomes. A significant percentage of postoperative pain relief may be attributed to patients being informed about how the acupuncture therapy will likely impact on their postoperative pain, thus channeling an effective placebo response (135). Expectation-dependent placebo responses are, in principle, mediated by the endogenous opioid system, and the ventromedial prefrontal cortex (vmPFC), the dorsolateral prefrontal cortex (dlPFC), the lateral orbitofrontal cortex (lOFC), hypothalamus,

and periaqueductal gray are generally regarded as crucial (136–138). The expectation-dependent placebo effect is similar to acupuncture analgesia, showing that an opioid-dependent cortical network becomes activated during a placebo response. The challenge of managing patients' expectations in musculoskeletal pain remains a significant issue. Clinicians must carefully determine the appropriate timing and approach to address negative expectations, weighing the potential benefits of minimizing nocebo effects against the potential risks of jeopardizing the therapeutic alliance and increasing drop-out rates. Clinicians may use the intensity of patients' expectations as a gauge to determine whether a direct challenge (i.e., optimization) or an indirect challenge of their beliefs (i.e., violation) is more appropriate, to preserve the therapeutic alliance and avoid damages (139).

Currently, total knee arthroplasty stands as the most efficacious intervention for advanced rheumatoid arthritis (RA), a prevalent inflammatory arthropathy (IA). It is noteworthy that a significant proportion of patients undergoing total knee arthroplasty for advanced RA present with comorbidities. A meta-analysis (140) reveals a substantial rise in the prevalence of fibromyalgia (FM) among individuals with inflammatory arthritis, with rates reaching 18–24% in those with RA. FM is typified by widespread and enduring musculoskeletal pain, frequently accompanied by psychological conditions such as anxiety and depression (141). The studies have found objective alterations or dysfunctions of the large Aβ and of the group of thin Aδ and C fibers (the so-called "small-fibers") in approximately 50% of FM patients (142). It is believed that the analgesic effects of electroacupuncture and transcutaneous electrical acupoint stimulation are mediated by the activation of these nerve fibers. This network meta-analysis demonstrates that acupoints, including Sanyinjiao (SP06), Zusanli (ST36), Hegu (LI04), and Taichong (LR03), exhibit potential for pain management following TKA. Specifically, acupuncture at Sanyinjiao exhibits the ability to mitigate hyperactivity within the hypothalamic–pituitary–adrenal (HPA) axis by reducing serum levels of norepinephrine and cortisol, thereby ameliorating non-specific symptoms associated with FM, such as insomnia, anxiety, and depression (143). Furthermore, acupuncture at Zusanli exhibits potential in the treatment of rheumatic immune diseases through immunoregulatory mechanisms and the inhibition of inflammatory cytokine release (144). Acupuncture administered at the Hegu acupoint has been found to stimulate the release of plasma β-endorphin, regulate the activity of the hypothalamic–pituitary system, and suppress both pain perception and emotional response (145). Similarly, acupuncture at the Taichong acupoint has been observed to induce alterations in brain activation signals and provide symptomatic relief for emotional and pain-related disorders (146). Consequently, acupuncture therapy not only effectively addresses postoperative pain and enhances knee function following TKA but also demonstrates clinical efficacy in the treatment of fibromyalgia, potentially exhibiting multiple therapeutic effects.

There are still some limitations in this study: (1) As a result of the distinctive characteristics inherent in acupuncture practice, certain studies failed to furnish comprehensive details regarding the specific randomization and blinding techniques employed during implementation. Since acupuncture operations cannot be blinded to patients, the principle of triple separation of clinical operators, efficacy evaluators, and statistical analysts can be utilized. (2) The risk of bias assessment of the included studies was mostly unclear, and the quality of the literature was low. Therefore, in future studies, reporting should be based on the Consolidated Standards of Reporting Trials (CONSORT) to ascertain the literature quality (147). (3) The absence of any analgesic regimen during the perioperative period for patients undergoing TKA contradicts the principles of ERAS. Consequently, a majority of the studies included in this analysis were semi-randomized controlled trials, which lacked placebo control groups. There exist variations in the parameters of EA and TEAS across different studies. Acupuncture therapy has many differences in the acupoint selection, manipulation, and frequency, which could cause heterogeneity. Well-designed subgroup analysis should have been conducted. (4) Furthermore, a majority of the studies included in the analysis were small-scale randomized controlled trials, which may introduce selection bias and implementation bias, consequently resulting in low quality of literature. (5) Due to limitations within the original literature, intervention measures were categorized into ACU + MA, EA + MA, TEAS+MA, AAT + MA, and MA interventions. The results suggest that combined therapies have better performance in improving the outcome indicators. However, there are many combinations of combined therapies, which will be further elaborated in subsequent studies. (6) The assessment of PPT was conducted using a restricted number of studies, potentially leading to biased outcomes. (7) The studies included in the analysis primarily emphasized the short-term effectiveness of acupuncture therapy in terms of alleviating postoperative pain and rehabilitating joint function after TKA surgery. However, the evaluation of long-term efficacy for acupuncture therapy remains inconclusive. Therefore, the overall effectiveness of acupuncture therapy in treating post-TKA pain warrants further scrutiny. (8) The majority of the studies included in this review were published in Chinese journals, which introduce a potential publication bias associated with Chinese culture.

In future research, a more detailed examination of various acupuncture therapies should be prioritized by researchers. While numerous studies have examined the mechanism and clinical outcomes of acupuncture in treating postoperative pain following TKA, there is a lack of exploration regarding the efficacy of varying acupoint selection, acupuncture depth, needle retention time, and treatment frequency. Future clinical research should prioritize investigating the regularity of acupoint selection and acupuncture methods in effectively managing postoperative pain in TKA patients and provide theoretical basis of acupuncture for the clinical treatment of postoperative pain. Furthermore, a variety of studies have explored the mechanisms of acupuncture, particularly focusing on signaling pathways and cytokines. However, the majority of studies examining signaling pathways have primarily utilized nodal signaling pathways as their subjects, resulting in a lack of coherence and comprehensiveness. Moreover, the precise signaling pathways underlying the effectiveness of acupuncture in managing postoperative pain following TKA remain inadequately understood, highlighting the necessity for expanded and comprehensive research efforts. Future investigations should integrate proteomics and genomics principles and methodologies to elucidate the specific regulatory mechanisms and distinctive features of acupuncture in TKA postoperative pain management, as well as find new clues for the treatment of TKA postoperative pain through animal studies of acupuncture.

5 Conclusion

The limitations of this study underscore the necessity for future clinical practice to address the following aspects: achieving consensus among clinicians and researchers to harmonize inclusion criteria for patient recruitment, designing study protocols and reporting results in strict adherence to the CONSORT principle, and registering study protocols on reputable registration platforms prior to trial commencement. Additional well-designed, large-sample, multi-centric clinical trials and comprehensive meta-analyses are necessary to further substantiate and enhance the validity of our results.

In general, different acupuncture therapies have advantages in terms of efficacy, safety, and patient compliance. EA + MA and TEAS+MA may be considered as optimal choices for mitigating postoperative pain in patients undergoing TKA, while ACU + MA may be preferable for enhancing postoperative knee function. AAT + MA could be regarded as an effective option for preventing postoperative nausea and vomiting, as well as dizziness and drowsiness. Moreover, the combination of acupuncture-related therapies with multimodal analgesia demonstrates significant overall benefits and safety, thus suggesting the utilization of these therapies in clinical settings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

NL: Conceptualization, Data curation, Formal analysis, Resources, Software, Writing – original draft, Writing – review & editing. GL: Data curation, Visualization, Writing – review & editing. XC: Data curation, Formal analysis, Funding acquisition, Supervision, Writing – review & editing. YX: Investigation, Resources, Writing – review & editing. YH: Conceptualization, Data curation, Formal analysis, Software, Writing – review & editing. DZ: Methodology, Software, Writing – review & editing. LW: Resources, Supervision, Writing – review & editing. SC: Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1361037/full#supplementary-material

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Catgut embedding in acupoints combined with repetitive transcranial magnetic stimulation for the treatment of postmenopausal osteoporosis: study protocol for a randomized clinical trial

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Background: To date, the clinical modulation for bone metabolism based on the neuro-bone mass regulation theory is still not popular. The stimulation of nerve systems to explore novel treatments for Postmenopausal osteoporosis (PMOP) is urgent and significant. Preliminary research results suggested that changes brain function and structure may play a crucial role in bone metabolism with PMOP. Thus, we set up a clinical trial to investigate the effect of the combination of repetitive transcranial magnetic stimulation (rTMS) and catgut embedding in acupoints (CEA) for PMOP and to elucidate the central mechanism of this neural stimulation in regulating bone metabolism.

Method: This trial is a prospective and randomized controlled trial. 96 PMOP participants will be randomized in a 1:1:1 ratio into a CEA group, an rTMS group, or a combined one. Participants will receive CEA, rTMS, or combined therapy for 3 months with 8 weeks of follow-up. The primary outcomes will be the changes in Bone Mineral Density scores, total efficiency of Chinese Medicine Symptoms before and after treatment. Secondary outcomes include the McGill Pain Questionnaire Short-Form, Osteoporosis Symptom Score, Mini-Mental State Examination, and Beck Depression Inventory-II. The leptin, leptin receptor, and norepinephrine levels of peripheral blood must be measured before and after treatment. Adverse events that occur during the trial will be recorded.

Discussion: CEA achieves brain-bone mass regulation through the bottom-up way of peripheral-central while rTMS achieves it through the top-down stimulation of central-peripheral. CEA combined with rTMS can stimulate the peripheral-central at the same time and promote peripheral bone mass formation. The combination of CEA and rTMS may play a coordinating, synergistic, and side-effect-reducing role, which is of great clinical significance in exploring better treatment options for PMOP.

Clinical trial registration: https://www.chictr.org.cn/, identifier ChiCTR2300073863.

KEYWORDS

catgut embedding in acupoints, postmenopausal osteoporosis, repetitive transcranial magnetic stimulation, protocol, randomized controlled trial

1 Introduction

Postmenopausal osteoporosis (PMOP) is a systemic metabolic disorder characterized by reduced bone mass, degenerative alterations in bone tissue microstructure, and an elevated risk of bone fragility and fractures. This condition occurs in women after menopause due to ovarian dysfunction and decreased estrogen levels (1). This disease is characterized by back pain, kyphosis, height loss, spinal deformities, and pathological fractures. Osteoporotic fractures significantly contribute to increased morbidity and mortality in postmenopausal women (2). Women have a higher incidence of fractures than men, with a fracture rate twice that of men starting at age 50. Low bone mass is a significant risk factor for fractures in postmenopausal women (3). PMOP is currently a public health problem faced by the world, which not only significantly impacts the physical health and quality of life of patients but also brings a significant economic burden to the healthcare system (4). The direct medical costs of OP in the United States were estimated to be between 13.7 and 20.3 billion dollars in 2005. The price will reach 25.3 billion dollars by 2025 (5, 6).

The clinical treatment methods for PMOP mainly include medication and non-medication (7–9). Bisphosphonates are still the first-line medicine for OP, but potential long-term adverse reactions must be considered (10). A survey found that 19% of postmenopausal women diagnosed with OP did not receive anti-OP drug treatment, and 52% of patients refused the physician's recommendation for drug treatment, mainly due to concerns about the potential side effects (11). Possible adverse reactions and patient resistance severely limit the clinical prevention and treatment of PMOP. Catgut embedding in acupoints (CEA) combines traditional acupuncture with modern medical theory. Guided by the idea of 'deep and long-lasting insertion to treat chronic and stubborn diseases', absorbable surgical sutures were creatively embedded deeply into acupoints during CEA to achieve sustained stimulation. Many clinical practices and studies have confirmed that CEA for PMOP has the advantages of good efficacy, safety, and reliability (12). The CEA has apparent advantages in overcoming and solving expensive medical costs, drug toxicity, and side effects, shortening traditional acupuncture treatment time, and improving patient compliance, which is worth further research (13). However, high-quality evidence from large-scale multicenter clinical randomized trials is still needed to support the treatment outcomes.

The nervous system also plays a regulatory role in bone remodeling and maintenance of bone mass. Scholars have found many neurotransmitters and hormones related to bone remodeling in the brain or brain-related organs and proposed mechanisms for crosstalk of the brain and bone (14–16). The theory of brain-bone mass regulation is of great significance for studying bone metabolism mechanisms. The brain regulates bone mass through neural-bone formation, neural-endocrine, and neuropeptide-bone regulation networks (17). Based on the methods of the functional magnetic resonance imaging (fMRI) technique, we speculated that the brain function and structure may play a crucial role in bone metabolism with PMOP. The CEA may exert its therapeutic effect on PMOP through the functional connection of the hypothalamic nuclei with the frontal cortex (18). CEA is a peripheral stimulation that regulates bone metabolism through the bottom-up, peripheral-central-peripheral pathway.

Repetitive transcranial magnetic stimulation (rTMS) generates a robust and rapidly changing magnetic field that induces current in the target area under the coil, thus activating cortical and subcortical neurons. It regulates neuronal excitability or inhibition, evaluates the corticospinal tract, and enhances brain plasticity (19, 20). This technique has been applied to evaluate the motor system, explore brain function, and investigate the pathophysiology of psychiatric disorders (21, 22). rTMS is currently an essential neuromodulation technique that can be used directly by stimulating the central targets in order to treat neurological diseases and peripheral systemic conditions (23, 24). Based on the neuro-bone mass regulation theory, we propose a central stimulation intervention to regulate bone metabolism by using the neuromodulatory effect of rTMS. We hypothesize that the combination of CEA and rTMS may have a coordinated, synergistic, and reaction-reduced effect, which has significant clinical value in exploring better treatment options for PMOP. The prevention and treatment of PMOP should not rely solely on peripheral interventions but also focus on central involvement. It is essential to integrate central and peripheral regulation for bone remodeling with the participation of the central and peripheral nervous systems.

CEA achieves brain bone mass regulation through the bottom-up peripheral-central way, while rTMS achieves it through the top-down stimulation of the central-peripheral (25). The combination of CEA and rTMS may achieve a bidirectional central-peripheral intervention on bone metabolism (26). Consequently, the study aims to explore the clinical effectiveness and safety of rTMS combined with CEA in treating PMOP from the perspective of central-peripheral regulation. We would like to preliminarily investigate the intrinsic correlation between CEA combined with rTMS, brain bone mass regulation, and clinical signs and elucidate the central mechanism of CEA combined with rTMS in regulating bone metabolism.

2 Methods

The study protocol is designed and performed according to the principles of the Declaration of Helsinki and in line with the guidelines of the clinical trial committee for PMOP. The Consolidated Standards of Reporting Trials (CONSORT) statement[1] has been used to develop the study methodology. This study's Clinical Trial Registration

1 https://www.consort-spirit.org/

Number is (ChiCTR2300073863) and has been registered at http://www.chictr.org.cn. The protocol of this study was approved by the Ethics Committee of Bao'an Hospital of Traditional Chinese Medicine, Shenzhen (KY-2023-001-30).

2.1 Design and study setting

A total of 96 participants meeting the diagnostic criteria for PMOP according to the guidelines of the clinical trial committee will be recruited at Bao'an Hospital of Traditional Chinese Medicine. Subjects will be informed of every study detail and sign an informed consent form.

This randomized, controlled clinical trial comprises three parallel groups. It compares the effectiveness of the individualized CEA group, CEA combined with the rTMS group and rTMS groups (Figure 1).

2.2 Participants recruitment

Three ways of recruiting participants will be used: firstly, we intend to recruit the participants from the clinics of Shenzhen Bao'an Hospital of Traditional Chinese Medicine. A workshop will be convened to formulate how to collect participants. In addition, posters will be placed outside the clinic to attract potential candidates. Secondly, Another is recruiting through radio, television, newspapers, etc. In these advertisements, we will introduce the target population briefly and offer free screening and treatment to suitable participants. Thirdly, we will conduct educational talks and offer clinic services to

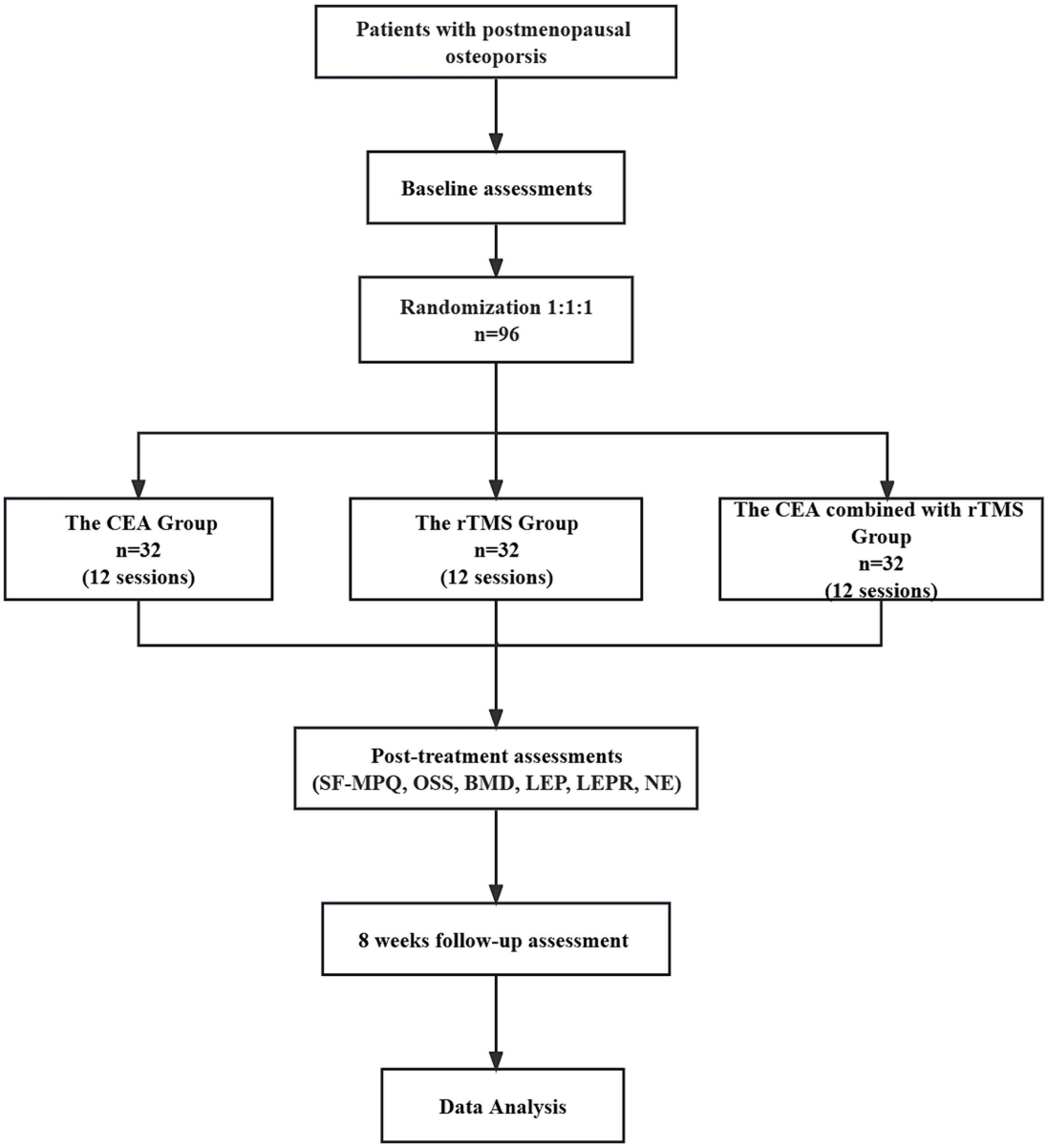

FIGURE 1
Flow chart.

postmenopausal women with OP. By disseminating basic knowledge, we may attract appropriate subjects.

2.3 Inclusion criteria

1 Patients who meet the Chinese and Western diagnostic criteria for PMOP. Western medical diagnostic criteria: Referring to the Clinical Practice Manual-Osteoporosis and Bone Mineral Disorders and the Primary Osteoporosis Primary Care Guidelines (2019) from the Chinese Medical Association, as well as the one formulated by American College of Clinical Endocrinologists (AACE) associated with the American College of Endocrinology (ACE) named as the 2020 AACE/ ACE Clinical Practice Guidelines: Diagnosis and Treatment of Postmenopausal Osteoporosis and the World Health Organization (WHO) diagnostic criteria for osteoporosis based on Dual-emission X-ray Absorptiometry (DXA) measurement. The diagnostic criteria for TCM identification are mainly formulated regarding the Guidelines for the Diagnosis and Treatment of postmenopausal osteoporosis (bone impotence) in Chinese Medicine (2019 edition). The Chinese medicine identification criteria is adopted from the Guidelines for Clinical Research on New Chinese Medicines on Kidney Deficiency formulated by the Ministry of Health of China in 2002.
2 Patients with right-handedness; junior secondary school education or above.
3 Age 45–70 years old female with natural menopause for over 2 years.
4 Those who have good compliance and understanding voluntarily join the project and agree to sign the informed consent form.

2.4 Exclusion criteria

1 Patients with diseases that do not fall into the category of PMOP or even primary OP, such as other conditions affecting bone metabolism: endocrine disorders (gonadal, adrenal, parathyroid, and thyroid diseases, etc.), immune diseases such as rheumatoid arthritis, gastrointestinal and renal diseases affecting the absorption and regulation of calcium and vitamin D, malignant conditions such as multiple myeloma, long-term use of glucocorticoids or other drugs affecting bone metabolism, various congenital and acquired abnormalities of bone metabolism, etc.;
2 Patients with malignant neoplasms, primary severe diseases of the cardiovascular, cerebrovascular, hepatic, renal, and hematopoietic systems, or either severe skin diseases or psychiatric disorders who are unable to cooperate or adhere to the completion of treatment;
3 Patients who have accepted anti-OP medication (excluding primary therapy) within the previous 6 months or who have been on the long-term and sustained use of drugs that may affect bone calcium metabolism;
4 Patients who have used psychiatric drugs such as antidepressants or anti-anxiety drugs in the past 6 months;
5 Those with structural abnormalities of the brain, such as occupying intracranial lesions, brain malformations, severe strokes (affecting brain structure), etc.;
6 Those with treatment contraindications such as allergy to CEA;
7 Those with contraindications to rTMS treatment: e.g., with aneurysm clips, implanted neurostimulators, pacemakers, automatic defibrillators, cochlear implants (electrodes) or visual foreign bodies, head-mounted with metal materials, etc.;
8 Those with a history of alcohol, drugs, or other kind of substance abuse or dependence within 1 year;
9 Those with creatinine clearance <35 mL/min;
10 Those who are unable to adhere to the treatment.

2.5 Drop-out and exclusion criteria

For those who did not complete the trial within 12 weeks±5 days, categorization will be made according to the reason for not completing the trial.

2.5.1 Drop-out

Including patient self-withdrawal due to poor efficacy, intolerance, refusal to account, loss to follow-up, and doctor dissuasion due to poor adherence, comorbidities, specialties, adverse reactions, etc.

2.5.2 Exclusion criteria

a Those who do not meet the inclusion criteria and are mistakenly included;

b Subjects with poor adherence, not following the designed treatment regimen strictly, or whose something would affect the observed results of the study during the trial;

c Subjects with incomplete information on various materials.

2.5.3 Confounding factors

The protocol prohibits a combination of anti-OP drug.

2.5.4 Discontinuation criteria

a Subjects who have experienced a severe adverse reaction or event that prevents them from continuing to be under treatment;

b Subjects who develop severe comorbidity or other systemic serious medical conditions during the trial and are unable to persist;

c Subjects who have poor compliance and do not cooperate with the relevant treatment despite repeated explanations;

d Subjects who request to withdraw from the study on their own;

e Subjects who take other drugs privately during the treatment period, which may interfere with the study results;

f The patient lost during the follow-up period for various reasons.

2.6 Randomization and allocation concealment

First, we intend to generate a random number table from 1 to 120 in Excel and made random number cards. Secondly, we paln to mark the random numbers and groups on the cards following the correspondence principle, putting them in opaque envelopes and disrupting the order of the envelopes. Then, all envelopes are to be placed into a box. Outpatients who met the inclusion criteria in the Rehabilitation Department of Shenzhen Bao'an Hospital of Traditional Chinese Medicine can draw one envelope from the box in the order in which they are treated. Individuals receiving an envelope with a

number less than or equal to 96 will be eligible to participate in our study. We intend to use Excel to generate a table of random numbers from 1 to 96. Subjects from 1 to 32 are assigned to follow Catgut embedding in acupoints at the CEA group. Subjects from 33 to 65 are designated for the combined treatment group (rTMS combined with the CEA group), while the remaining 32 are allocated to the rTMS group. Patients are randomly divided into three groups, each comprising 32 individuals. Each group is scheduled to receive the corresponding treatment measures.

2.7 Blinding

A professional acupuncturist will independently operate the participants in the CEA group, while an independent professional physician is tasked with treating the rTMS group. The patients in the combined treatment group are to be treated by two trained physicians who collaborate to complete the two intervention plans. The treatment therapists of each group could not obtain specific treatment modes for the other two groups. Upon completing the treatments for the three groups, they are to inform the evaluator of the group code corresponding to the participant. The evaluator is to conduct scale testing on the participants and collect and record data in the case report forms, without access to information about the patients' group allocations. The researchers responsible for statistical calculations are to remain blinded to the group allocations, having access only to the group codes.

2.8 Sample size calculation

This randomized controlled study evaluates the effects of three methods on postmenopausal patients with OP. Bone mineral density (BMD), McGill Pain Questionnaire Short-Form (SF-MPQ), Osteoporosis Symptom Score (OSS), Mini-Mental State Examination (MMSE), and Beck Depression Inventory-II (BDI-II), serum leptin, leptin receptor, norepinephrine level will be used as evaluation indicators. According to the preliminary test data, it was calculated that after treatment, the SF-MPQ score (PRI total score) in the CEA group decreased by 17.23 ± 2.84, that in the rTMS group decreased by 16.41 ± 1.77, and that in the CEA combined with rTMS group decreased by 17.40 ± 2.17. The two-sided test value $\alpha = 0.05$ was used. Test power $1\text{-}\beta = 0.95$. Using G*Power3.1.9.7 software and single factor analysis of variance in the F test (27, 28), the required sample size of $n = 87$ cases was calculated, and the shedding rate was set at 10%. The total sample size was 96 cases, and the required sample size for each group was 32 cases.

2.9 Interventions

Treatment strategies will be developed by consensus with experienced acupuncture practitioners and a neurologist. The trial is to include three groups: the CEA group, the combined group, and the rTMS group. The basic supplement regimen is as follows: 1000-1200 mg of calcium per day is recommended, which can be achieved through dietary intake or supplements. It is important to note that dietary calcium intake is recommended, but if dietary intake is insufficient, supplements can be used to compensate. Vitamin D intake of 800–1,000 international units (IU) per day is also recommended (29).

2.9.1 Study schedule

Baseline information on age, menopause age, weight, education, vital signs, and duration of illness will be collected and recorded (Table 1). Then, the primary outcomes will be the changes in BMD scores and total efficiency of Chinese Medicine Symptoms before and after treatment. Secondary outcomes will include the SF-MPQ, OSS, MMSE, and BDI-II every 4 weeks for 12 weeks of treatment and 8 weeks follow-up period. Adverse events that occur during the trial will be recorded. The leptin, leptin receptor, and norepinephrine levels of peripheral blood must be measured before and after treatment.

2.9.2 The CEA group

Our treatment method is based on previous literature reports (30).

The treatment group will undergo 12 weekly sessions of CEA for 3 months. The primary acupoints will be BL23, SP6, and RN4, with additional acupoints like BLI8, GB39, BL11, BL20, and ST36 added, depending on whether the case is a liver-kidney deficiency or kidney yang deficiency. During each treatment, RN4 is essential, while the other acupoints can be alternated between the left and right sides. The acupoint location method will follow the State Bureau of Technology Supervision standards. In addition, the operating procedure will be based on the National Standards of GB/T 21709.10–2008 manipulations of acupuncture and moxibustion, Part 10 Acupoint catgut embedding. Detailed information about the intervention group and acupoint location can be found in Tables 2, 3 of the STRICT checklist for reporting interventions in clinical acupuncture trials (Tables 2, 3).

2.9.2.1 CEA group materials

1 Disposable sterile burying kit: provided by the Shenzhen Bao'an Hospital supply room of Traditional Chinese Medicine.
2 Injection syringe: disposable sterile injection needle seven #(0.7*30 TWLB), Wuhan Wangguan Medical Equipment Co., Ltd.: State Food and Drug Administration Machinery (Quasi) No. 3151148, 2014.
3 Absorbable surgical suture, multi-strand braided structured polyglycolic acid PGA suture, specification: 3–0 (20metric) 1.5 cm/20 segments, [Zhejiang Kandlai Medical Devices Co. No. 3151299].
4 Andover 0.5% PVP-I Disinfectant Solution, Shenzhen Andover Disinfection High-Tech Co: Guangdong Health Disinfection Certificate (2016) No. 9087.
5 Medical Sterilization Swabs, Shun Kangzheng, Model KZ3-12, Foshan Shunde Kangzheng Sanitary Material Co. Company: Guangdong Food and Drug Administration Machinery Production License 20,010,167.
6 Aseptic Dressing, Product No.: DF-needle eye, Zhejiang Chun'an County Renhe Medical Supplies Industry and Trade Co. Zhejiang Food and Drug Administration Machinery (Permitted) Word 2014 No. 2640695.

2.9.2.2 Operating method (implantation with needles)

1 According to National Standards of P.R (GB/T 21709.10-2008), manipulations of acupuncture and moxibustion—Part 10.
2 As per the National Standards of P.R (GB/T 21709.10-2008), implanting needles for acupuncture and moxibustion involves cutting 3/0 thread into 1.5 cm pieces and soaking them in disinfectant.

TABLE 1 Trial flow and schedule: enrollment, interventions, and assessments.

Research stage			Duration of treatment (weeks)				Follow-up period (weeks)	
Inclusion/exclusion criteria			0	4	8	12	4	8
Sign the informed consent form			√					
		General information	√	√	√	√		
		Previous medical history	√					
		Clinical symptoms and physical signs	√	√	√	√		
Physical examination		Tongue manifestation, pulse, manifestation, weight	√			√		
		Vital signs: T, BP, P, R.	√			√		
Security check		Electrocardiogram	√			√		
		Liver function	√			√		
		Renal function	√			√		
		Blood lipids	√			√		
Intervention		CEA						
		rTMS						
		CEA combined with rTMS						
Efficacy indicators	Primary outcome	①BMD	√			√		
		②Total efficiency of Chinese Medicine Symptoms	√			√		
		③SF-MPQ	√	√	√	√	√	√
		④OSS	√	√	√	√	√	√
	Secondary outcome	⑤Leptin	√			√		
		⑥Norepinephrine	√			√		
		⑦Leptin receptor	√			√		
		⑧MMSE	√	√	√	√	√	√
		⑨BDI-II	√	√	√	√	√	√
Blood sample collection			√			√		
Randomization			√					
General assessment	Clinical efficacy					√		
	Compliance assessment		√	√	√	√		
	Adverse event		√	√	√	√		
	Safety evaluation		√			√		

T, Temperature; BP, Blood Pressure; P, Pulse; R, Respiration; CEA, Catgut Embedding in Acupoints; rTMS, repetitive Transcranial Magnetic Stimulation; BMD, Bone Mineral Density; SF-MPQ, McGill Pain Questionnaire Short-Form; OSS, Osteoporosis Symptom Score; MMSE, Mini-Mental State Examination; BDI-II, Beck Depression Inventory-II.

3 Patients are to be positioned prone for BL23, BL18, BL11, BL20 point implantation and supine for RN4, SP6, GB39, and ST36 implantation. After routine disinfection of the acupoint and surrounding skin with Anerdian, a self-made embedding needle is used to rapidly stick the needle into the acupoint with the right hand while the left thumb and forefinger tighten or pinch the skin around the acupoint. After receiving qi, the core is pushed, and the tubing is withdrawn slowly to complete the thread implantation deep down the acupoint. After checking for exposure of the thread out of the skin and bleeding, the wound is covered with gauze or a band-aid for 1–2 days.

4 The direction, angle, and depth of insertion must be considered to implant the needles into different acupoints properly. Acupoints such as BL23, SP6, RN4, and GB39 require a vertical puncture for approximately 0.8 to 1.0 cun (about 20-25 mm), while ST36 requires a similar punch for about 1.0 to 1.5 cun (about 25–40 mm). BL20 requires a vertical puncture of around 0.5 to 0.8 cun (about 13–20 mm), while acupoints such as BL18 and BL11 are required for proper needle insertion.

2.9.3 The rTMS group

The treatment will be completed by a trained professional therapist using a transcranial magnetic stimulator (YRD CCY-II from Wuhan Eredo). The motor threshold (MT) and dorsolateral frontal lobe (DLPFC) stimulation site are to be determined during the first treatment. The room temperature will be maintained at 16°C–23°C, and the patient will be lying flat on their side on the treatment bed. The motor-evoked potentials (MEPs) are to be recorded in the contralateral hand's interosseous muscle through the magnetic stimulator's electromyographic amplifier, with the center of the "8" coil placed on the right temporal cortex of the subject. The stimulation site and the stimulation volume are adjusted until at least 5 out of 10 stimulations evoke MEPs with an

TABLE 2 Acupoints selection.

Primary point	Additional point	
	Deficiency of liver and kidney	Deficiency of kidney yin
Shenshu (BL23) Sanyinjiao (SP6) Guanyuan (RN4)	Dazhu (BL11) Ganshu (BL18)	Xuanzhong (GB39) Zusanli (ST36) Pishu (BL20)

TABLE 3 Acupoints location.

Point	Location
BL23	1.5 cun lateral to the depression below the spinous process of the second lumbar vertebra
SP6	Posterior to the mesial border of the tibia and 3 cun above the tip of the medial malleolus
RN4	On the anterior midline, 3 cun below the umbilicus
BL18	1.5 cun lateral to the depression below the spinous process of the 9th thoracic vertebra
BL11	1.5 cun lateral to the lower border of the spinous process of the first thoracic vertebra
GB39	3 cun above the tip of the external malleolus, on the anterior border of the fibula
ST36	3 cun directly below Dubi (the lateral depression of the knee-joint) and one middle finger-breadth lateral to the anterior border of the tibia
BL20	1.5 cun lateral to the depression below the spinous process of the 11th thoracic vertebra

Cun=an acupuncture measurement unit; 1 cun corresponds to the study subject's thumb width.

amplitude more significant than 50 μV, at which point the magnetic flux is MT, and move 4 cm forward horizontally at the site where the MEPs are elicited, which is the DLPFC. We plan to utilize a positioning cap and a transcranial magnetic stimulator (YRD CCY-II from Wuhan Iredell) to accurately identify and target the specific location during the procedure (31). We intend to choose the right DLPFC point as the stimulation site. The stimulation intensity will be set at 80% of the resting movement threshold, with a frequency of 1 Hz, lasting 30s with an interval of 4 s, and 10 series to be performed continuously on the patient (32, 33). The treatment plan will consist of one session per day, 5 days a week, for 4 weeks (34, 35). Starting from the fifth week, the treatment plan changes to twice a week for eight consecutive weeks (36). In total, this treatment plan will last for 12 weeks and include 36 sessions.

2.9.4 The CEA combined with rTMS group

Subjects in this group will receive both the CEA and the rTMS treatment according to the respective regimens of the two therapies.

2.9.5 Adverse events

2.9.5.1 Mild reactions

1 Local aseptic inflammatory reactions, such as redness, swelling, heat, and pain, often occur within 1–5 days.
2 Systemic reactions may include a rise in body temperature within 4–24 h after treatment and an increase in blood count, which usually returns to normal in 3–5 days.

Most of the mild reactions are physiological after the treatment, do not need to be treated, and can be relieved on their own within a short period.

2.9.5.2 Severe reactions

1 Hot compresses can alleviate pain in the needling points.
2 Local redness, swelling, pain, fever, and other inflammatory manifestations caused by secondary infection can be resolved within 3–4 days.
3 Nerve injury can occur due to incorrect operation, over-stimulation, or carelessness but can be prevented carefully.
4 Bleeding may happen because of puncturing blood vessels or excessive stimulation. Compression bandages can be used to stop bleeding.
5 Local itching, redness, swelling, fever, etc., may be symptoms of an allergy to threads. Anti-allergic treatment can be given in such cases.

Appropriate actions are taken to address more severe reactions in accordance with the grading and management of adverse reactions in CEA (37). Effective measures include discontinuation of the trial or ethically appropriate additional mechanisms.

2.10 Outcome measurement: primary outcomes

2.10.1 BMD test

The patient's BMD of L2-L4 in the lumbar spine and BMD of the left femoral neck will be measured by DXA once before and after the treatment.

2.10.2 Total efficiency of Chinese medicine symptoms

According to the "Guidelines for Clinical Research on New Chinese Medicine," the efficacy assessment criteria for osteoporosis are as follows:

Significant efficacy: bone density examination shows an increase in bone density.

Effective: significant relief of pain, and bone density examination shows no decrease in bone density.

Ineffective: no improvement in all aspects compared to before treatment.

The efficacy index is calculated by integrating the scores before and after treatment, where the efficacy index = (score after treatment-score before treatment) / score before treatment × 100%.

The overall effective rate = (significant efficacy + effective) / n × 100%.

2.11 Outcome measurement: secondary outcomes

2.11.1 Clinical manifestation

SF-MPQ and OSS will be measured every four weeks for 5 months. All evaluation indicators will be assessed at six time points: baseline, mid-treatment (4 and 8 weeks of treatment), post-treatment (12 weeks), and 1 month and 2 months after the treatments.

2.11.1.1 SF-MPQ

The first part of the SF-MPQ consists of 15 pain descriptors, of which 11 are items about self-sense and four are about uncomfortable feelings. Each item has three levels, from 0 (painless) to 3 (severe) (Table 4).

The second part is a 10-centimeters-long visual assessment scale (VAS), marked as "painless" at one end and "intolerable pain" at the other end, on which the participants draw the level of pain (Figure 2).

The third part is the present pain level (PPI), generally used to indicate pain intensity on a scale. The Scale has five levels, from 0 (painless) to 5 (intolerable pain). PMOP patients were evaluated before and after treatment, including the current pain and how pain has been felt in the past week (Table 5).

2.11.1.2 OSS

According to the quantitative criteria for grading the significant clinical symptoms of OP in the "Technical Guidelines for Clinical Studies on New Chinese Medicines for Primary Osteoporosis." The subjects are assessed on a scale according to time points (Table 6).

2.11.2 Clinical objective indicators

The secondary outcome measures are (i) Leptin, (ii) Leptin Receptor (iii) Noradrenaline. The leptin, leptin receptor, and norepinephrine levels of peripheral blood must be measured before and after treatment.

Blood samples should be collected on the day of entry and the first day after the end of treatment for the CEA group, the rTMS group, and the CEA combined with rTMS group. Before sampling, all required tubes should be prepared and appropriately labeled with the study protocol number, subject number, study phase, period, and date and time of sampling. The authorized research nurse is responsible for collecting the blood specimens. After collection, the tubes are inverted and mixed. Blood is drawn in the order required by the collection process to prevent cross-contamination between different types of boxes. If a tube is contaminated, it should be replaced immediately with a spare tube and re-labeled. Vital signs are recorded before sampling. Blood is drawn from a venous elbow at 8:00 am in the fasting state. 3 mL of blood is collected in a pre-prepared tube, and after being centrifuged, the serum is collected for testing. 5 mL of blood is contained in a pre-prepared anticoagulation tube (20 μL/mL of peptidase, 20 μL/mL of 10% EDTA-Na2), centrifuged, and plasma collected for testing. Collect 5 mL of blood in a pre-prepared anticoagulation tube (20 μL of peptidase, 20 μL of 10% EDTA-Na2); after being centrifuged, the plasma is collected for testing.

2.12 Measures to prevent excessive loss of cases

1 Communicate in detail with patients about the trial process, provide adequate information, clarify their responsibilities and

TABLE 4 Short-form McGill Pain Questionnaire Part I.

	Pain Rating Index	None (0)	Light (1)	Medium (2)	Heavy (3)
Sensory rating	Throbbing pain				
	Piercing				
	Stabbing pain				
	Sharp pain				
	Cramping pain				
	Colic				
	Hot-burning pain				
	Continuous fixation pain				
	Swelling and pain				
	Pain caused by light touch				
	Splitting pain				
Emotional rating	Tiring-exhausting				
	Sickening				
	Fearful				
	Punishing-cruel				

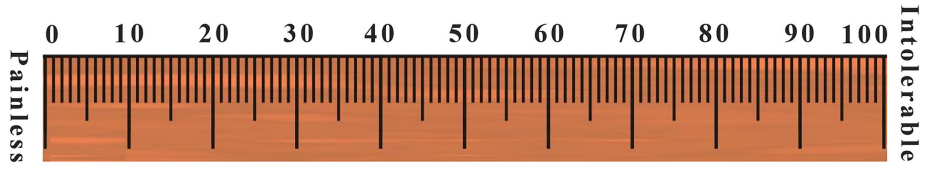

FIGURE 2
The VAS scale.

obligations and the importance of the trial, and sign the informed consent form.
2 Simplify the trial process as much as possible to reduce the burden on subjects. Reasonably arrange the time for data collection and treatment of subjects.
3 Actively respond to patients' feedback during treatment to improve patient compliance.
4 Develop standard operating procedures for data collection and measurement of subjective and objective indicators and strengthen training for investigators in data collection, communication skills, and scoring operations, which can improve patient compliance and reduce the incidence of missing data.
5 Establish a comprehensive case tracking system to ensure that case participation and follow-up can be effectively managed and recorded.

2.13 Safety assessment

Current studies about rTMS have shown few side effects. Given that this study is a low-risk intervention, small sample clinical mechanism research trial, there is no need for a dedicated data safety and monitoring committee. To ensure the rights of participants and the smooth running of the trial, we have developed a data safety and monitoring plan based on the specificity of the disease, subject population, interventions, and outcome indicators of the study. After review by the Ethics Committee, safety inspectors are appointed to track, record, report, and deal with adverse events.

Therapists need to follow the CEA process strictly to ensure the concept of sterility and safety. Comply with the graded treatment of adverse reactions to CEA, assess and effectively identify the grade of adverse reactions in patients promptly, reduce the occurrence of adverse reactions and attenuate their harm, and deal with them promptly (37). Strictly exclude contraindications to rTMS treatment, sign an informed consent form, and complete a safety screening assessment. We intend to select the intensity, frequency, and number of rTMS stimulations according to the treatment purpose since the individual differences in resting motor threshold (RMT) determination. It should be strictly limited to safe sequences and avoid sequences that induce seizures and other risks. The assessment and effective management of adverse effects during treatment should be strictly controlled. Although the current rTMS treatment has a low risk, it is still necessary to prevent rTMS-induced seizures. It has been reported that rTMS can induce seizures in both standard and epileptic patients when the stimulation frequency is between 10 and 25 Hz and the stimulation intensity is above the threshold (38). For example, if a patient experiences a seizure, treatment should be stopped immediately, and first aid should be administered. Application of rTMS near the affected ear should be avoided in patients with hearing symptoms (e.g., tinnitus or phantom hearing).

TABLE 5 Present pain intensity.

Pain Level	Description of pain intensity
0	Painless
1	Mild pain (occasionally annoying due to pain)
2	Moderate pain (often annoying but tolerable with restraint)
3	Severe pain (can only tolerate partial pain)
4	Terrible pain (severe pain, often causing moaning)
5	Unbearable pain (feeling the pain too much to commit suicide)

2.14 Statistical analysis

The data will be recorded and checked for accuracy, and the data related to baseline and clinical symptoms will be statistically analyzed using SPSS 27.0 software. The *t*-test will be performed for customarily distributed measures that meet the chi-squared test, and the *t'*test will be conducted for standards that meet the normal distribution but do not meet the chi-squared test. Independent sample *t*-tests are used between two groups, and paired sample *t*-tests will be used for pre-treatment and post-treatment comparisons within groups. Non-normally distributed measures are described by "median (interquartile range)" [*M (IQR)*], and non-parametric tests will be performed. *The Mann–Whitney U* test will compare two independent samples, and the *Wilcoxon Z* test will be used for pre-and post-treatment-comparisons. The scale scores at more than three of these time points are compared using repeated measures *ANOVA*. Correlations will be expressed as correlation coefficients (*r*). Correlations between the two measurement variables will be analyzed by Pearson correlation analysis if they conform to a normal distribution and Spearman analysis if they do not obey a normal distribution. Given that our study defines two primary outcomes, a Bonferroni correction will be applied, thus adjusting the significance level for individual outcome analyzes to $\alpha/2$ to control the overall type I error rate, setting $\alpha = 0.05$ (39).

TABLE 6 Quantitative criteria for clinical main symptom grading of OP.

Symptom	Light (score 1 points)	Medium (score 2 points)	Heavy (score 3 points)
Pain in the lower back***	1 ~ 3 degree	4 ~ 6 degree	7 ~ 10 degree
Soreness and weakness of waist and knees**	Occur after walking over 1 km	Occur after walking 300 ~ 1 km	Occur after walking under 300 m
Leg cramps**	Occur occasionally at night	Occur frequently at night	Occur frequently at day and night
Trudge*	Short-distance walking without discomfort within 100 m	Difficulty in walking short distances (10–100 meters)	Difficulty in walking (unable to exceed 10 m), or standing
Sedentary difficulty*	Less power to hold heavy	The intermediate state	Completely no power to hold heavy

① Pain level can generally be assessed by the VAS pain scale method; ② *** means score x 3; ** means score x 2; * means score x 1; ③ Subjects use diary cards to record symptoms, and the doctor communicates with the subjects after evaluation.

2.15 Dissemination

The study findings will be shared at scientific conferences and published in peer-reviewed journals. The study participants will also have the chance to receive the results through phone or email.

2.16 Trial status

Currently, the protocol is version 1.0, registered on 24 July 2023. Clinical registrations have been reviewed and approved, and we are now recruiting subjects.

3 Discussion

3.1 Feasibility analysis of rTMS combined with CEA for PMOP

The "brain-bone axis" is critical for bone metabolism, sensory innervation and endocrine connections between organs (1). The bone is rich in sensory and sympathetic innervation and interacts with the central nervous system (40, 41). The central regulation of bone mass can be divided into the following three main pathways: i) regulation of the sympathetic nervous system through neuronal signaling in the brainstem and hypothalamus; ii) the hypothalamus-pituitary neuroendocrine signaling pathway; and iii) direct action on bone cells through the hypothalamic secretion of neuropeptides (42). There is growing evidence that the nervous system plays an irreplaceable role in bone development and metabolism by directly or indirectly regulating the activity of osteoblasts (OBs) and osteoclastss (OCs) (43). Thus, based on the neuro-bone mass regulation theory, we aim to stimulate the nerve systems to explore novel treatments for PMOP.

A meta-analysis of our pre-published (44) showed that the efficacy of CEA for PMOP is equivalent to that of the drug control group and is safer. Our previous clinical trials have proved that CEA can increase serum estradiol levels and regulate bone metabolism and free radical levels in PMOP (12). Animal studies have demonstrated that CEA can alleviate oxidative stress resulting from estrogen deficiency. It exerted a regulatory effect on aromatic amino acids, specifically phenylalanine and tyrosine, and may influence the synthesis of monoamine neurotransmitters in ovariectomized rats. Notably, this regulatory effect appeared to surpass that of estrogen (45). Acupoint stimulation of bilateral Shenshu (BL 23) can increase pituitary ERα expression, reduce body weight in ovariectomized rats, and benefit the rats (46). In conclusion, Acupoint stimulation in the periphery may improve bone metabolism by modulating the level of central neurotransmitters (12).

Clinical studies have demonstrated that acupuncture with TMS therapy is more effective than monotherapy in improving clinical symptoms (47, 48). Acupuncture activates various brain regions through a bottom-up modulation approach, while TMS generates action potentials in cortical axons that spread to other neurons via synapses, resulting in neuronal activation that spreads excitation to neighboring cortical and subcortical regions (49). The combination of these two treatments creates a pattern of central-peripheral and closed-loop stimulation that is superior for improving neurophysiological function (50, 51). CEA combined with rTMS can stimulate the peripheral-central simultaneously, thus correcting the imbalance of brain bone mass regulation and promoting peripheral bone mass formation (52–54). The combination of CEA and rTMS may play a coordinating, synergistic, and side-effect-reducing role (55), which is of great clinical value in exploring better treatment options for PMOP.

3.2 Stimulating location of intervention modalities for PMOP

Prior research has indicated that bone loss is interconnected with alterations in the structure of the brain (56–60). We chose the DLPFC as the stimulating brain area based on the preliminary results of our clinical study of neuroimaging. Our previous clinical study found that the function and structure of the frontal cortex were altered in patients with PMOP. This alteration was significantly correlated with clinical symptoms. CEA may correct the bone metabolic imbalance by promoting restoring frontal cortex function in PMOP patients (18). rTMS is an effective means of stimulating the cerebral cortex for neuromodulation of the periphery (61). Based on the brain-bone mass regulation theory, we tried to use r-TMS to directly stimulate the frontal cortex to see whether peripheral bone metabolism would be altered. The DLPFC plays a vital role in the whole frontal network. It has been demonstrated that the DLPFC is associated with executing functions such as cognitive control, emotion regulation, and autonomic nervous system modulation (62). This region has been linked to autonomic nervous system modulation and endogenous pain inhibitory mechanisms (63). Based on the neuro-bone mass regulation theory, the neural networks in this region associated with the neuromodulation of bone metabolism may be an ideal stimulation target (64, 65). The DLPFC was chosen for stimulation to target effects on neural circuits associated with bone metabolic regulation (66). This option promotes restoring frontal cortex function by stimulating the right DLPFC, thereby correcting bone metabolic imbalances and improving clinical symptoms in PMOP patients.

Additionally, the technical feasibility and safety of rTMS are key factors. The right DLPFC was chosen based on its relative ease of localization and stimulation, thus ensuring the reproducibility of the trial and the accuracy of the results. Based on the brain bone mass regulation theory, this brain region is a compelling target for CEA in treating PMOP. We have reason to believe that by rTMS stimulation of this area and the effect mechanism of CEA, we can achieve bidirectional central and peripheral bone mass regulation.

3.3 Analysis of the selection of PMOP-related scales

PMOP is often called the "silent killer" due to its high incidence and elusive nature, making it difficult for patients to detect and make decisions promptly. Therefore, clinical assessment through a reliable and efficient scale is crucial. The SF-MPQ scale is a reliable, objective, and sensitive evaluation method that can score patients' pain characteristics, sensory features, emotional factors, etc.,

especially for assessing osteoporotic pain (67, 68). The scale includes emotional assessment items, such as weakness. Research has shown that OP and mental illnesses have similar biological pathways and common risk factors, such as old age, lack of physical activity, weight loss, and cognitive decline (69, 70). The symptom score of OP has a grading quantification feature, which is more detailed and scientific than other scales, and can evaluate OP-related symptoms from multiple dimensions.

Mental illnesses such as depression and anxiety are closely related to PMOP and need to be studied (71). There is a bidirectional regulatory relationship between OP and depression. On the one hand, OP causes physical pain and discomfort, leading to depression (72). On the other hand, depression accelerates the progression of OP (73). Emotional disorders such as depression and anxiety are closely related to bone metabolism. Studies have shown that chronic stress-induced emotional abnormalities cause bone loss through central nervous systems such as GABAergic neural circuits, sympathetic nervous systems, and glutamatergic neurons (74). CEA may also relieve emotional disorders such as anxiety and somatic anxiety by correcting the balance of excitatory and inhibitory amino acid neurotransmitters, which can affect the bone metabolism and play a role in treating PMOP (75). Depression is a risk factor for decreased BMD and can affect bone absorption and reconstruction processes by stimulating the sympathetic nervous system (SNS), leading to bone loss and OP. As an endocrine organ, bone can secrete bone factors that act on the hypothalamus, inducing depressive symptoms (76). The risk of cognitive impairment increases in postmenopausal women with OP (77, 78). Positive intervention can prevent or delay the occurrence of cognitive impairment in high-risk individuals. Consequently, We use the BDI-II and the MMSE to assess the psychological status and cognitive function in PMOP patients (79–82).

3.4 An exploration of the mechanisms of rTMS combined with CEA intervention in PMOP

Studies have shown that the brain-bone mass regulation is closely linked to leptin signaling (83). Leptin deficiency or resistance was associated with high BMD in mice (84). Leptin inhibits the increase in bone mass by suppressing brain-derived 5-hydroxytryptamine (5-HT) synthesis and serotonergic neuronal activity. In addition to this, the leptin increases sympathetic activity in the hypothalamus and releases the neurotransmitter norepinephrine (85). Norepinephrine binds to beta2 adrenergic receptors in bone, inhibiting bone-forming cells (OBs) activity (86). The central nervous system acts on adrenergic signaling to increase beta-adrenergic activity, reducing bone mass (87, 88). Epidemiological studies have shown that beta-adrenergic receptor blockers reduce fracture risk and increase BMD (89, 90).

In an aging or estrogen-deficient state, sympathetic excitability increases, and parasympathetic excitability decreases, resulting in an increase in norepinephrine and a decrease in acetylcholine (Ach) content in bone tissue, which stimulates osteoblast production of neuropeptide Y (NPY) by acting on the osteoclast surface receptor β2AR (91). Kajimura et al. (92) found that brain leptin signaling inhibited CREB (cAMP-reactive element binding protein) phosphorylation via sympathetic signaling in OBs, thereby inhibiting osteoblast proliferation while promoting activating transcription factor 4 phosphorylation, increasing Receptor Activator of Nuclear Factor-κB Ligand expression, stimulating osteoblast proliferation and differentiation, and reducing bone shape to promote bone resorption. Thus, leptin can reduce bone mass by regulating sympathetic activity (93). There is a complex interaction between sympathetic nerves, leptin, and norepinephrine, which can interact in several ways to influence bone metabolism.

Studies have shown that intervention with rTMS in DLPFC results in a corresponding change in leptin levels and that TMS may suppress food impulsivity in bulimic patients by modulating leptin levels (94). TMS has been found to modulate the neuroendocrine system, particularly leptin, by enhancing the PFC's inhibitory capacity, which in turn effectively reduces BMI and impulsivity (94). Electroacupuncture altered the strength of resting functional connectivity in two brain regions, dorsal caudate and precuneus, in obese patients. This change negatively correlated with lower leptin levels and body mass index (95). Studies have shown that CEA can achieve weight loss by modulating leptin levels in the hypothalamus and solitary tract nucleus and the MAPK pathway in the prefrontal cortex of obese mice (96). Therefore, we speculate that stimulation of the DLPFC by low-frequency rTMS combined with CEA therapy reduces leptin secretion, inhibits sympathetic activity, and reduces norepinephrine secretion, thereby regulating bone metabolism.

Ethics statement

This study was approved by the Medical Ethics Committee of Shenzhen Bao'an Hospital of Traditional Chinese Medicine (KY-2023-001-30). The trial was registered at https://www.chictr.org.cn/ (ChiCTR2300073863) on 24 July 2023.

Author contributions

JQ: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing. JX: Data curation, Formal analysis, Resources, Software, Visualization, Writing – original draft. YC: Data curation, Formal analysis, Methodology, Writing – original draft. ML: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. YP: Conceptualization, Data curation, Writing – original draft. YX: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision. GC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Astrocyte activation in hindlimb somatosensory cortex contributes to electroacupuncture analgesia in acid-induced pain

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Background: Several studies have confirmed the direct relationship between extracellular acidification and the occurrence of pain. As an effective pain management approach, the mechanism of electroacupuncture (EA) treatment of acidification-induced pain is not fully understood. The purpose of this study was to assess the analgesic effect of EA in this type of pain and to explore the underlying mechanism(s).

Methods: We used plantar injection of the acidified phosphate-buffered saline (PBS; pH 6.0) to trigger thermal hyperalgesia in male Sprague–Dawley (SD) rats aged 6–8 weeks. The value of thermal withdrawal latency (TWL) was quantified after applying EA stimulation to the ST36 acupoint and/or chemogenetic control of astrocytes in the hindlimb somatosensory cortex.

Results: Both EA and chemogenetic astrocyte activation suppressed the acid-induced thermal hyperalgesia in the rat paw, whereas inhibition of astrocyte activation did not influence the hyperalgesia. At the same time, EA-induced analgesia was blocked by chemogenetic inhibition of astrocytes.

Conclusion: The present results suggest that EA-activated astrocytes in the hindlimb somatosensory cortex exert an analgesic effect on acid-induced pain, although these astrocytes might only moderately regulate acid-induced pain in the absence of EA. Our results imply a novel mode of action of astrocytes involved in EA analgesia.

KEYWORDS

electroacupuncture analgesia, astrocytes, acid-induced pain, hindlimb somatosensory cortex, extracellular acidification

1 Introduction

Pain is an unpleasant signal that is associated with tissue damage and involvement of different brain structures, some of which are part of the pain matrix, including the primary somatosensory cortex (S1), primary motor and supplementary motor cortices, secondary somatosensory cortex, anterior cingulate cortex, insular cortex, prefrontal cortex, thalamus, amygdala, and hippocampus (1–9). Each of these regions plays a distinct role in different aspects of pain perception, such as the sensory, emotional, and cognitive dimensions of pain (10–12). Moreover, pain perception is not solely determined by sensory input but also by psychological factors. The prolonged pain experiences tend to induce emotional and cognitive impairments, such as anxiety, depression, and memory loss (12–14). Therefore, it is important to investigate the mechanisms of pain modulation and to use effective strategies for early control of this irksome phenomenon.

A decrease in tissue pH is observed following inflammation, ischemia, as well as infections, while the physiological tissue pH range typically falls between 7.35 and 7.45 (15, 16). Extracellular acidification can sensitize widely distributed acid-sensitive sensory neurons, making them more responsive to pain signals (13). In one article, repeated intramuscular injection of acidic saline into unilateral hindlimb muscles triggered hyperalgesia of the paw in rodents. This kind of acid-induced inflammation in the hindlimb activates pain-sensing receptors located at primary afferent fibers, transmitting pain signals to the spinal cord and ultimately to higher brain centers, including the hindlimb somatosensory cortex (S1HL) (17, 18). S1HL is organized in a layer-specific manner and has a bidirectional role in modulating subjective sensory information. Layer 6 (L6) of S1HL activation increases somatosensory sensitivity and evokes spontaneous nocifensive behavior, whereas L5 activation exerts an antinociceptive effect in inflammatory pain models (6, 19, 20). Moreover, inhibition of glutamatergic neuronal circuits from the ventral posterolateral nucleus of the thalamus to the S1HL reversed allodynia in the mice model of chronic pain (21). These studies were usually restricted to neurons of S1HL, although astrocytes exerting local regulatory activity in response to neuronal signaling molecules should be also considered as modulators of the pain pathway.

Astrocytes, which are abundant in the central nervous system (CNS), have been found to play a role in regulating neurotransmitter release and thereby inflammation. It has been reported that astrocytes are not merely passive supporting elements of nociceptive neurons, but actively participate in pain processing (22). In one study, selective activation of astrocytes in S1 reversed the aberrant pain-like behavior induced by partial sciatic nerve ligation (23). The function of cortical astrocytes in pain modulation is important for finding feasible approaches for pain management.

Due to concerns about the addiction and overdose of classical opioid analgesics, there is a continued emphasis on finding non-opioid alternatives for pain management. Acupuncture has been used to relieve acute and chronic pain for thousands of years in China. In the last few decades, electro-acupuncture (EA), namely electrical stimulation via the acupuncture needles, has frequently been used in clinics and has been proven effective in pain disorders (24, 25). Recent studies have revealed that the analgesic effect of EA in neuropathic pain took place probably through inhibiting astrocytes and microglia in the spinal dorsal horn (26), and through activating inhibitory neural circuits in the S1 (27). Therefore, we sought to investigate the potential role of EA and cortical astrocytes in acid-induced acute pain.

In this study, we assumed that EA analgesia might act by modulating astrocytic activity in the S1 to alleviate the acid-induced pain in rodents. To test this hypothesis, we first confirmed the analgesic effects of EA in the pH 6.0 phosphate-buffered saline (PBS)-induced pain model in male rats. Then, we performed selective activation or inhibition of astrocytes in the S1HL by chemogenetics, proving the moderate analgesic effects of astrocytic activation. Furthermore, EA was used after activating or inhibiting astrocytic functions, suggesting the positive correlation between astrocytes and EA. In addition to reducing thermal hyperalgesia in rats, EA upregulated the expression of glial fibrillary acidic protein (GFAP; one reactive astrocyte marker) in the S1HL. These results provide a novel view on the involvement of EA and S1HL astrocytes in early pain control.

2 Materials and methods

2.1 Animals

All experimental procedures were conducted following the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals and approved by the Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine (protocol code, DC1237, 01 January 2019). The experiments were performed on male Sprague–Dawley (SD) rats (weighing 220–250 g) aged 6–8 weeks that were purchased from Chengdu Dossy Experimental Animals Co., Ltd. Animals were housed at standard laboratory conditions (24 ± 2°C room temperature and 65 ± 5% relative humidity on 12/12 h conventional light–dark cycles) and fed with standard laboratory chow and tap water *ad libitum*. After adaptive domestication for 1 week, mice were divided into different groups based on random numbers generated by the IBM SPSS Statistic 25 software, and assigned to individual mice.

2.2 EA stimulation

EA stimulation was administered by using an electroacupuncture apparatus (HANS-200A Acupoint Nerve Stimulator, Nanjing Jisheng Medical Technology Co., Ltd., Jiangsu, China) at roughly the same time of the day (10:00 a.m. to 12:00 p.m.). One stainless-steel acupuncture needle (0.25 × 25 mm, Hwato-Med. Co., Jiangsu, China) was inserted into the left "Zusanli" acupoint (ST36), located about 6 mm down from the left fibular head, with a depth of 5–8 mm (Figure 1A). Another needle was applied to the region without acupoints, namely the stump of the tail. The position of ST36 in rats corresponds anatomically to its location in humans. For sham EA at ST36, the needle was inserted 2–3 mm deep into the skin dermal tissue and left there for 30 min, without any electrical stimulation. In the case of EA, the negative output of the stimulator was connected to the needle at ST36, and the auxiliary needle was connected to the positive output of the stimulator. The electrical current range was set at 1 mA, with a frequency of 15 Hz for 30 min (Figure 1A). The rats were immobilized by a self-made device during treatment (28).

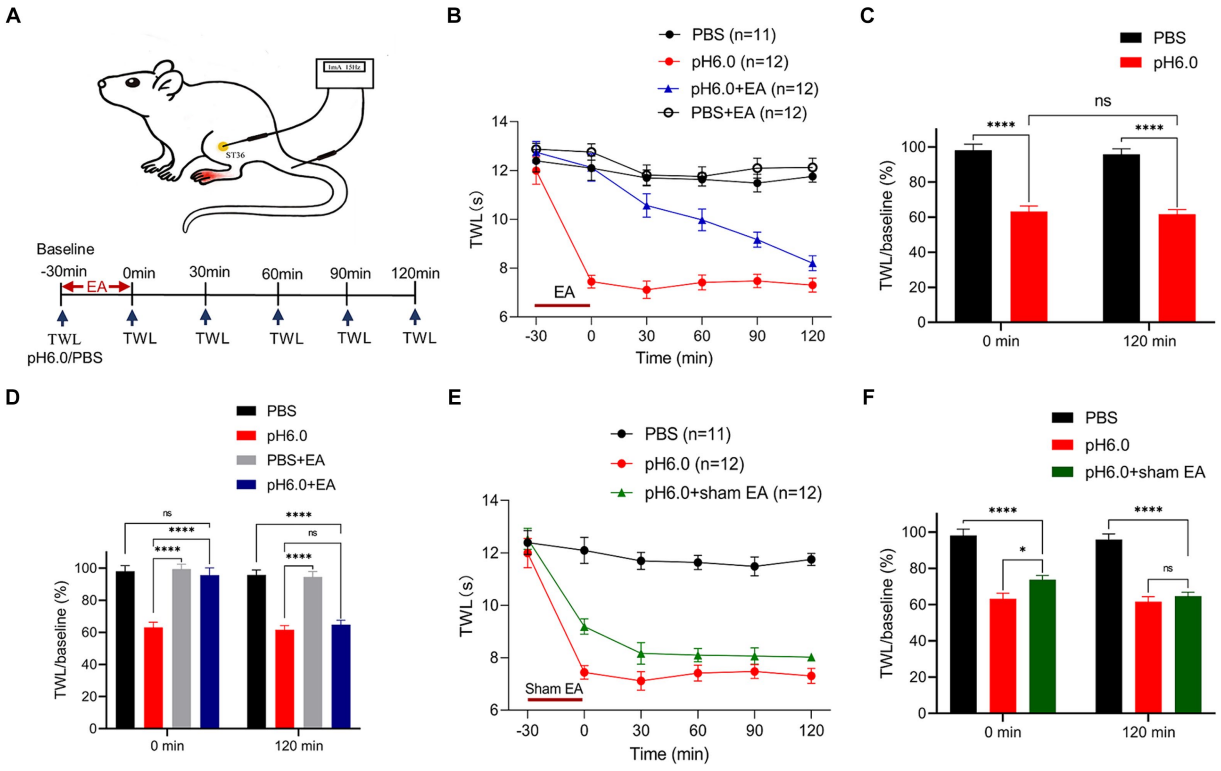

FIGURE 1
Electroacupuncture (EA) stimulation had an analgesic effect on pH 6.0-induced pain as measured in the left hind paw of rats. **(A)** Schematic diagrams showing the location of the "Zusanli" acupoint (ST36) and EA treatment in the rat, as well as the experimental timeline. **(B)** Time-dependent changes of thermal withdrawal latency (TWL) values after the application of normal or pH 6.0 phosphate-buffered saline (PBS) into the left hind paw and accompanying EA stimulation at ST36. Ratios of TWL values measured at the indicated times and at baseline (−30 min; TWL/baseline) at the 0- and 120-min time points without **(C)** and with EA **(D)**. **(E)** Time-dependent changes of the TWL values after sham EA stimulation. **(F)** TWL/baseline ratios at the 0-min and 120-min time points after sham EA stimulation. In this and in all further Figs, means ± S.E.M. values were calculated from measurements made in the indicated number of animals, as shown in brackets. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

2.3 Acid-induced pain models and behavioral testing

The pH of PBS (Sigma-Aldrich, Shanghai, China) was adjusted to 6.0 using acetic acid (Sigma-Aldrich) and sodium hydroxide (Sigma-Aldrich). 100 μL of PBS (pH 6.0) was injected into the left hind paw of SD rats to induce plantar hyperalgesia. Plantar pain threshold was determined as thermal withdrawal latency (TWL) by using a Thermal Stimuli Instrument (PL-200, Techman Software Co., Chengdu, China). The plantar surface of the left hind paw responds to thermal laser stimulation so that withdrawal, shaking, or licking of the left hind foot becomes apparent. Each rat was tested six times, with intervals of 5 min, every 30 min, including the following six points-in-time: −30 (baseline), as well as 0, 30, 60, 90, and 120 min. pH 6.0 PBS was injected at the point of 0 min (Figure 1A). All rats were placed separately into a transparent plastic enclosure (210 mm × 210 mm × 160 mm) on the surface of a vitreous platform (800 mm × 400 mm × 165 mm) for 30 min every day to get accustomed to the experimental conditions, 3 days before behavioral testing. All behavioral data were recorded by the same investigator who was blind to the experimental grouping. Rats with less than a 30% decrease in pain threshold at time-point 0-min were removed.

2.4 Stereotaxic surgery

The SD rats were anesthetized with isoflurane (5% for induction; 2% for maintenance; RWD Life Science, San Diego, CA, USA) and their head was fixed on a stereotaxic platform (RWD Life Science). 0.5 μL of adeno-associated virus (AAV) in a glass syringe was injected bilaterally into the S1HL (stereotaxic coordinates: AP -1.2 mm, ML ± 3.0 mm, DV -2.0 mm; see Figure 2B) at a rate of 0.05 μL/min with a microsyringe pump (RWD Life Science). An additional 10 min were allowed for diffusion and prevention of backflow. At the end of the surgery, 5 mg/kg enrofloxacin (RWD Life Science) was administered subcutaneously to the animals to prevent postoperative infection, and all animals were placed on heating pads (37°C) during surgery to keep their body temperature stable.

2.5 Chemogenetic manipulation

For chemogenetic manipulation, the following viruses were used in this study: rAAV-GfaABC1D-hM4D(Gi)-EGFP (titer: 2.02×10^{12} VG/mL, AAV2/5), rAAV-GfaABC1D-hM3D(Gq)-EGFP (titer: 2.10×10^{12} VG/mL, AAV2/5), rAAV-GfaABC1D-EGFP (titer: 2.10×10^{12} VG/mL, AAV2/5, all from Brain Case, China). The specific

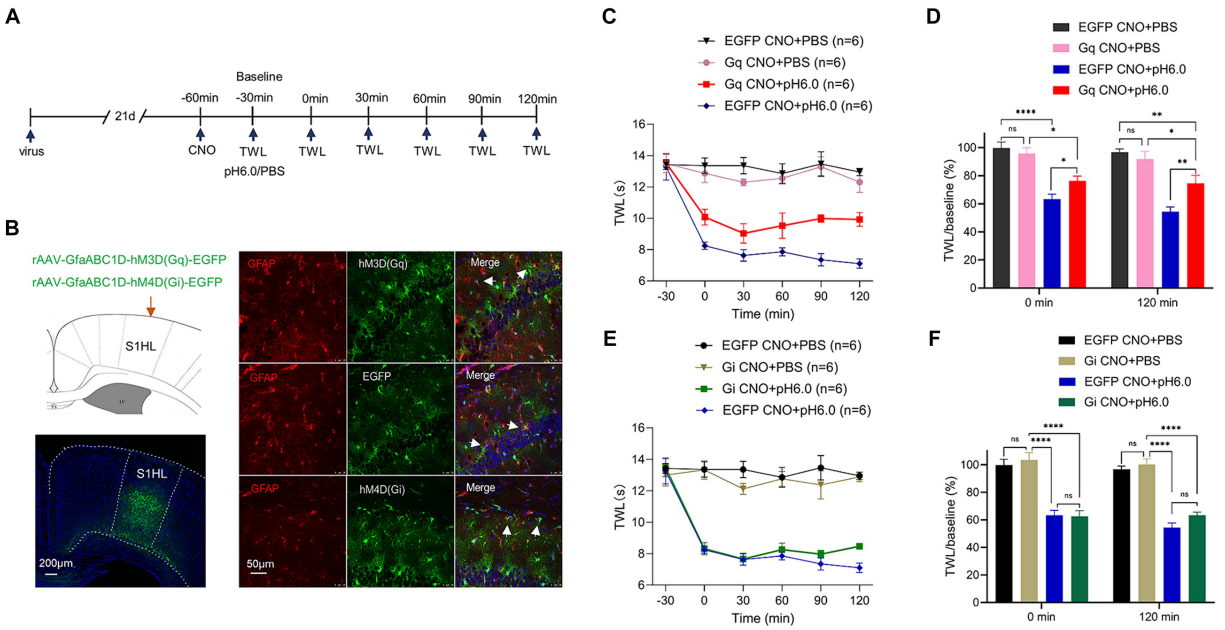

FIGURE 2
Chemogenetic activation of astrocytes in the hindlimb somatosensory cortex (S1HL) dampened pH 6.0-induced pain. **(A)** Diagram of the experimental time course. **(B)** Immunofluorescence results of viral expression in S1HL, and the co-location of the red GFAP biomarker of activated astrocytes, and the green chemogenetic protein, EGFP. Red fluorescence: GFAP; green fluorescence: hM3D (Gq), EGFP, or hM4D (Gi); blue fluorescence: DAPI. Arrowheads show co-staining of GFAP/hM3D (Gq), GFAP/EGFP, and GFAP/hM4D (Gi). **(C)** Change of TWL values after chemogenetic activation of astrocyte on pH 6.0-induced pain. **(D)** TWL/baseline ratios after chemogenetic astrocyte activation during normal or pH 6.0 PBS injection at the 0-min and 120-min time points. **(E)** Change of TWL values after chemogenetic inhibition of astrocytes on pH6.0-induced pain. **(F)** TWL/baseline values after chemogenetic astrocyte inhibition during normal or pH 6.0 PBS injection at the 0-min and 120-min time-points. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

application mode of the virus is documented in Supplementary Table 1. The expression of the virus was checked by immunofluorescence staining after all tests were finished.

At least 3 weeks were allowed to pass for the complete expression of the virus. The activity of astrocytes was modulated by the chemogenetic receptors hM3Dq (Gq) and hM4Di (Gi) (see Supplementary Table 1 for specific manipulations). Next, rats were intraperitoneally injected with 1 mg/kg of clozapine N-oxide (CNO; Sigma-Aldrich, Saint Louis, MO, USA) to activate Gq and Gi receptors and the baseline of TWL was measured 30 min later. The pH 6.0 PBS was injected into the left paw of the hindlimb after obtaining the TWL (baseline), which was determined subsequently every 30 min until the time point of 120-min (Figure 2A).

2.6 Immunofluorescent analysis

SD rats were anesthetized with 2% pentobarbital sodium (40 mg/kg; Sigma-Aldrich) and transcardially perfused with 200 mL of 0.9% NaCl followed by 4% paraformaldehyde (PFA). Their brains were prepared and fixed in 4% PFA for 24 h, then they were stored at −80°C after gradient dehydration. The collected tissues were embedded in Tissue-Tek OCT compound (Sakura Finetek, Umkirch, Germany) and cut into 15-μm-thick sections with a freezing microtome (CM1806, Leica, Zurich, Switzerland); then they were incubated with the following antibodies: Mouse anti-GFAP antibody (1: 200, Proteintech Group, Chicago, USA), Goat Anti-Mouse IgG H&L (1: 400, Bioss, Beijing, China), Goat Anti-Mouse IgG H&L/Cy3 (1: 400, Bioss). Images were acquired using a confocal laser scanning microscope (Zeiss LSM700, Oberkochen, Germany) and quantified using Image J software. The quantity of GFAP immunoreactivity was expressed as GFAP-positive area in percentage of the total area in which GFAP-labelled immunoreactivity was determined.

2.7 Statistical analysis

All values were expressed as Mean ± S.E.M. (standard error of means). The data were analyzed and plotted using IBM SPSS Statistic 25 and GraphPad Prism 9. The normality test was conducted in IBM SPSS Statistic 25; all data were normally distributed. Multiple comparisons of data were performed with GraphPad Prism 9. Multiple groups were compared by one-way ANOVA followed by the Bonferroni *post-hoc* test. The statistical significance was defined as follows: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$; *$p \leq 0.05$ was considered statistically significant.

3 Results

3.1 EA relieves pH 6.0-induced thermal hyperalgesia

To assess the analgesic effects of EA, we used the plantar injection of pH 6.0 PBS in the left hindlimb of SD rats to establish an acid-induced pain model and used the TWL test for 120 min to measure

the change of pain threshold during this time (Figure 1A). We found that every group (normal PBS, pH 6.0 PBS, PBS + EA, pH 6.0 + EA) showed a similar baseline of the TWL at the −30 min time-point (Figures 1B,E). The acidic PBS caused a pronounced fall in the TWL value, 30 min after injection to the left paw that remained stable for 120 min, although the low pH PBS was expected to become diluted constantly in the tissue; by contrast, the injection of PBS at a normal pH of 7.4 had no impact on the TWL (Figures 1B,C). The results suggested that plantar injection of pH 6.0 PBS induced acute thermal hyperalgesia, and the acid-induced pain model was successfully established.

EA treatment was applied to the ipsilateral acupoint ST36 for 30 min after injecting normal or acidic PBS (Figures 1A–D). EA abolished the effect of pH 6.0 PBS at 0 min and this antagonism continuously vanished throughout the following 120-min, when it finally was no longer apparent (Figure 1B). By contrast, EA had no effect on the TWL measured after the injection of normal PBS. Figure 1C shows that the application of pH 6.0 PBS had the same effect at 0 and 120 min when expressed as the ratio of TWL and its baseline value at these two time points. In contrast, the TWL ratio measured at 0-min did not change when EA was applied in combination with acidic PBS. Nonetheless, this effect of EA was only temporary, and completely disappeared at the 120 min time point (Figure 1D). We also investigated the effect of sham EA, and found that this treatment failed to alter the effect of the acidic PBS on the TWL (Figures 1E,F).

3.2 EA may enhance the expression of GFAP in S1HL

GFAP is the most widely used biomarker of reactive astrocytes (29). To investigate the influence of EA treatment on astrocytic activation, we conducted immunofluorescence staining and quantified the expression of GFAP in the contralateral (right) S1HL region after injection of normal and acidic PBS, applied in combination of the latter with EA or sham EA (Figure 3A). The injection of pH 6.0 PBS into the left hind paw did not change the amount of GFAP (percentage of GFAP area; see Methods), when compared with that measured after the injection of normal pH PBS (Figures 3A,B). In contrast, the application of EA after low pH stimulation, markedly increased the amount of GFAP staining (Figure 3B), probably indicating the activation of contralateral astrocytes and the consequent development of astrogliosis. The combination of pH 6.0 PBS with sham EA had no comparable effect, although the tendency of the amount of GFAP staining to increase might be due to the mechanical stimulation of subcutaneous tissue in the acupoint by the needle, without delivering an accompanying electrical current.

3.3 Astrocytic activation of S1HL alleviates pH 6.0-induced plantar pain

We next examined whether astrocytes regulated the pH 6.0-induced pain. Immunmohistochemistry showed that the chemogenetic receptors were in fact expressed in GFAP-positive astrocytes in the S1HL region within the different experimental groups (Figure 2B).

The graphs illustrate that the TWL baselines were not modified when either Gq or Gi receptors were expressed in rat brains and were afterwards activated by intraperitoneal injection of CNO (1 mg/kg) (Figures 2C,E). The stimulation of S1HL astrocytes via Gq activation failed to restore the normal TWL but slightly prolonged the time until the onset of the pH 6.0-induced paw withdrawal from thermal stimulation (Figure 2C). In partial disagreement with these findings, abolishing the influence of S1HL astrocytes by Gi-mediated inhibition did not produce any change of TWL in rats caused by acidic PBS (Figure 2E). The respective control measurement in rats whose S1HL region was infected with the EGFP-carrying rAAV, which however lacked the Gq or Gi components, did not interfere with the pain-inducing effect of normal or acidic PBS (Figures 2C,E). This becomes still better visible, when the percentage TWL/baseline ratios are being considered, as documented in the Figures 2D,F.

3.4 Selective control of S1HL astrocyte regulates the analgesic effect of EA

We have proven that the pH 6.0-induced hyperalgesia could be strongly suppressed by EA stimulation and rather moderately by astrocytic activation via Gq receptors alone. Considering the positive link between EA and astrocytes that was found in previous work (26, 27) we directed our attention to the relationship between EA-induced analgesia and astrocytic functions. To illustrate the involvement of the S1HL astrocytes in the pain control of EA stimulation, EA was applied for 30 min after activating the chemogenetic receptors Gq or Gi by CNO in the pH 6.0-induced pain model of rats.

The respective TWLs show that EA applied to rats with expressed Gq receptors in cortical astrocytes and added CNO, strongly potentiated the effect of EA (Figure 4A). This was evident also when the TWL/baseline ratios were taken into consideration (Figure 4B). To further elucidate the role of S1HL astrocytes, we repeated our experiments after inhibiting these astrocytes through the stimulation of their expressed Gi receptors by CNO. We found that inhibition of the activity of S1HL astrocytes conspicuously counteracted the analgesic effect of EA, whereas CNO administration to rats without available chemogenetic receptors (only EGFP present) was not able to remove this effect of EA (Figure 4C). As already pointed out, it is quite clear that the analgesic effect of EA was maximal at the time point of 0-min, and then gradually diminished until it disappeared at the time point of 120-min. Correspondingly, the antagonistic effect of astrocytic inhibition via Gi on EA effects was the largest at 0-min and totally vanished at 120-min (Figure 4D). This observation emphasized the involvement of astrocytes in EA-induced analgesia of acidic thermal hypersensitivity. Thus, the Gi-mediated inhibition of S1HL astrocytes suppressed, whereas the Gq- mediated activation potentiated the analgesic effect of EA against acid-induced pain.

4 Discussion

The main finding of our study is that EA applied to ST36 alleviated acid-induced muscular and cutaneous hyperalgesia through the modulation of S1HL astrocytes. Specifically, S1HL astrocytes were not, or only minimally involved in the sensation of peripheral acidic pain in rats, while these astrocytes unequivocally participated in

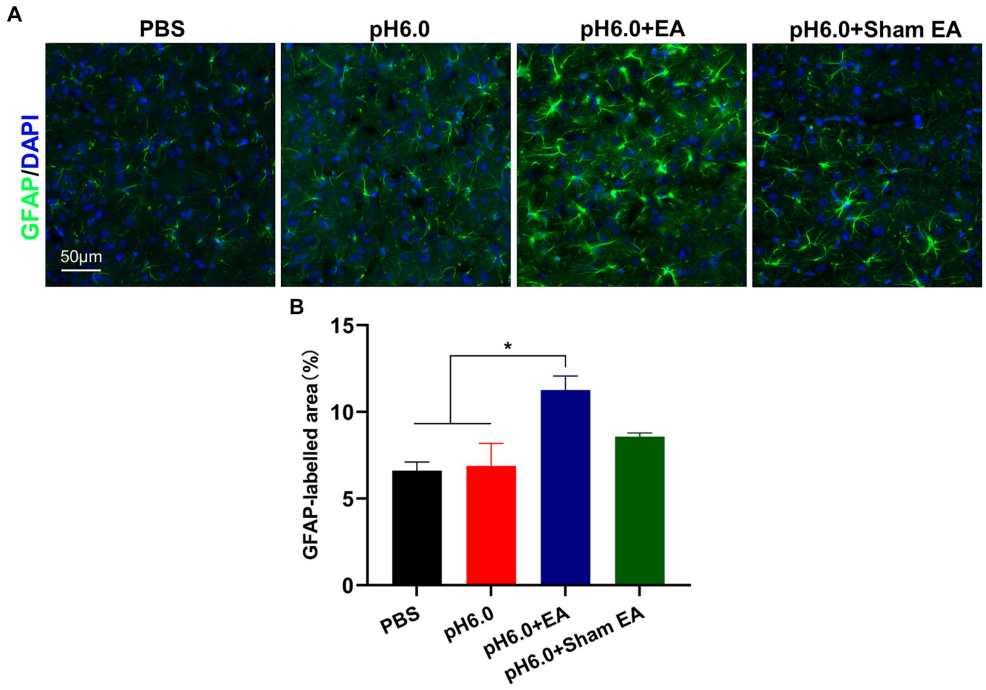

FIGURE 3
EA promoted astrocytes activation in the hindlimb somatosensory cortex (S1HL). **(A)** Immunofluorescence of GFAP expression of astrocytes after EA or sham EA in the contralateral (right) S1HL region. Green fluorescence: GFAP; blue fluorescence: DAPI. **(B)** The percentage of area with green fluorescence in relation to the total area in which GFAP immunoreatctivity was determined (n = 5).

EA-induced analgesia. Thus, astrocytes in the somatosensory cortex appear to be important stations in the pain pathway, that contribute via astrocyte-neuron interaction to EA-induced analgesia in acidic hyperalgesia.

It has been proven that tissue acidosis causes strong pain in humans and rodents (15, 16, 30). The present study utilizes a rat model in which acidic PBS was injected subcutaneously. This injection immediately decreased the TWL by approximately 40% below baseline; apparently a rapid drop of tissue pH led to localized hyperalgesia in rats. Previous investigations showed that plantar injection of pH 6.0 activated both acid-sensing ion channels 3 (ASIC3) and transient receptor potential vanilloid 1 (TRPV1) channel in rats, while mainly ASIC3 contributed to a lowering of the pain threshold (28, 31–33). ASIC3 is found to be expressed predominantly in peripheral sensory neurons and has been reported to be associated with acid-induced primary and secondary hyperalgesia (32, 34). Extracellular acidification would activate ASIC3 on primary sensory fibers to transmit the nociceptive signal through the spinal cord to S1 (26). Whether cortical astrocytes are involved in this pathway remains still unclear, especially because a few studies have reported, in contrast to our own findings, that reactive astrocytes facilitate pain transmission (22, 35). In our experiments, however, pH 6.0 injection did not upregulate the immunoreactivity of GFAP in S1HL, suggesting that acid-induced plantar pain cannot trigger the activation of cortical astrocytes. Moreover, chemogenetic inhibition of astrocytes failed to dampen plantar hyperalgesia either. Hence, our results provide evidence for the idea that cortical astrocytes participate probably only to a minor extent in the processing of peripheral ASIC3-mediated pain.

On the other hand, we found that Gi-mediated inhibition of S1HL astrocytes reversed the analgesic effect of EA stimulation, applied to ST36. By contrast, the Gq-mediated activation of cortical astrocytes had the opposite effect, and caused massive potentiation of the EA-induced analgesia. Gq-coupled receptors in astrocytes produce a sustained effect for more than 120 min, when activated by CNO (36); thus, stimulated S1HL astrocytes could produce a relatively long-lasting analgesic effect in combination with EA-induced analgesia. One astrocyte can contact thousands of synapses, which enables astrocytes to regulate local neurotransmission and extracellular microenvironment in the CNS (37, 38). For example, it has been reported that activation of S1 astrocytes by chemogenetics could reverse allodynia-like behavior previously established by partial sciatic nerve ligation. The underlying mechanism of this effect is that activation of S1 astrocytes results in synaptic plasticity of cortical circuits (23). Moreover, astrocyte activation has been found to block nociceptive transmission through the activation of endogenous adenosinergic mechanisms in the spinal cord (39). Adenosine, activating the adenosine A1 receptors (A1Rs) produces suppression of neuronal responses (40), resulting in inhibition of inflammation and pain (15, 41). Meanwhile, it is well established that astrocytes are the key regulators of extracellular levels of adenosine in the CNS (42, 43). Hence, it is likely that activated cortical astrocytes produce analgesia via adenosinergic modulation of cortical circuits. Future work should use astrocyte-specific conditional KO model mice to allow a better understanding of the biological role of adenosine in inflammation and pain.

The interaction between astrocytes and acupuncture is a frequented area of research. EA is commonly recognized to inhibit astrocyte activation and thereby to cause analgesia (44, 45). Here, we observed that EA could indeed relieve acid-induced pain, but this effect was reversed by the chemogenetic inhibition of astrocytic activity in

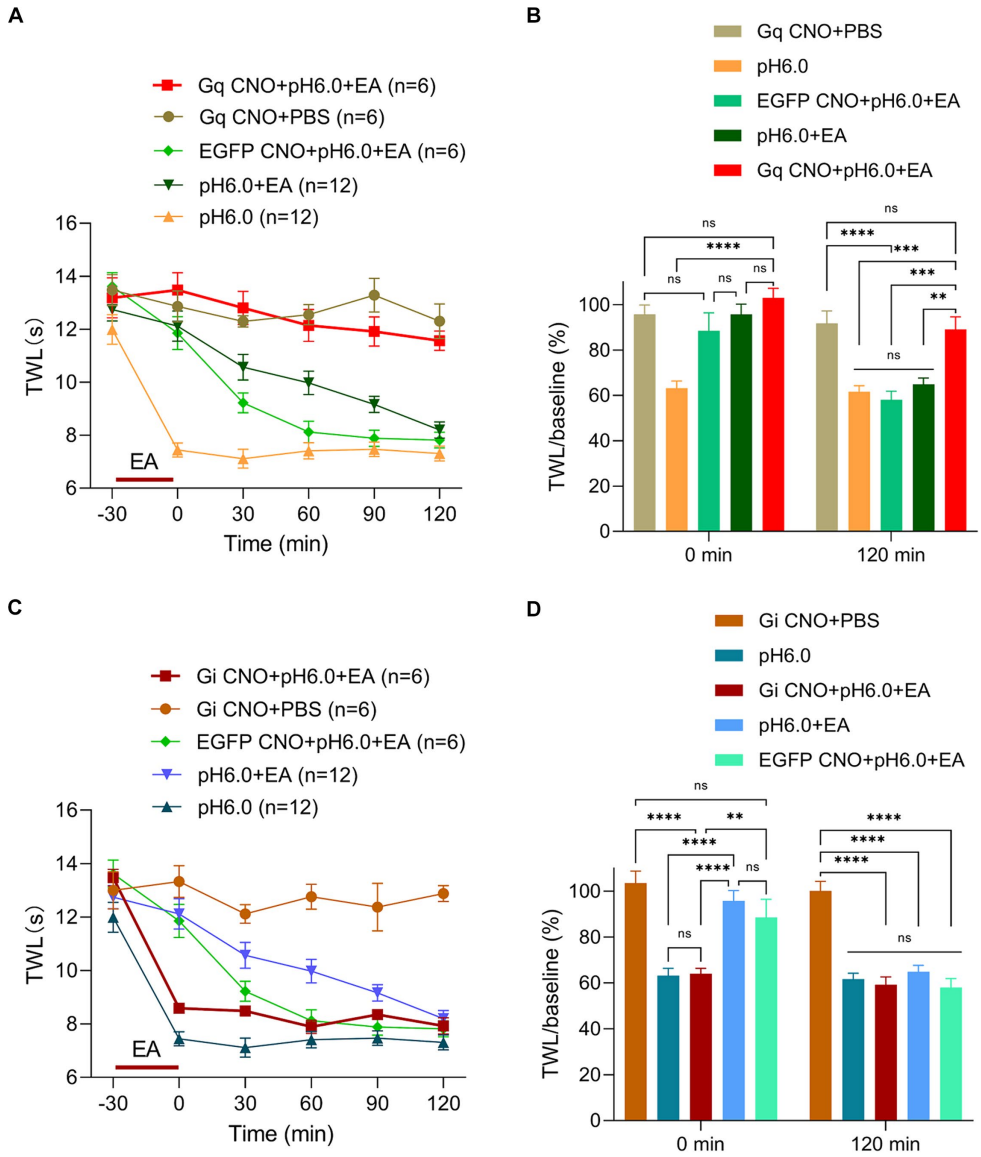

FIGURE 4
Astrocytes activation in S1HL plays a key role in EA analgesia. Experimental procedures were as described in Figure 2A and EA was applied from −30-min to 0-min, **(A)** Change of TWL values after chemogenetic astrocytes activation via hM3Dq and subsequent EA stimulation. **(B)** TWL/baseline ratios after chemogenetic astrocytes activation and EA stimulation during normal or pH 6.0 PBS injection at the 0-min and 120-min time points. **(C)** Change of TWL values after chemogenetic astrocytes inhibition via hM4Di and subsequent EA stimulation applied to the St36 acupoint on pH 6.0-induced pain. **(D)** TWL/baseline values after chemogenetic astrocytes inhibition and EA stimulation during normal or pH 6.0 PBS injection at the at 0-min and 120-min time-points.

S1HL. Thus, the astrocytic activation is essential for EA therapy of acid-induced hyperalgesia. The activation of S1 astrocytes by EA stimuli delivered to ST36 have been confirmed by the measurement of calcium transients in this area of the brain (46). In the brain cortex, activated astrocytes release ATP which is rapidly hydrolyzed to adenosine and thereby regulates synaptic transmission (47). Moreover, EA is reported to trigger the release of endogenous adenosine and to activate adenosine A1Rs at sensory nerve terminals to relieve inflammatory pain (42, 48, 49). We thus speculate that endogenous adenosine of cortical astrocytes may mediate EA-induced analgesia in acid-induced pain. The present study also showed that the combined use of EA and chemogenetic astrocyte activation potentiated the suppression of acid-induced acute hyperalgesia by EA. This brings us to the layer specificity of the cortex, as different layers may have opposite effects on pain control (6). Hence, ST36-mediated EA analgesia may rely on the astrocytic activation of one of the layers in S1HL, with some likelihood that of L5. However, in our experiments, the expression of Gq protein was observed in multiple layers of S1HL. Presently, it is not possible to decide which layer plays a decisive role in EA-mediated stimulation of S1HL astrocytes. It would be necessary to confine the expression of the Gq-carrying virus to individual layers of the S1HL to find out which cortical layer has the highest significance for EA analgesia. These finding may explain the discrepancy between our results and those of other groups of researchers (26, 27).

The present study further supports the involvement of astrocytic functions in acupuncture analgesia. It is important to note that the exact mechanisms through which EA influences astrocytic activation and acid-induced pain are not fully understood, and results may vary depending on the specific context and methodology of the studies. A limitation of our experiments is that we used only male rats, yet female rodents and humans are known to exhibit some differences in pain biology (50).

In conclusion, our data provide evidence for the assumption that cortical astrocytes exert an essential function in EA-induced analgesia of acid-induced pain. Combining EA stimulation with astrocytic activation by pharmacological means could be a viable approach for the early management of acute pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal studies were approved by the Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the owners for the participation of their animals in this study.

Author contributions

QY: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. JL: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. W-JR: Investigation, Methodology, Writing – review & editing. YZ: Investigation, Methodology, Writing – review & editing. TW: Investigation, Methodology, Writing – review & editing. PR: Resources, Writing – review & editing. H-YY: Resources, Writing – review & editing. PI: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. YT: Conceptualization, Funding acquisition, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1348038/full#supplementary-material

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Therapeutic efficacy of acupuncture point stimulation for stomach cancer pain: a systematic review and meta-analysis

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Purpose: In recent years, traditional Chinese medicine has received widespread attention in the field of cancer pain treatment. This meta-analysis is the first to evaluate the effectiveness and safety of acupuncture point stimulation in the treatment of stomach cancer pain.

Methods: For this systematic review and meta-analysis, we searched PubMed, Web of Science, Cochrane Library, Embase, WANFANG, China National Knowledge Infrastructure (CNKI), and Chinese Journal of Science and Technology (VIP) databases as well as forward and backward citations to studies published between database creation to July 27, 2023. All randomized controlled trials (RCTs) on acupuncture point stimulation for the treatment of patients with stomach cancer pain were included without language restrictions. We assessed all outcome indicators of the included trials. The evidence from the randomized controlled trials was synthesized as the standardized mean difference (SMD) of symptom change. The quality of the evidence was assessed using the Cochrane Risk of Bias tool. This study is registered on PROSPERO under the number CRD42023457341.

Results: Eleven RCTs were included. The study included 768 patients, split into 2 groups: acupuncture point stimulation treatment group (n = 406), medication control group (n = 372). The results showed that treatment was more effective in the acupuncture point stimulation treatment group than in the medication control group (efficacy rate, RR = 1.63, 95% CI 1.37 to 1.94, p < 0.00001), decreasing in NRS score was greater in acupuncture point stimulation treatment group than in the medication control group (SMD = –1.30, 95% CI –1.96 to –0.63, p < 0.001).

Systematic Review Registration: https://clinicaltrials.gov/, identifier CRD42023457341.

KEYWORDS

acupuncture point stimulation, stomach cancer pain, therapeutic efficacy, traditional Chinese medicine, meta-analysis

Background

Stomach cancer ranks as the fifth most prevalent form of cancer worldwide and stands as the third leading contributor to cancer-related mortality (1). Pain represents one of the prevailing symptoms among individuals diagnosed with cancer. Within populations afflicted by solid tumors, the collective incidence of clinically significant chronic pain varies from 15% to exceeding 75% (2). From a pathophysiological perspective, chronic cancer pain stems from two primary factors. The first is directly linked to the tumors themselves, while the second is associated with diverse anticancer interventions, including surgery, chemotherapy, and radiation therapy. Tumor expansion and pain resulting from compression constitute approximately 75% of cancer-related pain, while treatment-induced discomfort comprises about 25% of such pain. These types of pain can be further categorized as nociceptive, stemming from ongoing tissue damage, or neuropathic, arising from nerve impairment or dysfunction (3). Factors encompassing fear, anxiety, and depression can collectively contribute to heightened pain levels and occurrences of breakthrough pain (4). The World Health Organization (WHO) furnishes guidelines for the pharmacological and radiotherapeutic control of cancer pain, underscoring the judicious utilization of opioids (5). Nonetheless, the opioid crisis has exacerbated the complexities of pain management, shedding light on the necessity for nonpharmacological treatment approaches (6, 7).

Traditional Chinese medicine (TCM) has a rich history of practice and is progressively gaining broader recognition for its potential in delivering remedies and therapeutic interventions for various diseases and physiological conditions (8, 9). Acupuncture point stimulation is a general term for a class of Chinese medical therapies that have been widely used in clinical practice by intervening at acupoints, especially in alleviating perioperative pain, decreasing intraoperative stress, enhancing the body's immunity, improving patient comfort, and decreasing the incidence of postoperative complications. There are three main acupuncture point stimulation methods in relieving cancer pain, including acupuncture, moxibustion and acupoint injection. Acupuncture, as the predominant modality within traditional Chinese medicine for physical intervention, has gained widespread application in the management of chronic pain (10). Studies have shown that acupuncture may relieve neuropathic pain by inhibiting P2X7R (11). Evidence derived from clinical trials has demonstrated the safety and efficacy of acupuncture as an adjunctive therapy for alleviating cancer-related symptoms (12, 13). Moxibustion, a traditional therapeutic practice within TCM, entails the application of ignited mugwort (Artemisia vulgaris) either directly or indirectly on acupuncture points or specific body regions, with the aim of treating or preventing various diseases (14, 15). Presently, there is a burgeoning global interest and prevalence in the practice of moxibustion (16). The therapeutic technique of acupoint injection is extensively documented and has demonstrated faster and more potent clinical outcomes compared to muscle and subcutaneous injections (17). All three acupoint-related treatments play a pivotal role in the management of pain associated with stomach cancer (18).

Before this, numerous prior meta-analyses have examined the application of TCM for cancer-related pain. However, the majority of these analyses have centered exclusively on acupuncture as a methodology and encompassed studies involving pain across diverse types of cancers (19–21). Consequently, as clinical trials continue to advance, we maintain that a more targeted meta-analysis is essential to evaluate the effectiveness of acupressure point stimulation in addressing pain associated with stomach cancer. This approach encompasses well-defined outcome measures. Furthermore, our study represents the most comprehensive meta-analysis of acupressure point stimulation therapy, encompassing all pertinent recent studies available to date. Notably, this study stands as the inaugural exploration within TCM for the treatment of stomach cancer pain.

Methods

Search strategy and data mining

Literature databases including PubMed, Web of Science, Cochrane Library, Embase, WANFANG, China National Knowledge Infrastructure (CNKI), and Chinese Journal of Science and Technology (VIP) were systematically searched for randomized controlled trials (RCTs) focusing on acupressure point stimulation for stomach cancer-related pain. These searches encompassed literature published from the inception of each database up to July 27, 2023, in order to retrieve pertinent research. This search process was conducted collaboratively by two authors. In instances where disparities arose during the process, the authors would engage in consultation with a senior author to arrive at a consensus. The search terms employed were confined to "acupressure point therapy," "pain," and "stomach cancer." The keywords of interventions included "Acupressure point stimulation" OR "Acupressure point therapy" OR "acupuncture" OR "Acupuncture" OR "Electroacupuncture" OR "Fire needle" OR "Acupuncture point injection" OR "Acupressure points" and the keywords of disease included "stomach cancer" OR "Neoplasm, Stomach" OR "Gastric Neoplasms" OR "Neoplasm, Gastric" OR "Cancer of Stomach" OR "Stomach Cancers" OR "Cancer, Gastric" OR "Gastric Cancer, Familial Diffuse" and "pain" OR "Pain, Burning" OR "Suffering, Physical" OR "Physical Suffering" OR "Pain, Migratory" OR "Pain, Radiating" OR "Ache". During the search procedure, the initial step involved utilizing interventions as criteria to obtain relevant research articles. Subsequently, a similar approach was employed to retrieve results related to stomach cancer pain, and the outcomes of the first and second steps were merged. All retrieved reports from various databases were imported into a citation management software (EndNote, version 20) for subsequent analysis. No particular limitations were imposed on the types of articles included. Furthermore, an exhaustive review of all pertinent previously published meta-analyses and their reference lists was conducted. It is important to note that, to the best of our knowledge, there have been no recent updates on this topic to allow for a more precise assertion regarding the absence of recent reports. Details of the search strategies were shown in Supplementary File S1.

The selection of studies/inclusion criteria

We applied the following set of inclusion criteria during the report selection process: (1) Patients were diagnosed with "pain of stomach cancer" based on explicit diagnostic (inclusion) criteria. This criterion was irrespective of age, gender, duration, or source of cases, and patients did not have any other concurrent diseases. (2) The reports

were randomized controlled trials that investigated the use of acupressure point stimulation (which includes acupuncture, acupuncture point injection, or moxibustion) as a therapeutic intervention. (3) The assessment of patients' conditions was conducted using standardized efficacy evaluation criteria, such as Numeric Rating Scale (NRS) scores, efficacy rates, etc. Reports written in any language were eligible for inclusion. Exclusion criteria encompassed: (1) Studies involving animal experiments, (2) Repetitive experiments, (3) Studies with incomplete data (e.g., missing sections like conference abstracts), (4) Studies published prior to the year 2000, and (5) Studies in which additional treatments alongside acupressure point stimulation (e.g., acupuncture combined with traditional Chinese medicine) were applied in the treatment group.

Quality assessment

The risk of bias inherent in the included randomized controlled trials was evaluated using the revised Cochrane Risk of Bias Tool (RoB-2). For each of the following aspects, namely random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias, a determination of low, unclear (indicating some concerns), or high degree of bias was assigned. The outcomes of this bias assessment were then graphically depicted using the Revman 5.4 software.

Statistical analysis

The outcomes, including the significantly efficient rate, efficacy rate, and adverse reactions, alongside the sample sizes of the investigated studies, were input into the Revman software for conducting meta-analysis. The results were then visualized through forest plots. The level of heterogeneity was evaluated using the I^2 index, where values up to 30% indicated mild heterogeneity, 31–50% suggested moderate heterogeneity, and values exceeding 50% indicated substantial heterogeneity. In cases where effects displayed heterogeneity ($I^2 > 50\%$), a random effects model was employed for the analysis. Conversely, a fixed effects model was utilized when the data appeared to be homogeneous. The calculated outcome measures and their corresponding 95% confidence intervals (CI) were illustrated in the forest plot. To determine statistical significance, a p-value less than 0.05 was considered indicative. During the analysis, we categorized the data into three sub-groups based on different methods of acupuncture point stimulation, and performed subgroup meta-analysis accordingly. Additionally, for a more in-depth analysis of acupuncture points, we utilized the GEMTC package in R version 4.3.0. Sensitivity analysis of the study using a case-by-case culling approach. Publication bias was estimated with a funnel plot.

Results

Search results

At the outset, our search using the designated terms yielded a total of 585 potential research articles. Among these, 131 duplicate studies were eliminated through EndNote 20. Upon reviewing the titles and abstracts, 404 studies were identified as irrelevant and subsequently excluded. Furthermore, 307 citations were discarded due to their nature as reviews or conference materials. Subsequently, a thorough examination of the full text was conducted for 109 articles. Among these, 94 were excluded for reasons such as involving combination medications, excessive time since publication, being retrospective studies, or not being pertinent to stomach cancer and acupuncture point therapy. A meticulous evaluation of the full text was then undertaken for the remaining 15 citations. In this phase, an additional 4 studies were excluded due to insufficient data. Ultimately, after careful scrutiny, a total of 11 clinical studies met the criteria and were deemed suitable for inclusion in the meta-analysis (22–32) (Figure 1).

Characteristics of the included studies

The studies incorporated in Table 1, from which the clinical data were extracted, were published within the time frame spanning 2002 to 2022. All of these studies were conducted within China. The collective of 11 randomized controlled trials encompassed a total of 768 patients. The patients in these studies were pathologically diagnosed with stomach cancer. Among these, 406 individuals received acupressure point stimulation treatment, while the remaining 362 were assigned to control groups. Eligibility criteria for enrollment in these studies were assessed, revealing that seven studies exclusively employed acupuncture as the therapeutic intervention for stomach cancer pain (22, 25, 26, 28, 30, 32). In these six papers, all acupuncture treatments used silver needles to puncture the relevant acupuncture points, rather than using newer acupuncture treatments such as electrical or thermal stimulation. One study used electroacupuncture as an intervention (24). Two studies implemented acupuncture injections for 63 patients (27, 29), and two studies employed moxibustion for addressing stomach cancer pain (23, 31). Within the control groups, seven studies adopted the World Health Organization's recommended three-step analgesia approach (22, 23, 25, 26, 28, 30, 31). Two studies utilized Dumeraldine injections (27, 29), one study administered fentanyl (32), and another study employed conventional pain relief methods (24). Regarding the nature of stomach cancer pain, one study concentrated on postoperative pain following stomach cancer surgery (24), while a study looked at stomach cancer outbreak pain (28). The remaining studies pertained to chronic pain associated with stomach cancer.

Quality assessment

The results of the methodological assessment are shown in Figure 2. Of the 11 studies that referred to random allocation methods, 4 were assessed as low risk because they used a table of random numbers (22, 24, 28, 31), 5 were categorized as unclear risk of bias because they provided insufficient information, and 2 were classified as high risk because they grouped patients in the order of their admission to the hospital (25, 30). None of the 11 studies described the allocation concealment process in sufficient detail to be judged as unclear risk of bias. In 11 studies, blinding of subjects or administrators was not possible because of significant differences in the use of acupuncture treatment between treatment and control groups (22–32). The completeness of the outcome data of all studies was judged to

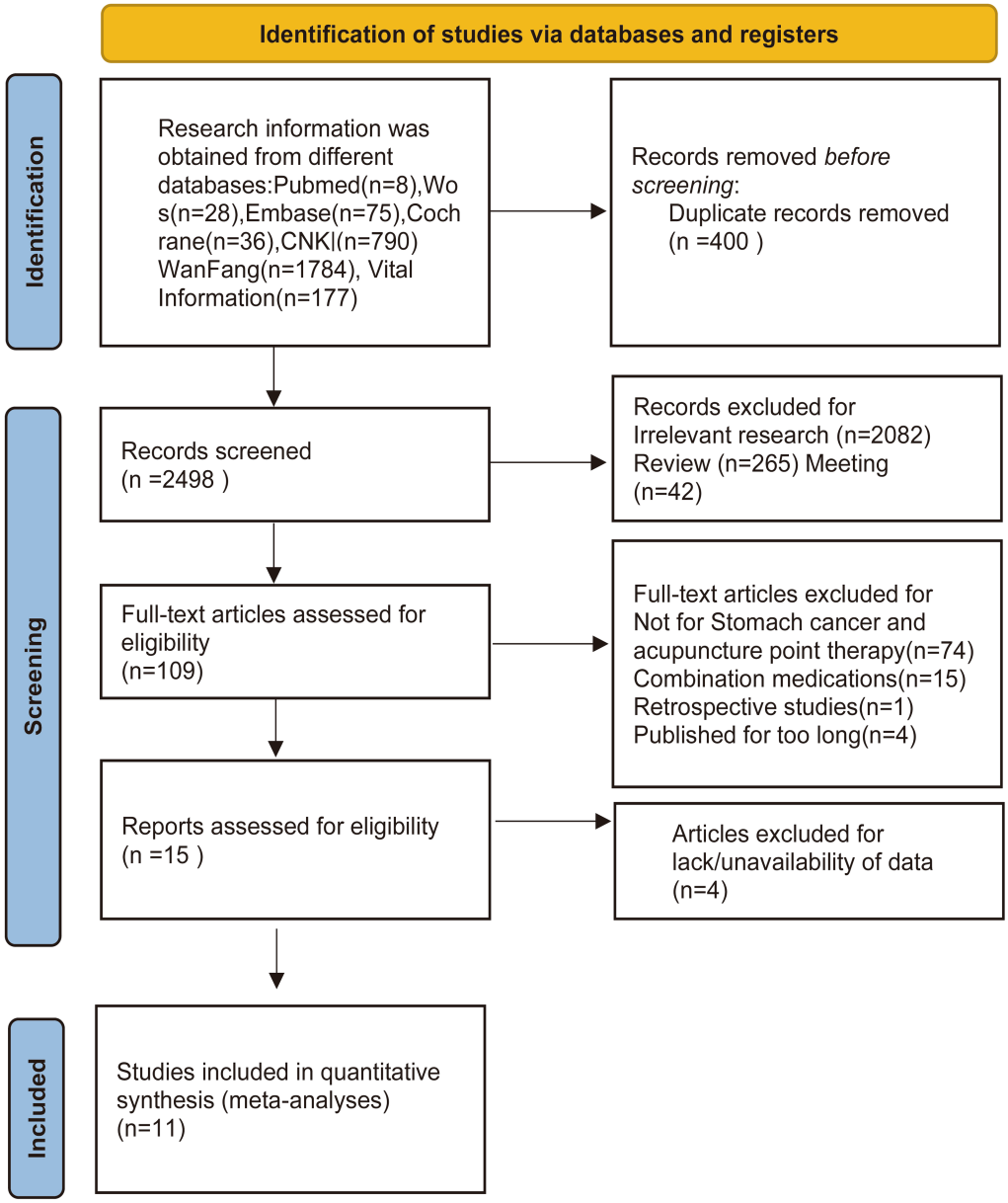

FIGURE 1
Flow diagram showing the screening and selection process of reports to be included in the meta-analysis.

be at low risk of bias. Eleven studies were categorized as having a low risk of bias for selective reporting because all prespecified endpoints were reported and were rated as having a low risk of bias for selective reporting. Two studies (27, 29) were rated at high risk of bias for selective reporting because the endpoints were poorly reported. There were insufficient data to judge other risks of bias in 11 studies (22–32) (Table 2).

Results of individual studies

Effects on NRS score of patients with stomach cancer pain

In four of the studies, NRS Scores were evaluated among a total of 242 participants (22, 24, 28, 32). NRS pain score uses the Numeric Rating Scale for Pain Levels to assess the pain level of the patient. Self-rating on a 10-point scale based on the degree, which is categorized into 1–10, allows for the classification of pain into different degrees based on the corresponding number, i.e., 0 for no pain, 1–3 for mild pain, 4–6 for moderate pain, and 7–10 for severe pain. A notable observation emerged wherein the NRS Scores were lower in cases where acupressure point stimulation treatment was administered. Given the substantial heterogeneity detected between these studies ($I^2 = 82\%$, $p = 0.0009$), a random-effects model was applied. The analysis demonstrated a statistically significant difference in NRS Scores (Standardized Mean Difference, SMD = −1.30, 95% CI −1.96 to −0.63, $p < 0.001$). We performed a sensitivity analysis of the results using the one-by-one exclusion method, and the results were statistically significant after arbitrarily excluding one study, indicating the robustness of the results (Table 3). This outcome suggests that the

TABLE 1 Characteristics of included studies.

Author	Country	Treatment group (males/females)	Control group (males/females)	Treatment group	Control group	Intervention duration and frequency	Inclusion outcome measures
Ban Niya-Baheti (22)	China	30 (17/13)	30 (22/8)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	Moxibustion for 20 min	NRS
Cao and Chen (23)	China	49 (27/22)	48 (23/25)	Moxibustion + Three-step Analgesia Method	Three-step Analgesia Method	Twice a day for 30 min	Analgesic effect
Gao (24)	China	30 (20/10)	30 (17/13)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	1 time daily for 30 min	NRS, Analgesic effect
Li et al. (25)	China	30 (16/14)	30 (13/17)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	Moxibustion for 30 min,1 time per day	Analgesic effect
Mi et al. (26)	China	32 (12/19)	30 (10/20)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	30 min each time, once every other day	Analgesic effect
Dou et al. (27)	China	43 (23/20)	38 (20/18)	Acupoint Injection	Intramuscular Injection	NA	Analgesic effect
Xia (28)	China	29 (25/4)	23 (16/7)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	NA	NRS, Analgesic effect
Zhan and Wan (29)	China	20 (NA)	20 (NA)	Acupoint Injection	Intramuscular Injection	NA	Analgesic effect
Zhang and Liu (30)	China	60 (44/16)	30 (18/12)	Acupuncture + Three-step Analgesia Method	Three-step Analgesia Method	2 times a day	Analgesic effect
Zou (31)	China	48 (26/22)	48 (24/24)	Moxibustion + Three-step Analgesia Method	Three-step Analgesia Method	2 times a day	Analgesic effect
Jiang et al. (32)	China	35 (17/18)	35 (16/19)	Acupuncture + Fentanyl	Fentanyl	1 time per day	NRS, Analgesic effect

acupressure point stimulation treatment exhibited superior improvement within the treatment group compared to the control group receiving conventional pain relief methods (Figure 3).

Effects on significant efficacy rate of patients with stomach cancer pain

According to the evaluation standard of pain relief effect formulated by WHO, the efficacy assessment is divided into 4 levels: (1) complete relief: the pain disappears, (2) effective relief: the pain is significantly reduced after taking the drug, which basically does not affect the patient's normal sleep, (3) mild relief: the pain is significantly reduced after taking the drug, but it has a certain effect on normal sleep, and (4) ineffective: there is no relief of the pain after taking the drug. We define complete relief and effective relief as significant effective relief. A comprehensive meta-analysis encompassing nine studies, involving a total of 648 participants, was conducted to assess the significant efficacy rate (23, 25–32). The outcomes indicated a noteworthy increase in the significant efficacy rate within the acupressure point stimulation group in comparison to the control group (Relative Risk, RR = 1.63, 95% CI 1.37 to 1.94, $p < 0.00001$). We performed a sensitivity analysis of the results using the one-by-one exclusion method, and the results were statistically significant after arbitrarily excluding one study, indicating the robustness of the results (Table 4). Of significant note, there was no detectable heterogeneity among these studies ($I^2 = 0\%$, $p = 0.68$) (Figure 4).

Effects on efficacy rate of patients with stomach cancer pain

A meta-analysis involving ten studies and encompassing a total of 704 participants was carried out to assess the significant efficacy rate (23–32). Given the observed high data heterogeneity between the two groups ($I^2 = 59\%$, $p = 0.009$), a random-effects model was employed for comparisons. We performed a sensitivity analysis of the results using the one-by-one exclusion method, and the results were statistically significant after arbitrarily excluding one study, indicating the robustness of the results (Table 4). The findings of our analysis revealed that, in comparison to the control group, acupressure point

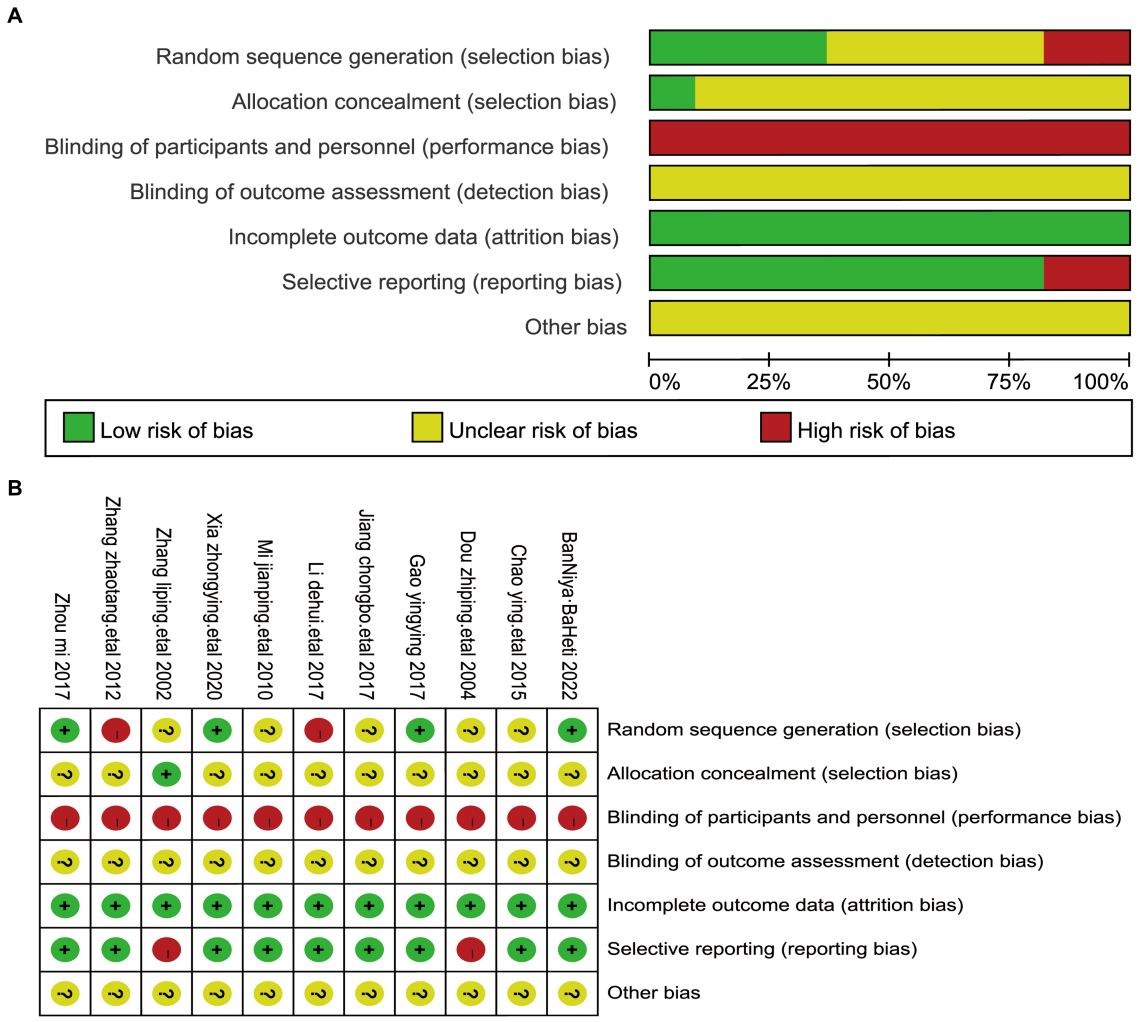

FIGURE 2
The figure represents the risk of bias assessment for the studies selected in the meta-analysis. **(A)** RoB graph: risk of bias graph—provides a visual summary of bias risk across studies, with green (low risk), yellow (unclear), and red (high risk) segments for bias categories. **(B)** RoB summary: risk of bias summary—details bias risk for each study in the meta-analysis, using colored circles (+ for low risk,? for unclear, and – for high risk) for bias categories.

stimulation led to a notably higher rate of effective treatment (Relative Risk, RR = 1.17, 95% CI 1.04 to 1.31, $p < 0.01$) (Figure 5).

Adverse reactions

A meta-analysis examining adverse reaction rates across four studies involving medication was conducted (25, 26, 29, 32). The primary adverse effects reported were nausea and vomiting. The pooled analysis of these four studies revealed that out of the 115 patients in the medication groups, 45 individuals experienced nausea (39.1%). In contrast, among the 117 patients receiving acupressure point stimulation, only 25 encountered nausea (21.3%) (Figure 6A). Similarly, across the four studies, 32 of the 115 patients in the medication groups experienced vomiting (27.8%), while only 18 of the 117 patients undergoing acupressure point stimulation therapy reported vomiting (15.3%) (Figure 6B). We performed a sensitivity analysis of the results using the one-by-one exclusion method, and the results were statistically significant after arbitrarily excluding one study, indicating that the results were robust. These findings collectively suggest that acupressure point stimulation therapy demonstrates a relatively higher level of safety when compared to the control group receiving medication.

Sub-group analysis

Sub-group analysis of the effects on significant efficacy rate

During the sub-group meta-analysis of the included studies, a classification into three distinct subgroups was performed based on the diverse methods of stimulating acupuncture points in patients with stomach cancer pain. Within these subgroups, five studies employed acupuncture (25, 26, 32, 28, 30), two studies exclusively employed moxibustion (23, 31), and two studies utilized acupuncture point injections. Upon analyzing these three subgroups (27, 29), it was observed that the significant treatment response achieved through acupuncture injections (Relative Risk, RR = 1.86) surpassed that of

TABLE 2 Quality assessment of all the studies.

Studies	Characteristics of studies						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ban Niya-Baheti (22)	Low	Unclear	High	Unclear	Low	Low	Unclear
Cao and Chen (23)	Unclear	Unclear	High	Unclear	Low	Low	Unclear
Gao (24)	Low	Unclear	High	Unclear	Low	Low	Unclear
Li et al. (25)	High	Unclear	High	Unclear	Low	Low	Unclear
Mi et al. (26)	Unclear	Unclear	High	Unclear	Low	Low	Unclear
Dou et al. (27)	Unclear	Unclear	High	Unclear	Low	High	Unclear
Xia (28)	Low	Unclear	High	Unclear	Low	Low	Unclear
Zhan and Wan (29)	Unclear	Low	High	Unclear	Low	High	Unclear
Zhang and Liu (30)	High	Unclear	High	Unclear	Low	Low	Unclear
Zou (31)	Low	Unclear	High	Unclear	Low	Low	Unclear
Jiang et al. (32)	Unclear	Unclear	High	Unclear	Low	Low	Unclear

TABLE 3 Sensitivity analysis of NRS showing pooled results after excluding one study.

Study of removal	Ban Niya·Baheti (22)	Gao (24)	Jiang et al. (32)	Xia (28)
SMD	−1.38 [−2.32, −0.45]	−0.99 [−1.46, −0.53]	−1.28 [−2.24, −0.32]	−1.54 [−2.22, −0.87]

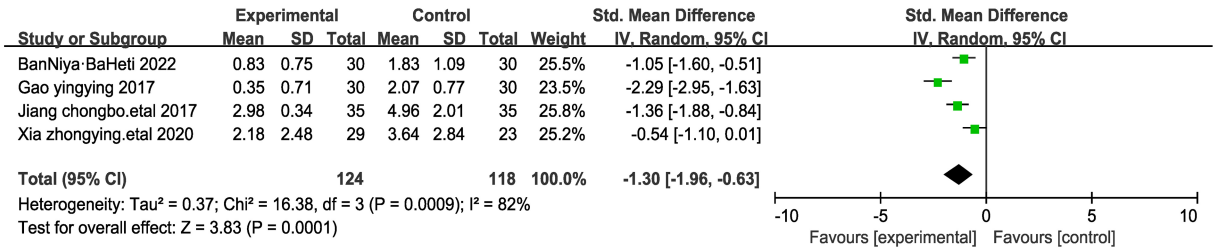

FIGURE 3
Forest plots of NRS score of stomach cancer pain after acupressure point stimulation treatment. The plot lists the included studies by the first author and publication year, showing the mean NRS scores for both experimental and control groups, along with their standard deviations and total number of participants. The weight of each study in the meta-analysis is indicated, reflecting its contribution to the overall effect size.

acupuncture (RR = 1.43) and moxibustion (RR = 1.83) (Figure 7). This pattern could suggest the potential superiority of acupuncture points in treating stomach cancer pain.

Sub-group analysis of the effects on efficacy rate

We categorized the studies into three subgroups based on the distinct methods of stimulating acupuncture points in patients with stomach cancer pain. Among these, five studies employed acupuncture (25, 26, 32, 28, 30), two studies solely focused on moxibustion (23, 31), and two studies utilized acupuncture point injections (27, 29).

In these three subgroups, the notable treatment response achieved through acupuncture injections (Relative Risk, RR = 1.31) surpassed those of acupuncture (RR = 1.08) and moxibustion (RR = 1.26) (Figure 8). Once again, these findings reinforce the positive outcomes associated with acupuncture across various acupuncture point stimulation techniques.

TABLE 4 Sensitivity analysis of efficient showing pooled results after excluding one study.

Study of removal	Cao and Chen (23)	Dou et al. (27)	Jiang et al. (32)	Li et al. (25)	Mi et al. (26)	Xia (28)	Zhan and Wan (29)	Zhang and Liu (30)	Zou (31)	Gao (24)
SMD of significant efficacy rate	1.56 [1.30, 1.88]	1.56 [1.30, 1.87]	1.69 [1.40, 2.03]	1.59 [1.32, 1.91]	1.67 [1.38, 2.04]	1.65 [1.37, 1.98]	1.66 [1.38, 1.99]	1.63 [1.34, 1.98]	1.64 [1.36, 1.98]	NA
SMD of efficacy rate	1.14 [1.02, 1.28]	1.13 [1.02, 1.26]	1.19 [1.05, 1.34]	1.18 [1.04, 1.34]	1.20 [1.08, 1.34]	1.19 [1.04, 1.35]	1.17 [1.03, 1.33]	1.15 [1.02, 1.30]	1.17 [1.02, 1.33]	1.14 [1.03, 1.28]

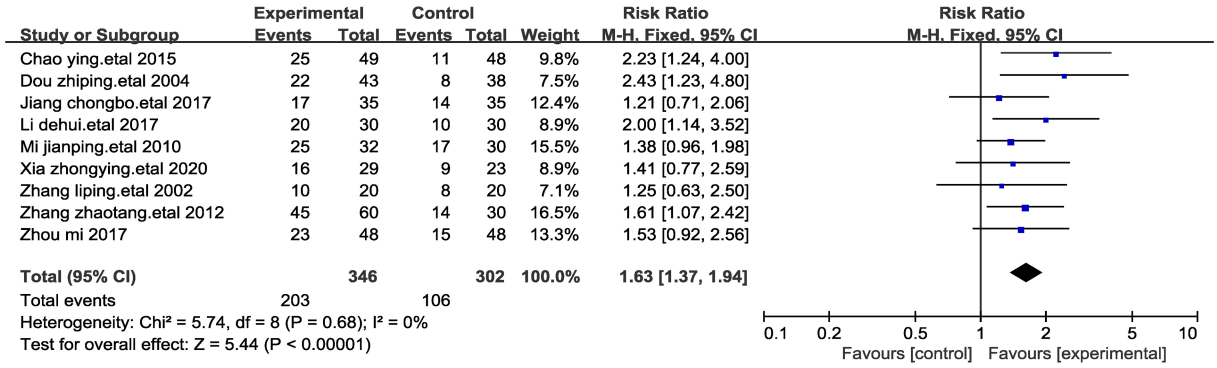

FIGURE 4
Forest plots of significantly efficient of stomach cancer pain after acupressure point stimulation treatment. The plot lists the included studies by the first author and publication year, showing the significantly efficient for both experimental and control groups, along with their risk ratio and total number of participants. The weight of each study in the meta-analysis is indicated, reflecting its contribution to the overall effect size.

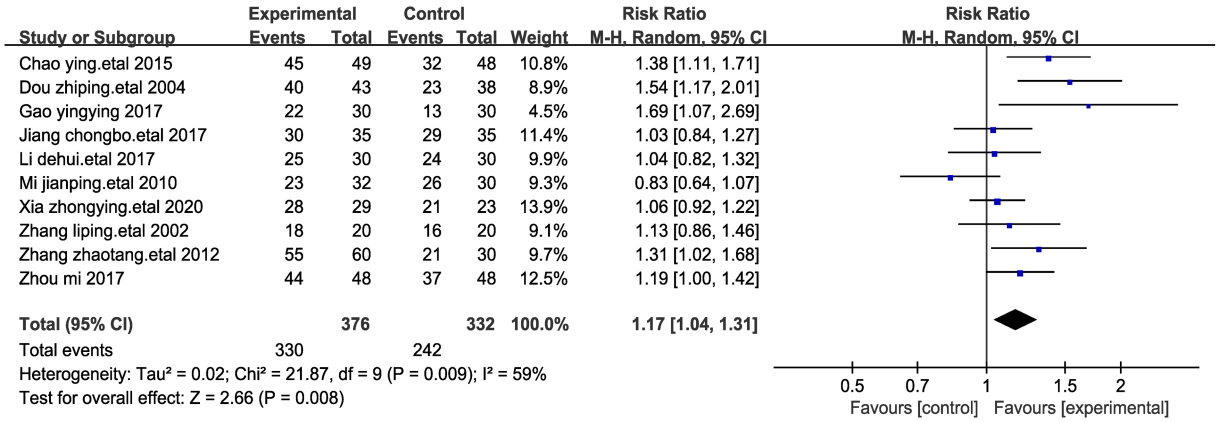

FIGURE 5
Forest plots of efficient of stomach cancer pain after acupressure point stimulation treatment. The plot lists the included studies by the first author and publication year, showing the efficient for both experimental and control groups, along with their risk ratio and total number of participants. The weight of each study in the meta-analysis is indicated, reflecting its contribution to the overall effect size.

Analysis of the frequency of acupuncture point use

We conducted a comprehensive analysis of all the acupuncture points employed in acupuncture point stimulation. Utilizing the GEMTC package in R version 4.3.0, we determined the frequency of usage for different acupuncture points. The graphical representation displayed a mesh diagram, highlighting the prominent utilization of certain acupuncture points. Specifically, the Sanyinjiao and Zusanli acupuncture points were the most frequently used. Additionally, the Zhongguan and Neiguan acupuncture points also saw widespread application. This outcome holds valuable implications for future acupoint treatments targeting stomach cancer pain, assisting medical practitioners in making informed choices regarding acupuncture point selection for treatment (Figure 9).

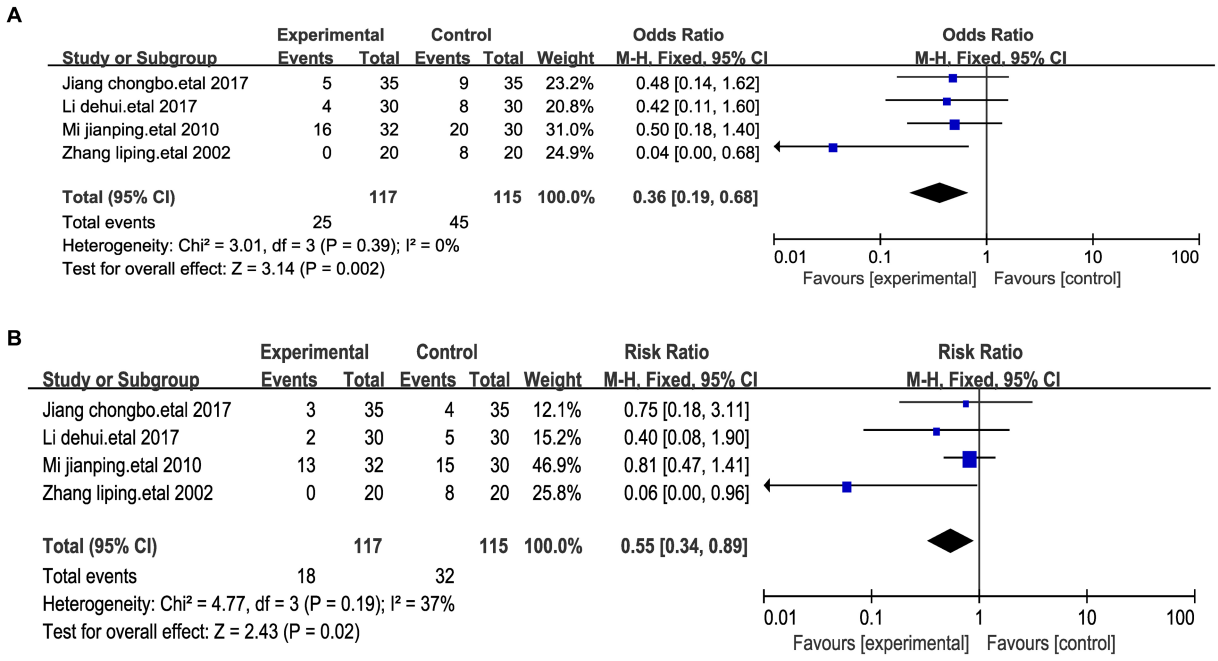

FIGURE 6
Forest plots of the adverse effects after treatment. **(A)** Forest maps of nausea. **(B)** Forest maps of vomiting.

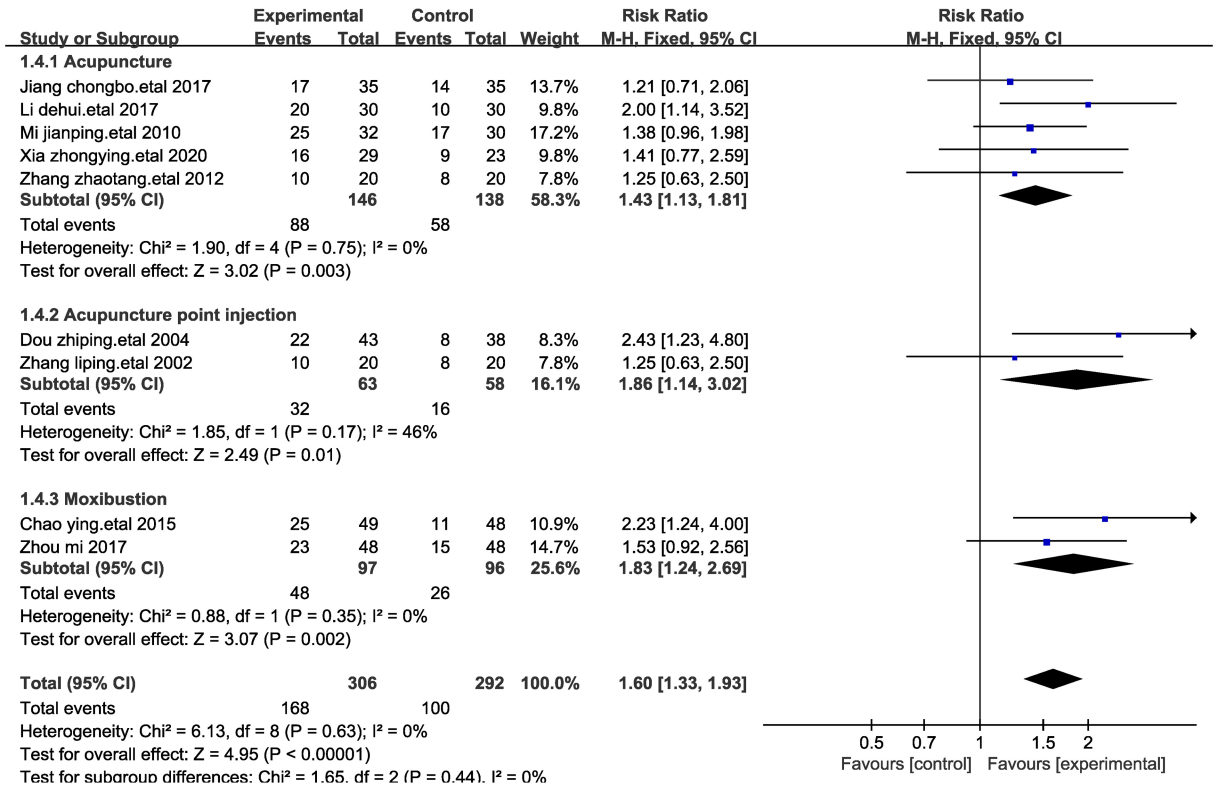

FIGURE 7
Forest plot for subgroup analysis with significant efficiency impact. This figure shows a forest plot of the different studies included in the meta-analysis assessing the effect of treatments such as acupuncture, acupoint injections and moxibustion on stomach cancer pain. Each study is listed by first author and year of publication, showing the total number of events in the trial and control groups and the corresponding weights. Risk Ratio (RR) and corresponding 95% confidence intervals (CI) provided a quantitative assessment of the effect size of each study.

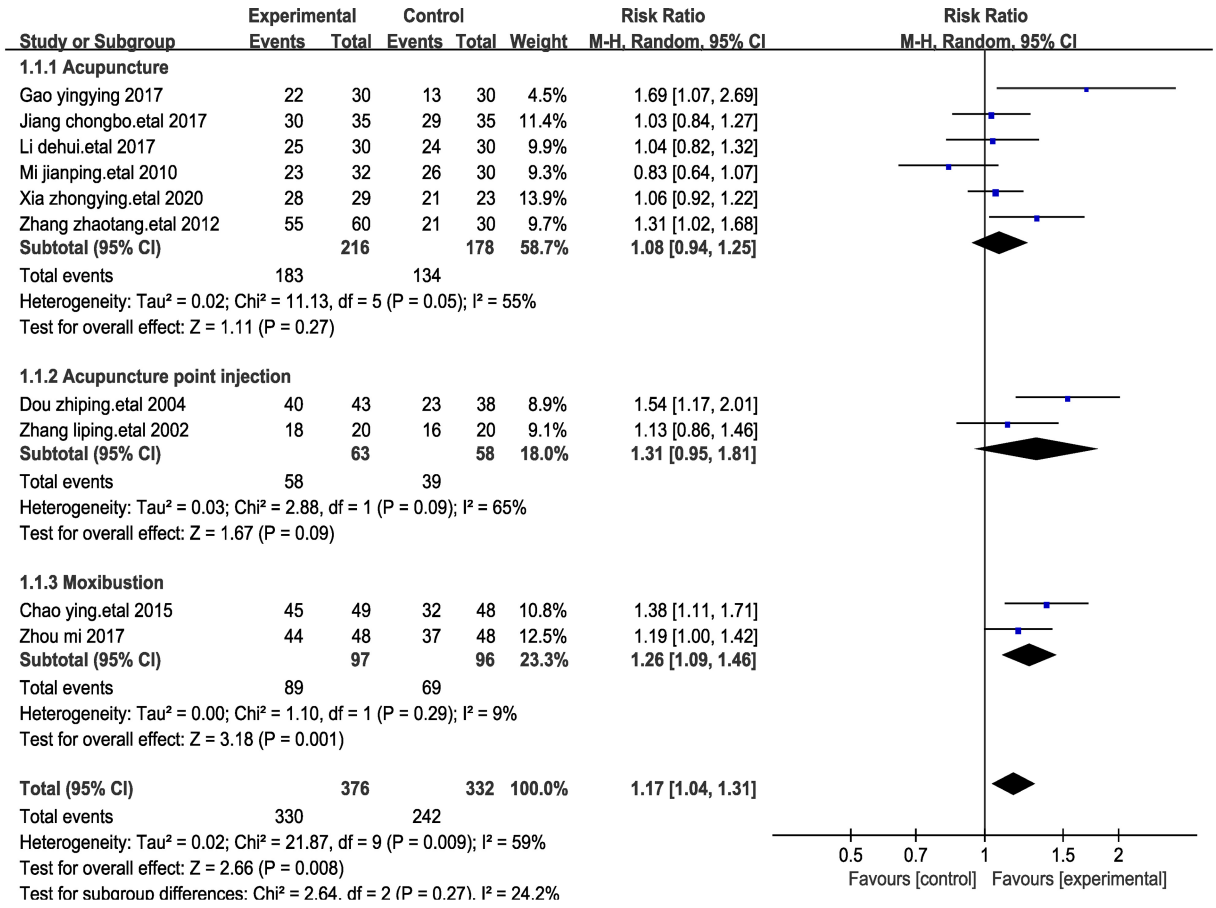

FIGURE 8
Forest plot for subgroup analysis with efficiency impact. This figure shows a forest plot of the different studies included in the meta-analysis assessing the effect of treatments such as acupuncture, acupoint injections and moxibustion on stomach cancer pain. Each study is listed by first author and year of publication, showing the total number of events in the trial and control groups and the corresponding weights. Risk Ratio (RR) and corresponding 95% confidence intervals (CI) provided a quantitative assessment of the effect size of each study.

Publishing bias

We performed a funnel plot analysis of the literature on the use of acupressure point stimulation and medication. The results showed that multiple funnel plots were asymmetric, indicating publication bias (Supplementary Figure S1).

Discussion

Before treating pain, traditional Chinese medicine such as acupuncture had been widely used to treat a wide range of ailments, and it has shown good results in different aspects. For example, within the realms of diabetes and neurological disorders, acupuncture exhibits remarkable advantages (33–36). Network meta-analyses have previously explored traditional Chinese medicine interventions, including acupuncture (37). In 2023, a scoping review of systematic reviews and meta-analyses was conducted to assess the effectiveness of acupuncture as a treatment for cancer-related pain (38). In the context of the scoping review, a total of 25 systematic reviews focusing on acupuncture for cancer pain management were incorporated. These reviews encompassed a diverse array of primary studies characterized by varying study designs and qualities. The review confirmed the efficacy of acupuncture in mitigating cancer-related pain. However, traditional Chinese medicine treatments such as moxibustion have often been neglected in the realm of cancer pain research, and pain associated with different types of cancers has rarely been examined separately. Recognizing this gap in the existing literature, we decision to conduct this meta-analysis holds significance. Through this meta-analysis, we aimed to thoroughly analyze the therapeutic effectiveness of acupuncture point stimulation specifically in the context of stomach cancer pain. This initiative contributes to filling the research void and providing valuable insights into the potential benefits of acupressure point stimulation for individuals dealing with stomach cancer pain. Acupuncture points constitute a cornerstone within the acupuncture theory of Oriental medicine, along with meridian pathways (39). Extensive endeavors have been directed towards unraveling the scientific underpinnings that govern the functions of acupuncture points and meridian pulses. For example, the characteristics of acupuncture points and meridian pulses, including electrical (40), temperature (41), anatomical (42), and photon (43) characteristics, have been identified. In addition to the direct characteristics of acupuncture points, several studies using bioimaging technology, such as electroencephalography

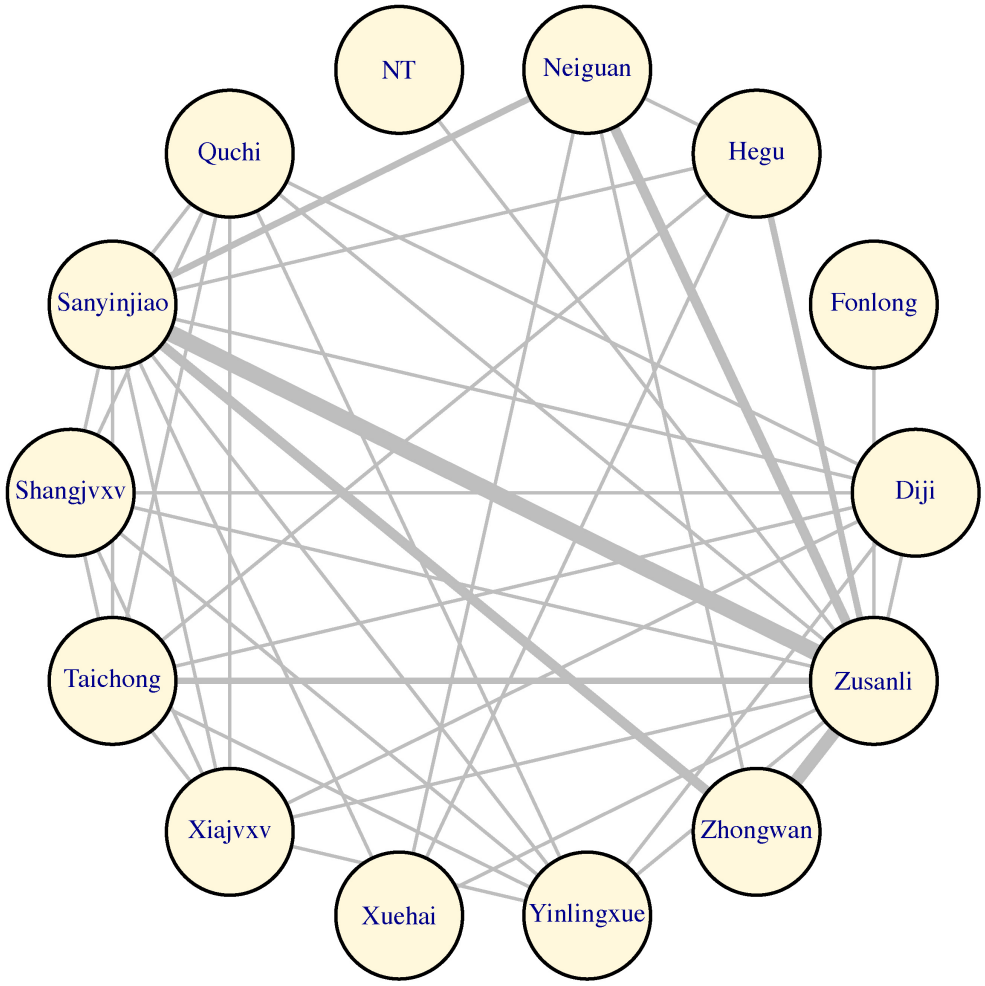

FIGURE 9
The reticulation that occurs at different acupoints during treatment. This figure represents the network relationship between different acupuncture points. Each circle represents a specific acupuncture point, e.g., "Neiguan" or "Zusanli," and the lines between them indicate interactions or correlations. The thickness of the lines may represent differences in the strength of the association, but this is not explicitly stated in the figure notes. The overall network diagram provides a visual way to understand and analyze the possible synergistic effect or combination of different acupuncture points in treatment.

(EEG) and functional magnetic resonance imaging, have evaluated the effects of the physical stimulation of acupuncture points on the human body (44–46). Indeed, acupuncture points also serve a role in analgesia. A previous study showcased the efficacy of acupuncture point stimulation in achieving analgesic effects in the context of lumbar spine pain (47).

The findings from this meta-analysis strongly indicate that acupressure point stimulation treatment holds a greater therapeutic efficacy compared to pharmacotherapy administered in isolation. This conclusion is substantiated by the observed reduction in NRS scores and the higher treatment efficiency evident within the acupressure point stimulation group. Importantly, it should be highlighted that none of the included studies reported any serious adverse events among patients subjected to acupressure point stimulation treatment. Furthermore, acupressure point stimulation treatment demonstrated improved outcomes even in terms of adverse reactions. This aligns with earlier research that has also highlighted the efficacy of acupressure point stimulation in mitigating adverse effects (48). Subgroup analyses further suggest that acupoint injections yield more favorable treatment outcomes.

Nevertheless, it's important to acknowledge that the considerable heterogeneity across the included studies poses a constraint on drawing definitive conclusions. Despite the promising outcomes, our study is not without limitations. For instance, studies with small sample sizes were incorporated, and certain studies were deficient in terms of available data. Furthermore, some studies lacked clear and comprehensive details. And due to study limitations, the outcome metrics of the included studies were not abundant, limitations that highlight the current lack of comprehensive clinical trials in this area. These limitations highlight the pressing necessity for additional well-designed randomized controlled trials with larger patient cohorts. Bridging the evident gap between preclinical research and clinical studies requires a concerted effort to generate more robust evidence and enhance our understanding of the potential benefits of acupressure point stimulation treatment.

Conclusion

To our knowledge, this is the first study dedicated to evaluating the clinical efficacy of acupressure point stimulation in the treatment of patients with stomach cancer pain. In essence, acupressure point stimulation demonstrated significant improvements in safety, significantly efficient ratio, efficient ratio, and reduced the NRS score in patients with stomach cancer pain. Nevertheless, these promising observations are based on a limited number of studies with relatively small cohorts, necessitating further large, well-designed clinical trials for confirmation. Undoubtedly, more discoveries related to the mechanism of therapeutic action will be revealed in the future, as well as ways to maximize the benefits of acupressure point stimulation therapy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

XZ: Conceptualization, Data curation, Formal analysis, Writing – original draft. JZ: Conceptualization, Data curation, Writing – original draft. LJ: Methodology, Writing – original draft. SZ: Visualization, Writing – original draft. YG: Project administration, Writing – original draft. JT: Conceptualization, Writing – original draft. TP: Data curation, Writing – original draft. XQ: Visualization, Writing – original draft. HC: Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. SH: Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1334657/full#supplementary-material

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Global trends of acupuncture clinical research on analgesia from 2010 to 2023: a bibliometric and visualization analysis

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Objective: Acupuncture, acknowledged as a potent non-pharmacological therapy, is frequently employed to alleviate pain. Despite its widespread use, there has been a lack of overarching bibliometric analysis of clinical research on acupuncture analgesia. We aimed to summarize current patterns, hotspots, and development trends in this field through bibliometric analysis.

Methods: This study evaluates academic publications retrieved from the Web of Science database (2010.01–2023.09) concerning acupuncture analgesia in clinical settings. All primary and secondary studies on humans were included. To track global developmental trends, we employed several software for analyzing annual publication volumes, countries/regions, institutions, authors, cited authors, journals, cited journals, references, and keywords and to draw collaborative networks and reference co-citation network maps.

Results: The final search encompassed 7,190 relevant studies, including 1,263 randomized controlled trials (RCTs) and 1,293 systematic reviews and meta-analyses. The results indicated a gradual increase in the number of annual publications on acupuncture analgesia in clinical practice. Among countries and institutions, China (2,139) and Chengdu University of Traditional Chinese Medicine (258) ranked first. Liang FR (89 articles) was the most prolific author, while MacPherson H (604) was the most cited author. MEDICINE (455) was the most productive journal, and Pain (2,473/0.20) ranked first in both the frequency and centrality of cited journals. Notably, the most frequently cited reference was a systematic review of individual patient data on acupuncture carried out for chronic pain that was published by Vickers Andrew J in 2012 (156). Burst analysis identified frontier research areas for 2010–2020, encompassing network meta-analysis, case reports, dry needling, lumbar disc herniation, cancer, post-herpetic neuralgia, insomnia, and bibliometric analysis.

Conclusion: This study outlines current trends and potential future research hotspots in clinical acupuncture analgesia over the past decade. Findings emphasize the necessity for enhanced international collaboration to improve research output and translation.

KEYWORDS

acupuncture, analgesia, bibliometric analysis, hotspots, visualization analysis

Introduction

Pain is a common, intricate condition marked by the body's physiological and psychological responses to noxious stimuli, significantly impacting the patient's quality of life. Without appropriate treatment, persistent chronic pain may lead to complications such as hypochondria, depression, insomnia, and decreased appetite (1). The quest for effective pain treatments has been a subject of growing interest in healthcare practitioners. While pharmacotherapy, psychological approaches, and placebos are employed in clinical pain management, studies revealed limited efficacy and potential for substance abuse, including cocaine and opioids (2–4). Thus, a safe and efficacious alternative treatment is imperative.

Acupuncture, a potent non-pharmacological therapy in complementary and alternative medicine, is widely used for managing various diseases, particularly in clinical healthcare settings (5). Numerous studies have demonstrated the efficacy and safety of acupuncture in treating acute and chronic pain, such as shoulder pain (6), low back pain (7), and migraine (8), significantly enhancing the patient's quality of life. The mechanism of acupuncture includes various physiological pathways (4), including the release of endorphins and other neurotransmitters, which play a vital role in the analgesic process. This mechanism is akin to the body's natural pain-relieving process and is free of the side effects of many medications. With minimal side effects such as minor bleeding, bruising, dizziness, or fainting, notably less severe than those associated with non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (e.g., gastric ulcers, constipation, respiratory depression, and addiction) (2–4). Furthermore, acupuncture stimulates the body's immune and circulatory systems, further enhancing its analgesic effects, which makes acupuncture a viable, low-risk option for pain management.

Acupuncture analgesia has been widely studied and applied in clinical practice. Consequently, understanding research trends and hotspots in this field is crucial for researchers. Bibliometrics, an interdisciplinary field using mathematical statistics for quantitative analysis of literature and knowledge dissemination, focuses on metrology characteristics to explore the dynamic characteristics of science and technology (9). Overcoming the subjective limitations of traditional reviews, bibliometrics facilitates the identification of crucial research directions, an understanding of developmental trends, and the recognition of hotspots in medical fields. More importantly, visualized maps provide valuable insights, aiding in the identification of established and emerging research areas for guiding clinical practice and decision-making (10). Since 2010, bibliometric studies on acupuncture analgesia have been emerging, covering various types of pain (6–8). However, these studies are limited to a single pain field, and there is no bibliometric analysis on acupuncture analgesia in clinical practice. Therefore, we aimed to use bibliometric analysis to encapsulate the progress and results of acupuncture analgesia in clinical research from 2010 to 2023, demonstrating the research trends and development trajectories and evaluating the analgesic effect of acupuncture, providing better guidance for research and clinical practice.

Abbreviations: Univ Chinese Med, University of Traditional Chinese Medicine/University of Chinese Medicine; Evid-Based Comple Alternat Med, Evidence-Based Complementary and Alternative Medicine; Acup Med, Acupuncture in Medicine; J Altern Comple Med, Journal of Alternative and Complementary Medicine; Cochrane Db Syst Rev, Cochrane Database of Systematic Reviews; BMJ-Brit Med J, BMJ-British Medical Journal; RCT, randomized controlled trial; EA, electro-acupuncture; FC, functional connectivity; IF, impact factor; WOS, Web of Science; SCI-expanded, Science Citation Index Expanded; SA, sham acupuncture; TA, true acupuncture; KOA, knee osteoarthritis.

Materials and methods

Data sources and search strategies

All data were sourced from the Science Citation Index Expanded (SCI-E) within the Web of Science Core Collection (WoSCC) databases (11). Relevant publications were systematically identified through a comprehensive search and extraction process. To avoid omissions, we employed synonyms for "acupuncture," "pain," and "clinical" topics to collect data. The search time was from 1 January 2010 to 1 September 2023, resulting in the identification of 8,118 records. Subsequently, we refined the dataset to include only articles and reviews (n = 7,888), restricted the language to English only (n = 7,730), and excluded animal experiments involving rats, mice, and dogs (n = 523). Through manual scrutiny, we further eliminated redundant publications (n = 17). Finally, a total of 7,190 records were retained for analysis. For transparency, the specific retrieval strategy and flow chart are shown in Supplementary Table 1, Supplementary Figure 1.

Data analysis

By using the mainstream bibliometric analysis tools, including CiteSpace (12, 13) (V6.2.R4, Drexel University, Philadelphia, PA, USA), VOSviewer (14–16) (Version1.6.19, Centre for Science and Technology Studies, Leiden University, Leiden, Netherlands), and R software (version 3.6.3), we conducted a bibliometric analysis (17). The integration of both CiteSpace and VOSviewer was essential for robust analysis, considering variations in algorithms and analysis thresholds (12–16).

VOSviewer is a powerful tool used for constructing and visualizing bibliometric networks based on countries/regions, institutions, journals, co-cited journals, and references of the publications. The visualized map contains three key elements, namely, size, distance, and colors. Nodes representing different entities, such as countries, institutions, and journals, vary in size based on the number of publications. In addition, the distance between nodes indicates their relatedness, with closer proximity signifying stronger links. Thicker links and shorter distances denote closer cooperation. Different colors signify distinct clusters.

CiteSpace presents the relationship between the literature on scientific knowledge maps that enable scholars to sort past research paths and depict prospects, allowing researchers to have a clearer view of the trends and directions in their research fields. The CiteSpace network map encompasses nodes, links, and colors. Node size corresponds to the number of publications with different

elements, such as authors and cited authors. The larger the node, the greater the number of publications or citations in different subjects or domains. A purple circle on the outermost layer of a node denotes high centrality (node centrality > 0.1), highlighting articles with a significant impact and serving as key turning points in the field. Links between nodes represent their co-occurrence in the same publication, with thinner links indicating less frequent co-occurrence. In addition, the color of the links represents the year of first appearance, with warmer colors denoting more recent years. CiteSpace conducts analyses based on authors, co-cited authors, co-cited references, keyword citation bursts for forecasting the possible hotspots, and clustering analysis for revealing the main topics. Similarly, centrality is assessed, where high centrality is deemed crucial in connecting nodes. Parameters were set as below: (1) Time slicing (2010–2023), year per slice, and each figure's pruning were changed based on the needs of the map; (2) term sources were selected; and (3) node type was selected at a time. Meanwhile, the R package bibliometrix was used to output the collaboration map of countries.

Results

Annual publication

From 1 January, 2010 to 1 September, 2023, a total of 7,190 documents were analyzed in our study. Of these, 5,226 (73%) were articles and 1,964 (27%) were reviews, resulting in an annual average of 553 publications. The publications on acupuncture analgesia in clinical settings exhibited a consistent growth trend (Figure 1A). Notably, between 2010 and 2012, the number of annual publications remained relatively stable. However, starting from 2012 onward, there was a gradual and sustained increase, surpassing 500 papers by 2017. While there was a slight decrease in 2018, the overall trend depicted robust growth, peaking at 826 in 2022 (Figure 1B).

Since 2010, there has been a consistent year-on-year increase in the number of publications across all research types. This trend is particularly notable in the of systematic review and meta (SRME) of clinical studies, as well as the numbers of RCTs, case reports/case series, and study protocols. Although the data from 2023 do not cover a full year, the trend indicates the continued use of acupuncture as a complementary and alternative therapy for analgesia in clinical settings.

Distribution of countries/regions and institutions

Over the past 13 years, a total of 6,581 research institutions from 108 countries or regions published articles. Collaboration patterns among major countries or regions in acupuncture analgesia are shown in Supplementary Figures 2, 3. The result shows that China largely cooperated with the USA, England, South Korea, Italy, Australia, Singapore, and Japan. Supplementary Table 2 shows that most of the articles published were mainly derived from China (2,139 papers, 29.75%), followed by the USA (1,670 papers, 23.23%), South Korea (540 papers, 7.51%), England (476 papers, 6.62%), Australia (362 papers, 5.03%), and Canada (337 papers, 4.69%). In addition to the number of publications, centrality is considered a benchmark for judging research quality. Notably, the USA had the highest centrality of 0.21, emphasizing its pivotal role and significant influence in this field, followed by France (0.20) and Spain (0.15). China, with a slightly lower centrality (0.05), maintained an exceptional position in the collaboration network, fostering close ties with numerous countries.

The top 10 research institutions contributing 7,190 publications are listed in Supplementary Table 3. Half of these institutions were from China (5/10), followed by the USA (3/10) and South Korea (2/10). Chengdu University of Traditional Chinese Medicine (Chengdu Univ Chinese Med) published the most research papers (3.59%), followed by Beijing University of Chinese Medicine (Beijing Univ Chinese Med) (3.39%), Kyung Hee Univ, Harvard University (Harvard Univ), and Guangzhou University of Traditional Chinese Medicine (Guangzhou Univ Chinese Med). However, Harvard Univ had the highest centrality of 0.23, followed by Beijing Univ of Chinese Med (0.14), Harvard Medical School (0.13), University of Toronto (Univ Toronto) (0.10), and Univ California System (0.10). There was a close cooperative relationship among these institutions.

The institutions that published more than seven papers were analyzed using VOSviewer (Supplementary Figure 4), with 405 institutions included in the analysis network. Supplementary Figure 4B displays the distribution of institutions according to the average time of occurrence. Harvard Univ, Univ Toronto, Univ York, and Univ Oxford conducted relevant studies earlier. Meanwhile, research institutions represented by Chengdu Univ Chinese Med, Nanjing Univ of Chinese Med, Guangzhou Univ of Chinese Med, Tianjin Univ of Chinese Med, London South Bank Univ, Western Univ, Univ Hosp Zurich, and Univ Rey Juan Carlos started the research on acupuncture analgesia in clinical practice more recently. In addition, small-scale collaborations were established between some international institutions, but the low network nodes indicated a lack of global interagency collaboration. However, this finding does not fully explain the limited collaboration in the clinical application, highlighting the collaboration cannot be overstated.

Analysis of authors and cited authors

The co-occurrence analysis conducted by the authors revealed the cooperation relationships among the authors, forming a co-occurrence map comprising 275 nodes and 461 links (Supplementary Figure 5A). These publications involved 32,676 authors, and Supplementary Table 4 lists the top 10 frequent authors in terms of publication volume and centrality. Liang FR from Chengdu Univ Chinese Med authored or co-authored the most articles (89 articles), followed by Li Y from the same institution (78 articles) and Wang Y from the China Institute of Guangzhou Univ Chinese Med (72 articles). However, centrality ranking was the most important. Lee MS, with a centrality of 0.13, ranked highest. As the founder of the International Society for Complementary Medicine Research and consultant to the Cochrane Collaboration in complementary and alternative

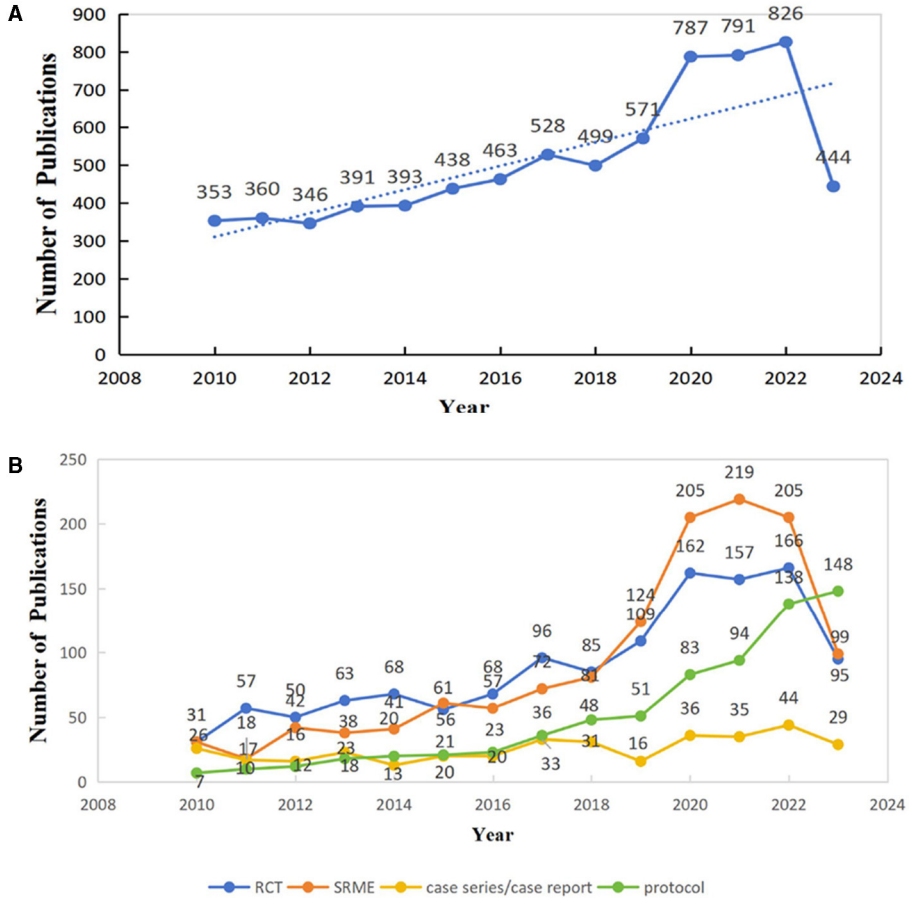

FIGURE 1
(A) Number of annual publications and growth trends of acupuncture analgesia in clinical practice globally. **(B)** Main study design trends in published clinical studies of acupuncture analgesia.SRME, systematic review and meta; RCT, randomized clinical trial.

medicine, Lee has published 66 articles in this field. Liang FR, the second-ranked author with a centrality of 0.12, serves as the vice president of the World Federation of Acupuncture and Moxibustion Societies, contributing extensive research on the clinical efficacy of acupuncture points for many years, and his articles covered many diseases, including chronic stable angina and migraine. Both authors have collaborated with others, but the level of collaboration between them is relatively low. Supplementary Figure 5A indicates a weak collaborative relationship among previous groups, forming numerous small-group collaborative networks. In recent years, an author from Spain has formed larger research groups but with less collaboration with mainstream groups internationally.

The co-citation map of the cited authors comprises 280 nodes and 2,342 links (Supplementary Figure 5B). MACPHERSON H was the most cited author (604 times), followed by Vickers AJ (510 times), Linde K (463 times), Moher D (380 times), and Witt CM (353 times). In terms of centrality, the top six cited authors were Vickers AJ (0.11), Han JS (0.11), Furlan AD (0.11), Macpherson H (0.09), Linde K (0.09), and Manheimer E (0.09). Clearly, they have demonstrated significant academic influence in the field. Notably, even though the articles written by the top-ranked cited authors were mostly published before 2020, they have been frequently cited in recent years, suggesting that acupuncture researchers are paying more attention to pain in clinical practice. Detailed information about the cited authors is shown in Supplementary Table 5.

Analysis of journals and cited journals

In this study, a total of 1,483 journals have published papers in this field, with 69 journals that published more than 15 papers being selected for visualization (Supplementary Figure 6). The top 10 academic journals that published about 24.75% of the publications are enumerated in Supplementary Table 6. Sorted by publications, the most productive journal was *Medicine* (455 publications), followed by *Evid-Based Comple Alt Med* (289 publications) and then *Trials* (192 publications). According to the Journal Citation Reports of 2022, the average impact factor (IF) of these top 10 journals was 3.65. Among them, the leading journal with the highest IF (8.40) and highest H-index (244) was *Cochrane Db Syst Rev*, indicating its significant influence in the field of acupuncture analgesia. Of note, these journals were mostly located in the USA or England.

Supplementary Figure 6B presents a co-citation analysis of 590 journals, with a threshold of 80 citations from 29,341 journals. Seven clusters corresponding to seven colors in the figure highlight specific areas with varying clinical focus. Supplementary Table 7 outlines the top five journals in terms of frequency, which were more than 1,400, and *PAIN* had the most frequency (2,473) and citations (6,714), followed by *Cochrane Db Syst Rev*, *BMJ-Brit Med J*, *Evid-Based Comple Alt Med*, and *Acup Med*, and the top five journals in terms of centrality were *PAIN*, *Cochrane Db Syst Rev*, *BMJ-Brit Med J*, and *J Altern Comple Med*. In an analysis of co-citation and centrality, *PAIN* was identified as the core journal for acupuncture analgesia in clinical practice, and its published articles reflect the fundamentals of the research field.

Keyword analysis

Keyword co-occurrence analysis can be performed to echo research themes, reflect research hotspots, and monitor frontier shifts in a field. Furthermore, cluster analysis provides a more holistic picture of the structure and evolution. In this study, all keywords were classified into seven clusters by CiteSpace (Figure 2): Cluster 0: "Knee osteoarthritis (red)," Cluster 1: "Postoperative pain (yellow)," Cluster 2: "Post-dural puncture headache (fluorescent green)," Cluster 3: "Ultrasound-guided injection (green)," Cluster 4: "Dry needling (blue)," Cluster 5: "Case report (indigo blue)," and Cluster 6: "Post-herpetic neuralgia (purple)." The magnitude of the keyword circle within each cluster was commensurate with the frequency of its appearance. The connecting links between each keyword were intricate, suggesting a complex connection between them. The mean silhouette was used to evaluate the clusters. The total silhouette value exceeded 0.7 (>0.5), implying a high degree of credibility in the obtained outcomes. The modularity (Q) was 0.4502 (>0.3), indicating that the clustering structure was substantial. The S values of the total silhouette were 0.7537, suggesting that the distribution and homogeneity of the clusters were well-defined, and the cluster was believed to be highly effective and persuasive.

High-frequency keywords showed a popular theme, while high-centrality keywords reflected the status and importance of the corresponding research content in this field. As listed in Table 1, the top ten high-frequency keywords were as follows: "randomized controlled trial" (1,44), "management" (1,248), "pain" (1,052), "acupuncture" (1,020), "clinical trial" (672), "low back pain" (570), "therapy" (524), "systematic reviews" (512), "efficacy" (503), and "prevalence" (464). The top 10 high centrality keywords were as follows: "management" (0.29), "acupuncture" (0.16), "electro-acupuncture" (0.15), "pain" (0.12), "prevalence" (0.10), "low back pain" (0.08), "randomized clinical trial" (0.08), "diagnosis" (0.07), "tumors" (0.06), and "headache" (0.06). "Burst keywords" refer to keywords cited frequently over some time, indicating the frontier areas. The top 25 keywords of the citation burst are shown in Figure 3, and burst detection reveals important milestones in the field. The keywords "physiotherapy," "accuracy," and "aspiration" had a longer emergence time. In addition, the most significant and strongest citation burst belonged to "placebo." Notably, since 2020, the keywords "network meta-analysis," "case report," "dry needling," "lumbar disc herniation," "cancer," "bibliometric analysis," "post-herpetic neuralgia," and "insomnia" have been more prominently concentrated, indicating promising developments.

Based on the cluster map, timeline diagrams could illustrate the panorama, the historical evolution, and the frontiers of hotspots in the research field over the last 13 years. The keyword clustering of research continued up to the present and mainly involved #0 acupuncture, #1 postoperative pain, #2 FMRI, #3 ultrasound, #4 dry needling, #5 diagnose, and #6 post-herpetic neuralgia. As displayed in Figure 4, timeline visualizations organize clusters horizontally, mapping each from left to right according to publication dates, displayed at the visualization's bottom edge in CiteSpace. The arrangement of clusters follows a vertical, size-based descending order. The keywords in this field from 2010 to 2023 focused on randomized clinical trials, pain, management, electro-acupuncture, dry needling, tumors, and neuropathic pain, which were the most basic and important research directions. In recent years, keywords such as survivors, network, tennis elbow, and post-herpetic neuralgia have appeared. The multidisciplinary intersection such as bibliometrics is the current hotspot and trend of scientific research, which will significantly promote the development of the depth and breadth of scientific research.

Cited references analysis

Co-citation analysis is crucial for identifying the key literature. A total of 186,873 cited references from the 7,190 publications were analyzed as co-cited references. Figure 5 displays the clinical acupuncture analgesia network with 295 nodes and 993 links. Table 2 shows the top 10 cited references sorted by the number of citations. These references were landmark references in the field and set the stage for future research. These references, spanning from 2009 to 2020, include three clinical trials, three systematic reviews and meta-analyses, two guidelines or guidance, one PRISMA statement, and one on headache disorders classification.

Vickers et al. (18) article stood out with 156 co-citations and the highest centrality (0.46). Focusing on acupuncture for chronic pain, it emphasized the efficacy of acupuncture beyond a placebo, providing clarity on its clinical utility. In addition, this article is an excellent demonstration in clarifying the utility of acupuncture analgesia in clinical practice. Notably, Vickers AJ' s meta-analysis update ranked second in citations and centrality, suggesting that the authors and their two articles had a dominant influence in the field. Detailed data of the remaining highly cited articles are listed in Table 2.

Discussion

This study investigated the literature on clinical acupuncture analgesia, employing the bibliometric analysis to characterize publications, analyze co-occurrences and clustering, and reveal current landscapes and frontier topics. As the first bibliometric study in this area, it aims to guide future research directions.

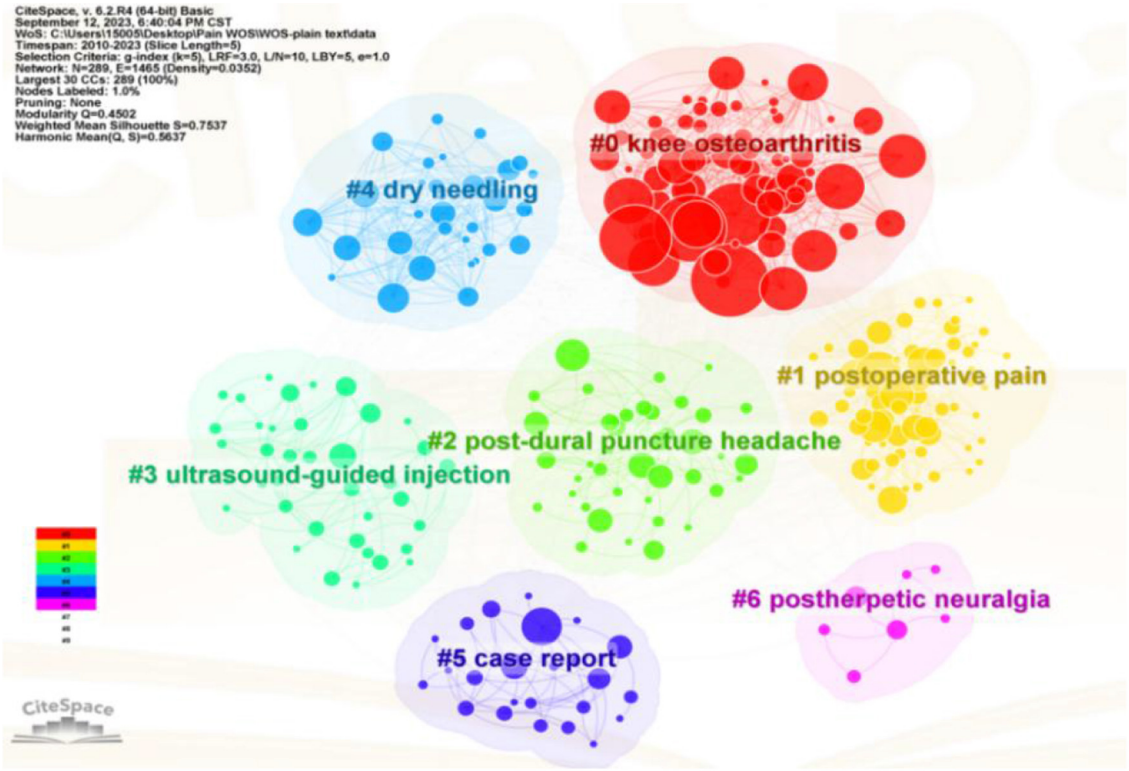

FIGURE 2
Visualization of keyword cluster analysis co-occurrence. In the co-occurrence network map, the nodes indicate the corresponding keywords, the size of the nodes denotes the number of articles containing the keywords, and the connecting lines between the nodes indicate the relationship between the keywords.

TABLE 1 Top 10 keywords related to the research of acupuncture analgesia in clinical practice.

Ranking	Occurrences	Keywords	Ranking	Centrality	Keywords
1	1,447	Randomized controlled trial	1	0.30	Management
2	1,248	Management	2	0.16	Acupuncture
3	1,052	Pain	3	0.15	Electro-acupuncture
4	1,020	Acupuncture	4	0.12	Pain
5	672	Clinical trial	5	0.10	Prevalence
6	570	Low back pain	6	0.08	Low back pain
7	524	Therapy	7	0.08	Randomized controlled trial
8	512	Systematic reviews	8	0.07	Diagnosis
9	503	Efficacy	9	0.06	Tumors
10	464	Prevalence	10	0.06	Headache

Basic information

From 2010, the output of annual publications related to acupuncture analgesia in clinical practice has steadily increased. The number of publications in 2022 was the highest, accounting for 11.49% of all publications, which suggests a growing research interest in this field. Two main reasons contribute to this phenomenon: the evolving focus of modern medicine on patients' quality of life (26) and the proven clinical efficacy of acupuncture analgesia in reducing drug dosages and adverse effects and serving as an opioid alternative (24, 27). Research conducted between 2010 and 2023 in China has shown rapid growth, surpassing the USA in a number of publications after 2018, while in other countries or regions, the number of annual publications was basically stable, indicating that research has gradually shifted from the USA, the acknowledged center of the Western world, to China, the central power of the Eastern world. Despite China leading in the production of published papers, the

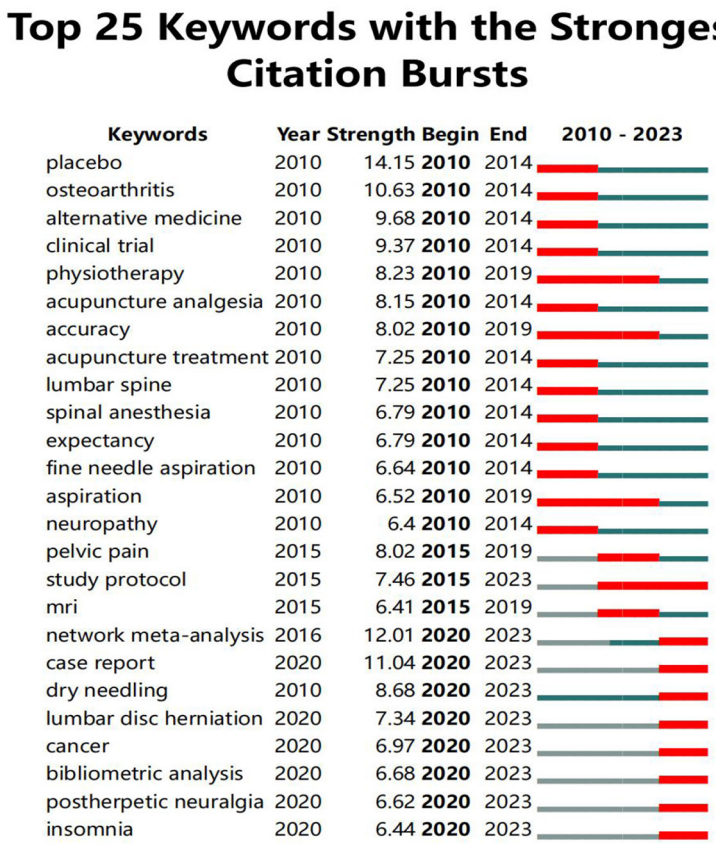

FIGURE 3
Top 25 keywords with the strongest citation bursts of acupuncture analgesia in clinical practice. The green line means the whole period, and the period during which a keyword's burst was identified is shown by the red line.

USA maintains higher centrality (0.21 vs. 0.05), highlighting its continued dominance in acupuncture analgesia research. The UK, Germany, and Canada, as major research powers, exhibit well-established collaboration networks, emphasizing their substantial contributions to international cooperation. This finding suggested the growing acceptance of acupuncture as a complementary therapy. Conversely, despite China and South Korea having a long history with acupuncture and numerous clinical trials (28), their actual contribution and influence are relatively limited.

In the institutional cooperation network, Chengdu Univ Chinese Med, Beijing Univ Chinese Med, and Kyung Hee Univ stood out for their comprehensive strength. Chengdu Univ Chinese Med and Beijing Univ Chinese Med, as pioneers in Chinese medicine, were vital medical innovation research bases and have trained a large number of professional medical and health talents in acupuncture and moxibustion. Kyung Hee Univ, a research-centered university, has leading research institutions and academic centers worldwide. As early as 1976, The Korean Medicine Hospital of Kyung Hee University was the first research institution in the world to successfully conduct acupuncture anesthesia for cesarean operations and held the first World Congress of Acupuncture, which had high authority.

However, Harvard Univ held the most centrality globally, reflecting its influence in acupuncture analgesia and the broader medical field. China and its relevant scientific institutions still need to improve publication quality and international cooperation to boost influence. Most noteworthy is the fact that there was no institution from the UK and Australia, among the top five countries with the most publications, listed in the top 10 list, possibly because the institutions conducting research for acupuncture anesthesia in those two countries were relatively fragmented and the support base for cooperation was also not enough, so domestic collaboration between agencies was more important than international collaboration. International collaboration is currently insufficient, necessitating improved communication and cooperation.

Co-authorship analysis indicated communication between academics in the research area, which is an important indicator of scholarly collaboration (12–16). Our analysis of authors and organizational affiliations revealed a significant collaboration among Asian researchers in acupuncture analgesia. The top 10 authors, all contributing over 50 articles, included Liang FR (89 articles) from Chengdu Univ Chinese Med, a key figure in this field. In terms of centrality, among the top five most cited authors, three authors, namely, Liang FR, Lao LX, and Zheng H, were high-impact authors from China. In terms of the authors' cooperation network, there were multiple mature cooperation teams with a certain degree of cooperation. However, the cooperation was

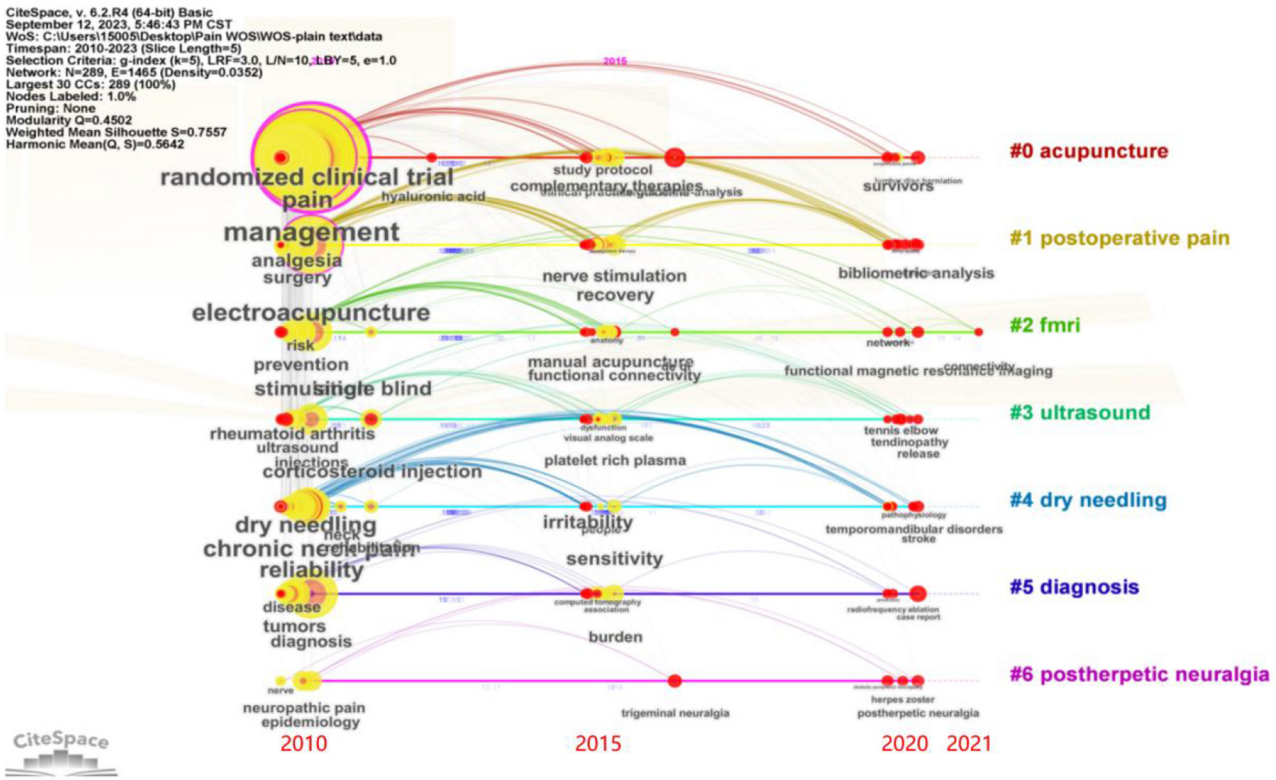

FIGURE 4
Timeline diagram of keywords in the field of acupuncture analgesia in clinical practice. The color-coded curves denote co-citation connections formed within specific years, the large nodes, or those with red halos—for their notable citation metrics or sudden increases in citations. Below these timelines, the year's top three cited works are shown, with the highest-cited work at the bottom.

relatively less stable, which indicated that cooperation between prolific authors was limited to smaller groups, and they tended to work with stable collaborative teams and were largely confined to their respective institutions.

Through the analysis of co-cited authors, the top five cited authors with the most citations (2,310 times) were from Europe and the USA, such as Macpherson H (England), Vickers AJ (USA), LindeI K (Germany), Moher D (Canada), and Witt CM (Germany), while those published by Vickers AJ (USA), Han JS (China), Furlan AD (Canada), Macpherson H (England), and Linde K (Germany) had the highest centrality in articles. MacPherson H, as the first author, was a "core strength" researcher in this field. In addition, he focused on the evaluation of the effectiveness and safety of acupuncture and the neuroimaging research on the mechanism of acupuncture. For example, MacPherson et al. presented an updated reporting guideline in 2010, which stood for *Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture* (29). Citations might not be the best index of publication quality; although a considerable number of articles were from Asia, improvement in the quality of these articles was necessary.

Through the analysis of these journals, we found that the top 10 academic journals published 1,773 articles, accounting for 25% of all articles, and the results of this analysis suggested that these journals had a strong interest in articles regarding acupuncture analgesia in clinical practice but is different from the findings of the previous study, which may be due to the limitation of the study pertaining to the field of acupuncture analgesia (30). *MEDICINE* was the most critical journal and has made significant contributions in this field. Although *COCHRANE DB SYST REV* ranked fifth with only 130 publications, it ranked second for citations with the highest IF (8.40) and H-index (273), indicating that this journal was very influential in this field and was worth learning for scholars. Notably, the 10 journals with the highest outputs, with the exception of *COCHRANE DB SYST REV*, generally had low impact factors (average IF <3) but still had a number of articles that received a high number of citations. Most of these journals were relevant to complementary alternative therapies and pain research. However, publishing clinical studies on acupuncture analgesia in high-quality journals is still a challenge. According to the analysis of the cited journals, the top-ranking journal for both frequency and centrality was *PAIN*. These data will help future scholars to select appropriate journals to reference or submit articles in related fields.

Research frontiers and trends

Keywords and references can reflect the content of the research, which is helpful in identifying hotspots and frontiers from their frequency, centrality, and clustering distribution (31). From cluster-related topics, we can identify the current frontiers from the perspective of research areas; knee osteoarthritis (32), postoperative

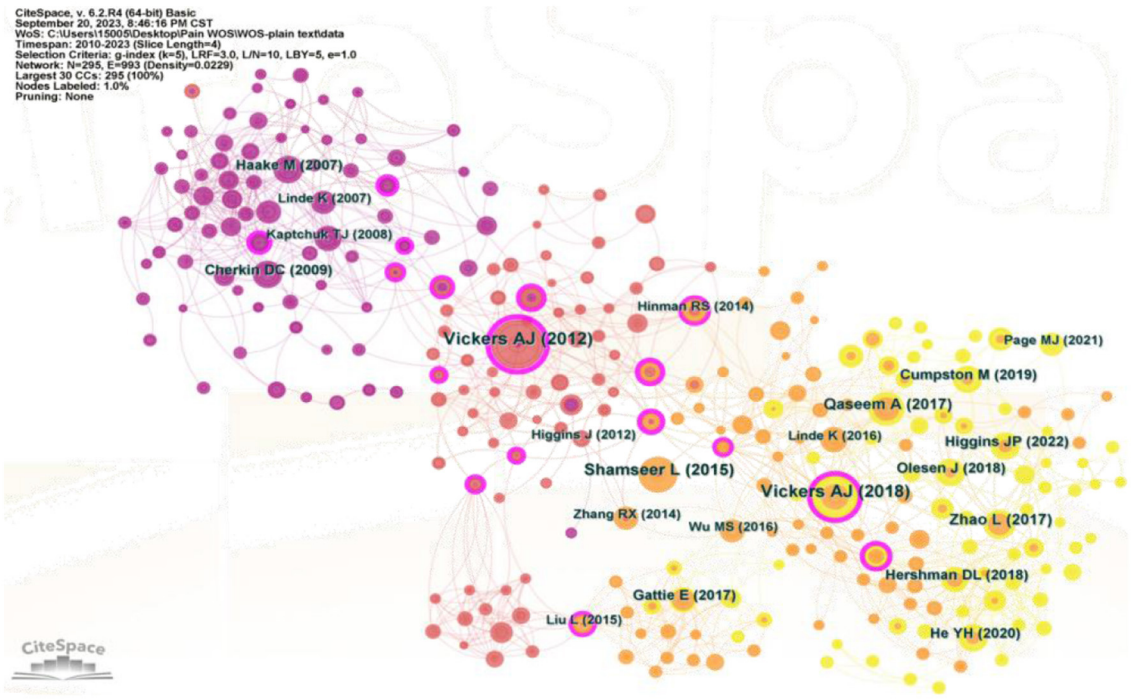

FIGURE 5
Visualization of co-cited references. Each node represents a paper, the node size indicates the number of times that the paper has been cited, and the links between nodes reflect the strength of co-citations, while the node color indicates the citation year.

pain (33), post-dural puncture headache (34, 35), dry needling (36), case report (35, 37), and post-herpetic neuralgia (38) are the areas of the main research focus, which shows that researchers are highly interested in acupuncture analgesia for different disease types. In addition, a burst keyword can indicate cutting-edge research topics and reveal studies that have potential or are of interest. Since 2020, the burst keywords used were "network meta-analysis," "case report," "dry needling," "lumbar disc herniation," "cancer," "bibliometric analysis," "post-herpetic neuralgia," and "insomnia," indicating that researchers currently focus on those promising developments. The researchers are interested in case reports on acupuncture analgesia, exploring the analgesic effects of different types of acupuncture (dry needling); relieving pain-induced adverse effects, such as insomnia; and incorporating a cross-disciplinary (bibliometric analysis) approach to exploring future directions in the treatment of pain with acupuncture. From 2015, this protocol has gradually become a hotspot. We believe the design and improvement of protocols on acupuncture will be hot topics of research in the future (20, 39–42).

High-frequency keywords and burst keywords (RCTs and clinical trials) demonstrated that researchers are very interested in verification of the effectiveness of acupuncture analgesia in clinical practice, and the effectiveness has been the focus of this research area. Through visualization of co-cited references, and as observed in the highly cited paper, some guidelines recommending acupuncture for chronic pain are the most cited, which also suggests that the effectiveness of acupuncture for chronic pain remains the focus of researchers in this field (43, 44). The top 1 reference by frequency and centrality is a meta-analysis of individual patient data on acupuncture for chronic pain, which confirms the effectiveness of acupuncture for lower back and neck pain, osteoarthritis, chronic headache, and shoulder pain (18). Of note, the top three highly cited papers were all related to meta-analysis. This result suggests that researchers have gone beyond looking for evidence of the effectiveness of acupuncture from RCTs or trials, both by looking for high-quality evidence via evidence-based medicine and by following standard guidelines for reporting interventions in acupuncture clinical trials to implement meta-analyses on acupuncture analgesia (20).

Strengths and limitations

In this study, we employed a more comprehensive search strategy to systematically organize the subject terms involving acupuncture, which was not available in previous bibliometrics related to acupuncture, to avoid the impact of omitted literature on the results of the study. Second, by using bibliometrics, we performed a visual analysis of literature, provided a channel for researchers to summarize research status and key research forces, and predict the development trends in the field. In addition, this study distinguished itself from previous studies limited to a single field of acupuncture analgesia, adding value for clinical researchers. To our knowledge, this is the first bibliometric analysis of acupuncture analgesia in clinical practice. Moreover, various methods are used to analyze data, allowing for a multidimensional

TABLE 2 The top 10 highly cited papers in the field of acupuncture analgesia in clinical practice (2010–2023).

Rank	Counts	Title	Author	Journal	Publication year	Centrality	2022 IF	DOI
1	156	Acupuncture for chronic pain: individual patient data meta-analysis	Vickers et al. (18)	Arch Intern Med	2012	0.46	38.99	10.1001/archinternmed.2012.3654
2	129	Acupuncture for chronic pain: update of an individual patient data meta-analysis	Vickers et al. (19)	J Pain	2018	0.34	4.00	10.1016/j.jpain.2017.11.005
3	93	Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement	Shamseer et al. (20)	Systematic Reviews	2015	0.00	3.70	10.1186/2046-4053-4-1
4	79	Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American college of physicians	Qaseem et al.	Ann Intern Med	2017	0.09	39.20	10.7326/M16-2367
5	73	The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial	Zhao et al. (21)	Jama Intern Med	2017	0.06	38.99	10.1001/jamainternmed.2016.9378
6	62	Headache classification committee of the international headache society (IHS) the international classification of headache disorders, 3rd edition	Olesen J	Cephalalgia	2018	0.03	4.90	10.1177/0333102417738202
7	62	A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain	Cherkin et al. (22)	Arch Intern Med	2009	0.04	38.99	10.1001/archinternmed.2009.65
8	61	Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions	Cumpston et al. (23)	Cochrane Db Syst Rev	2019	0.03	8.40	10.1002/14651858.ED000142
9	58	Clinical evidence for association of acupuncture and acupressure with improved cancer pain: a systematic review and meta-analysis	He et al. (24)	Jama Oncol	2020	0.07	28.40	10.1001/jamaoncol.2019.5233
10	57	Effect of acupuncture vs. sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial	Hershman et al. (25)	Jama-J Am Med Assoc	2018	0.09	120.70	10.1001/jama.2018.8907

Arch Intern Med has been renamed Jama Intern Med.

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interpretation of conclusions and offering insights into potential global research collaborations.

First, our search was restricted to English-language publications, as non-English articles constitute a small percentage (about 2%) of total articles in WoS. It is expected that the overall trends of our results might be similar to the results without language restrictions. As one of the most authoritative scientific and technological literature retrieval tools, WoS could not cover all the research on acupuncture analgesia in clinical practice. The journals included in the SCI-E of WoS database are described as world-leading journals due to a rigorous selection process. Thus, publications in WoS still can be a representative of research in the discipline. Second, despite efforts to incorporate numerous search terms, the study might have overlooked some terms, potentially neglecting the latest research trends. Third, the study did not include papers published after the search date due to the continuous updates to the database, resulting in potential gaps in literature retrieval. In addition, the number of clusters and the label of clusters in the network analysis will vary depending on the resolution of clustering and the subjective views of the authors. Finally, affiliations may not precisely differentiate associated organizations; for instance, Harvard Med School and Harvard Univ are separately analyzed.

Conclusion

In conclusion, acupuncture analgesia is valuable for research and clinical applications. Offering a comprehensive overview from 2010 to 2023, the findings serve as a valuable reference for potential collaborations and highlight opportunities for future developments in this field. The findings indicate a rapid expansion, with China leading in publication numbers and the USA demonstrates greater influence in this field. However, limited collaboration between countries and institutions may hinder progress. Increased cooperation and data exchange among institutions and scholars are essential, contributing to the further expansion and international acceptance of acupuncture.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Z-QL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing. X-FW: Conceptualization, Data curation, Formal analysis, Investigation, Writing—original draft. CF: Conceptualization, Data curation, Formal analysis, Writing—original draft. Y-TF: Conceptualization, Methodology, Supervision, Writing—review & editing. J-PL: Conceptualization, Formal analysis, Funding acquisition, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1368988/full#supplementary-material

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Effects of acupuncture for Bell's palsy patients in the acute phase and its impact on facial nerve edema: a study protocol for a randomized, controlled trial

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Background: Bell's palsy is an acute peripheral facial neuropathy, which is one of the most common causes of facial palsy of lower motor neurons. Facial nerve swelling is commonly observed in Bell's palsy. Acupuncture therapy has been widely used in the treatment of Bell's palsy. However, whether acupuncture can be effectively used in the acute stage is still controversial. There are no clinical trials conducted previously to evaluate the effect of acupuncture on facial nerve edema in Bell's palsy patients. The study aims to evaluate the potential efficacy of different acupuncture modalities on Bell's palsy patients in the acute phase, its effect on facial nerve edema, and to preliminarily explore its possible mechanism.

Methods and analysis: In this randomized, controlled trial, 165 Bell's palsy patients with unilateral onset within 3 days will be recruited and randomly assigned to either the electroacupuncture group ($n = 33$), the acupuncture group ($n = 33$), the sham acupuncture group ($n = 33$), the blank control group ($n = 33$), or the acupuncture control group ($n = 33$) in a 1:1:1:1:1 ratio. The participants will receive 4 weeks of treatment and 8 weeks of follow-up. The five groups of participants will receive the following treatments: A: Electroacupuncture + Medication (prednisone acetate tablets, mecobalamin tablets, and vitamin B1 tablets); B: Acupuncture + Medication; C: Sham Acupuncture + Medication; D: Medication only; and E: Acupuncture only. The primary outcome will be the effectiveness rate of different acupuncture modalities in improving facial nerve function after the intervention period. The secondary outcomes will be the recovery speed, the diameter of the facial nerve, the echo intensity and thickness of facial muscles, blood flow parameters of the facial artery, the serum inflammatory level, safety evaluation, and adverse events. Preliminary exploration of its mechanism of action occurs through inflammation and immune response. The difference between groups will be assessed using repeated measure analysis of covariance (ANCOVA) and trend chi-square.

Discussion: The trial will evaluate the efficacy and facial nerve edema of acupuncture for Bell's palsy patients in the acute phase and preliminarily explore its possible mechanism. The results thus may provide evidence for clinical application.

Clinical trial registration: https://www.chictr.org.cn/bin/project/edit?pid=133211, identifier ChiCTR2100050815.

KEYWORDS

Bell's palsy in the acute phase, acupuncture, electroacupuncture, edema of the facial nerve, randomized clinical trial

Introduction

Bell's palsy is an acute peripheral facial neuropathy, which is one of the most common causes of facial palsy of lower motor neurons (1). Bell's palsy is defined as an acute unilateral facial nerve palsy or paralysis, with an onset time of less than 72 h, and has unknown etiology. It accounts for 50% of all facial nerve paralysis cases (2), and the incidence rate has been reported between 11.5 and 53.3 per 100 thousand persons (3). The facial nerve is the longest nerve in the human body that traverses through the bone canal, and thus, its anatomical characteristic makes it easy to cause local blood circulation obstacles after an injury and cause nerve edema. The etiology of Bell's facial palsy remains unclear. The only confirmed finding is that the inflammation and edema of the facial nerve in the narrow styloid foramen can lead to the compression of the facial nerve canal. Facial nerve swelling is commonly observed in Bell's palsy and has been reported during decompression surgery (4, 5). The different stages of facial palsy are defined as follows: acute phase: 1–7 days; resting phase: 8–20 days; and recovery period: 21–70 days (6). Acupuncture has been widely used in the treatment of Bell's palsy and has achieved satisfactory results to date (7). Several clinical and laboratory studies have found that acupuncture can effectively promote the recovery of facial nerve injury, effectively shorten the course of the disease, and reduce various complications (8, 9). Especially in Asian countries, such as Korea, Japan, and China, there are a large number of patients who have been managed by acupuncture therapy as the initial treatment. The findings of clinical practice in our department and some prior studies have proved that early use of acupuncture in acute Bell's palsy can significantly slow down the progress of facial nerve injury, improve the curative effect, shorten the clinical recovery time, and thus reduce the sequelae (10, 11). "Clinical Guidelines for diagnosis and treatment of Traditional Chinese Internal Medicine" and other guidelines made a Grade A recommendation that acupuncture should be involved in the treatment of facial palsy as soon as possible, and the patients with mild or severe facial palsy may be treated with any one of acupuncture, western drugs, or acupuncture combined with drugs (12). However, some experts usually do not accept acupuncture as the recommended strategy for the management of the acute stage of facial nerve injury, possibly because they are afraid that the potential application of acupuncture in the acute stage can aggravate nerve edema (2). However, Fang et al. have used thick needle therapy to treat acute ischemic facial nerve injury in rats. It was found that the swelling degree of the facial nerve in the treatment group was markedly lower than the control group on days 1, 3, 5, and 7, which promoted the regression of the facial nerve edema in the bone canal (13). However, there is no prior report on the potential effects of acupuncture for facial edema in patients with acute Bell's palsy.

For the objective quantification of the facial nerve edema, enhanced magnetic resonance imaging (MRI) can be effectively used to observe facial nerve ischemia and edema, but it is actually contrast-enhanced rather than physical nerve swelling, which is costly, time-consuming, and associated with many limitations (14, 15). Neuroultrasound is a non-invasive examination method to objectively describe facial nerve edema. It can facilitate real-time image acquisition to describe the structural changes of the nerve and has the advantages of cheap price, easy access, and bedside use (16). In addition, pathological studies have confirmed that local ischemia of the affected lateral nerve in patients with Bell's palsy could be often observed. Because the direction of blood flow of the facial nerve is mainly from proximal to distal, the microcirculation of facial skin might also get adversely affected after Bell's palsy attack (17). For example, Yin et al. (18) observed the potential changes in the blood flow at the facial acupoints of patients with Bell's palsy by Doppler ultrasound and found that there were significant differences in the average velocity, final diastolic velocity along the maximum velocity curve, peripheral resistance index at the four facial acupoints between the affected side and the healthy side, and between patients with different facial palsy degrees. Therefore, color Doppler ultrasound can dynamically and quantitatively monitor the changes in the facial artery blood flow parameters in patients with Bell's facial palsy during acupuncture treatment, which can be used as an important basis for the analysis of observed curative effects.

At the same time, ultrasound can also evaluate the muscle condition of patients with facial palsy by observing the area, depth, and echo intensity of facial muscles. Volk et al. used quantitative muscle ultrasound to assess the muscle area, thickness, and echo intensity of 2 masticatory muscles and 6 facial muscles in 20 patients with chronic facial palsy. The results showed that the lateral muscles of the paralyzed side decreased significantly, and the echo intensity of other facial muscles increased markedly except that of the frontalis and orbicularis oculi muscles (19).

Therefore, we have designed a randomized controlled trial (RCT) to examine the possible efficacy of different acupuncture modalities on patients with Bell's palsy in the acute phase and the improvement of facial nerve edema using appropriate randomization and rigorous blinding conditions. The objectives of this trial are as follows:

(1) To evaluate the efficacy of different acupuncture modalities on patients with Bell's palsy in the acute stage;
(2) To assess whether different acupuncture modalities can effectively relieve facial nerve edema in patients with Bell's palsy in the acute stage;
(3) To analyze whether different acupuncture modalities can significantly improve facial blood circulation and muscle activity in patients with Bell's palsy in the acute stage;

(4) To provide reference for the timing of different acupuncture modalities intervention;
(5) To explore the mechanisms that can contribute to both inflammatory and immune responses.

Methods and analysis

Study design

This will be a single-center, randomized, controlled clinical trial. The study has been approved by the ethics committee of the First Affiliated Hospital of China Medical University (CMU1H). It will be conducted from October 2021 to December 2025 in the Traditional Chinese Medicine (TCM) Department, Emergency Department, Ultrasound Department, and Neurology Department of CMU1H, which is the largest comprehensive hospital in northeast China. All the participants will be informed about the study and sign written informed consent before participating in the trial. Eligible patients will then be randomly divided into the electroacupuncture group (EA + medicine), the acupuncture group (A + medicine), the sham acupuncture group (SA + medicine), the blank control group (pure medicine), and the acupuncture control group (pure acupuncture) at a ratio of 1:1:1:1:1. The first three groups will be treated with electroacupuncture, acupuncture, or sham acupuncture five times a week based on medicine therapy. The blank control group will be treated with medicine only, and the acupuncture control group will be treated with acupuncture five times a week without medicine-based treatment. The treatment course will last for 4 weeks and thereafter follow up for 8 weeks. This trial is designed in strict accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and the recommendations of Standards for Reporting Intervention in Controlled Trials of Acupuncture (STRICTA) (20) and will be reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist (21). The trial flow chart is shown in Figure 1, and the study design schedule is shown in Table 1. Supplementary material S1 contains the complete spirit list.

The treatment course will last for 20 days (4 weeks) and thereafter follow up for 8 weeks. First, the subjects will be informed of informed consent and screening. Then, they will be randomized into five different groups. The four groups related to acupuncture will be treated with acupuncture 5 times a week for a total of 4 weeks (20 days); the blank control group will receive the medicine therapy (see "Intervention" for details). The clinical data will be evaluated at

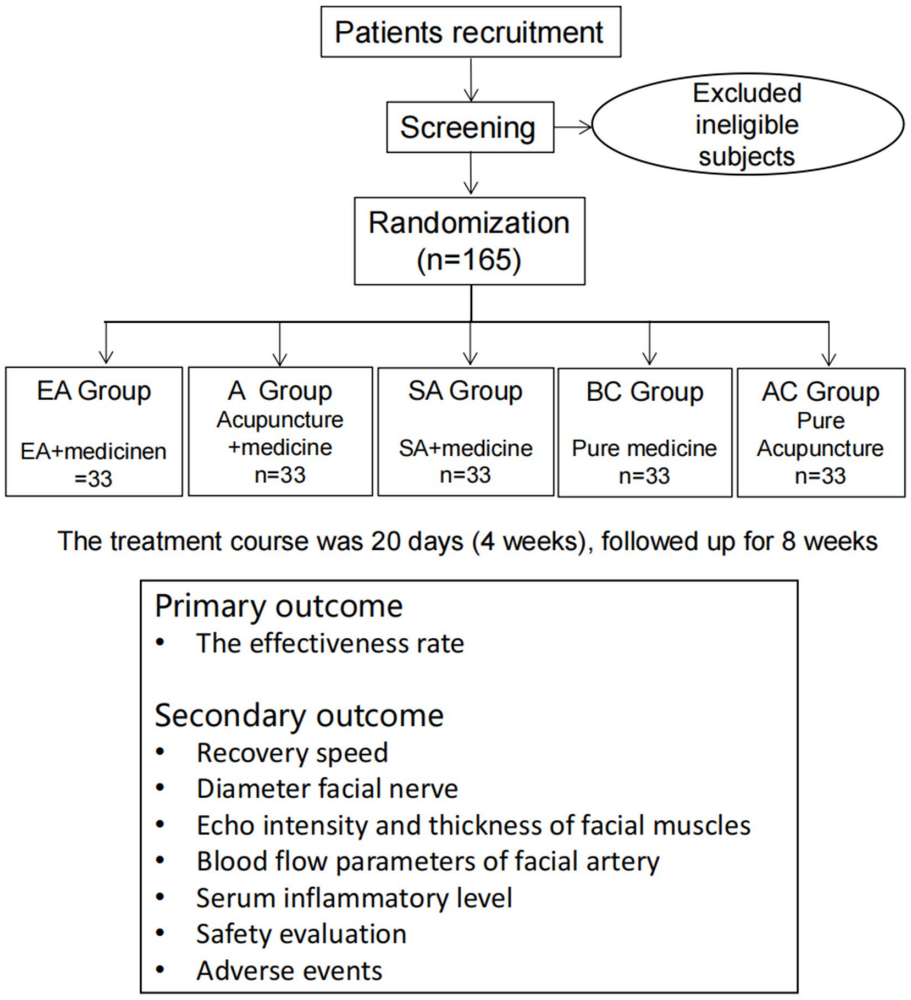

FIGURE 1
Flow chart of the planned study. EA: electroacupuncture; A: acupuncture; SA: sham acupuncture; BC: blank control; and AC: acupuncture control.

TABLE 1 The designed schedule for the data collection.

Time point	Screening period	Intervention period					Follow-up period	
	Day 0	Day1	Day 5 (Week1)	Day 10 (Week2)	Day 20 (Week4)	Once daily until discharge	Week 8 ± 3 days	Week 12 ± 3 days
Enrolment								
Informed consent	×							
Eligibility screening	×							
Randomization	×							
Allocation	×							
Interventions								
The electroacupuncture group	—	—	—	—	—	—	—	—
The acupuncture group	—	—	—	—	—	—	—	—
The sham acupuncture group	—	—	—	—	—	—	—	—
The blank control group	—	—	—	—	—	—	—	—
The acupuncture control group	—	—	—	—	—	—	—	—
Assessments								
SFGS	×		×	×	×	×	×	×
HBGS	×		×	×	×	×	×	×
The diameter of facial nerve	×		×	×	×		×	×
Echo intensity and thickness of facial muscles	×		×	×	×		×	×
Blood flow parameters of the facial artery	×		×	×	×		×	×
Therapeutic mechanism index	×		×	×	×		×	×
Safety index	×		×	×	×			
Adverse events			×	×	×	×		
Success of blinding					×			

baseline, days 5, 10, and 20 (weeks 1, 2, and 4), and weeks 8 and 12 of treatment. The Sunnybrook facial grading system (SFGS), the House-Brackmann facial nerve grading system (HBGS), and adverse events will be evaluated daily during treatment. During treatment, adverse events will be recorded in the Case Report Form (CRF) at any time.

Participants

Recruitment strategy

The participants of the study will be recruited from the outpatient, emergency, and ward departments of the CMU1H using WeChat advertising and posters. Interested patients can enquire from the clinician about the various details of the project through telephone or direct meetings. The investigator will also describe the purpose, content, research process, benefits, and risks of the study to the participants in detail. The researchers will screen the patients according to the study protocol, and eligible patients will then be recruited for the clinical trials.

Inclusion criteria

The study includes the following inclusion criteria:

(1) Participants who aged between 18 and 70 years;

(2) Participants who meet the diagnostic criteria for Bell's palsy, HBGS should be graded from II to VI, and the total score of SFGS should be ≤89;
(3) The onset is less than or equal to 3 days;
(4) The onset is unilateral; and
(5) Participants who agreed to participate in the investigation and sign the written informed consent.

Exclusion criteria

Participants who will meet any of the following conditions will be excluded:

(1) Participants who have otitis media, mastoiditis, labyrinthitis, mumps, and other complications of peripheral facial palsy;
(2) Participants who have a prior diagnosis of peripheral facial palsy caused by posterior fossa lesions such as acoustic neuroma, skull base meningitis, intracranial metastasis of cancer, and multiple sclerosis;
(3) Participants diagnosed with the central facial palsy;
(4) Participants diagnosed with Hunt's syndrome;
(5) Participants with serious cardiovascular and cerebrovascular diseases, diabetes, hypertension, serious primary diseases of the liver, kidney, lung, and blood system, malignant tumors, ulcers of the digestive system, and bleeding tendencies are expected to fail to complete the test;
(6) Participants who might be enrolled in other clinical trials within 1 month; glaucoma patients; and pregnant or lactation women or patients with severe allergic conditions. Those who have neurological, mental illness, illiteracy, or poor compliance in the screening process will not be eligible to fill in the questionnaire.

Sample size

The calculation of the sample size is based on the effective rate of acupuncture in the treatment of patients with Bell's palsy in the acute stage. According to the previous studies (22, 23) and pre-experimental analysis of the research group, it is estimated that the effective rate of the EA group is 98%, the A group is 95%, the AC group is 85%, the SA group is 74%, and the BC group is 70%. We used PASS 15 software to calculate and set $\alpha = 0.05$ and $\beta = 0.1$, and the results showed that the total sample size was at least 147 cases. It was observed that based on the ratio of the sample size of 1:1:1:1:1 in each group and considering the loss of follow-up rate of 10%, an optimal sample size of 33 participants should be recruited in each group. Therefore, a total of 165 participants should be recruited for this RCT.

Randomization

A random sequence will be generated based on block randomization by an independent research assistant using the software SPSS 26.0. The various eligible participants will be randomly divided into five groups with a 1:1:1:1:1 ratio. The treatment allocation codes will be enclosed by an independent researcher in sequentially numbered opaque envelopes until the first treatment schedule. To minimize coding interruptions, the chief investigator and result evaluators will also turn a blind eye to the treatment allocation.

Blinding

The blinding method will not be fully suitable for both patients due to the obvious difference in types of intervention between the BC group and the other groups. However, laboratory technicians, ultrasound doctors, and statisticians will be completely blinded. At the same time, this trial will be blinded to recruited patients, the acupuncturists, data collectors, assessors, and statisticians between the other four groups. Patients will be treated in separate rooms or a curtain will be used to cover the bed, while patients will be wearing an eye mask. In the sham acupuncture group, the acupoints will be on the face and the back of limbs, and the operation experience will be consistent with that of acupuncture.

Interventions

The interventions will be combined with the guidelines (3) published by the American Academy of Neurology (AAN) and the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) in 2013 and the preliminary experiments of this study (2). Acupuncture will be performed by three different experienced acupuncturists in accordance with STRICTA (19). The subjects in each group, except the blank control group, will receive either acupuncture, electroacupuncture, or sham acupuncture treatment 5 times per week for 4 weeks. Except for the acupuncture control group, patients in each group will receive the following medications. Prednisone acetate tablets will be administered orally at 30 mg per day for 5 days, then it will be reduced by 5 mg per day until discontinued for 10 days (Sinopharm, Rongsheng Pharmaceutical Co. LTD., Jiaozuo, China); Mecobalamin tablets of 0.5 mg will be orally administered, 3 times a day (Eisai (China) Pharmaceutical Co., LTD., Jiaozuo, China); and Vitamin B1 tablets of 10 mg will be administered orally 3 times a day (Fuzhou Haiwang Fuyao Pharmaceutical Co., LTD., Fuzhou, China). During the study, subjects will not be allowed to use traditional Chinese medicine treatment methods other than those prescribed medications to treat the disease (e.g., traditional Chinese medicine preparations, tuina therapy, etc.). The participants can withdraw from the trial for any reason and at any point in time. Researchers can remove participants from the trial with any of the following conditions: (1) the legal representative of the patient requested to withdraw from the study, (2) serious adverse events, and (3) death.

The acupuncture group and the acupuncture control group

The disposable sterile acupuncture needles will be used (0.25 × 40 mm, Suzhou Acupuncture Supplies Co., LTD., China). In all sessions, patients will be treated with eight core acupuncture points and four additional acupoints. The core acupoints will be BL02 (Cuanzhu), GB14 (Yangbai), ST2 (Sibai), SI18 (Quanliao), ST4 (Dicang), ST6 (Jiache), LI4 (Hegu), and LR3 (Taichong), and the additional acupoints can be chosen from the following points: middle

TABLE 2 Acupuncture points and methods.

Acupoint types	Acupuncture point	Direction	Depth (mm)	Electroacupuncture point
Core acupoints	BL02 (Cuazhu, affected side)	Oblique stab in the direction of the eyebrow arch	3–10	No
Core acupoints	GB14 (Yangbai, affected side)	Downward inclined stab	3–10	Yes
Core acupoints	ST2 (Sibai, affected side)	Perpendicular to the skin	3–10	No
Core acupoints	SI18 (Quanliao, affected side)	Perpendicular to the skin	3–10	Yes
Core acupoints	ST4 (Dicang, affected side)	Transversely toward ST6	3–10	Yes
Core acupoints	ST6 (Jiache, affected side)	Transversely toward ST4	3–10	Yes
Core acupoints	LI4 (Hegu, healthy side)	Perpendicular to the skin	3–10	No
Core acupoints	LR3 (Taichong, healthy side)	Perpendicular to the skin	3–10	No
Additional acupoints	DU26 (Shuigou)	Perpendicular to the skin	3–10	No
Additional acupoints	LI20 (Yingxiang, affected side)	Oblique to the nasal root along the nasolabial groove	3–10	No
Additional acupoints	EX-HN5 (Taiyang, affected side)	Lateral epicanthic spur	3–10	No
Additional acupoints	Ex-HN17 (Yifeng, affected side)	Perpendicular to the skin	3–10	No

TABLE 3 The location of stimulation points in the sham acupuncture group.

Stimulation point	Direction	Affected/ Healthy side
Stimulation point 1	The midpoint of the line between GB14 (Yangbai) and ST8 (Touwei)	Affected side
Stimulation point 2	The midpoint of the line between ST05 (Daying) and ST4 (Dicang)	Affected side
Stimulation point 3	The midpoint of the line between ST07 (Xiaguan) and SI18 (Quanliao)	Affected side
Stimulation point 4	The midpoint of the connection between the styloid process of the ulna and the olecranon	Healthy side
Stimulation point 5	The midpoint of the line between EX-HN5 (Taiyang) and SP5 (Shangqiu)	Healthy side

ditch askew plus DU26 (Shuigou); nasolabial fold becomes shallow add LI20 (Yingxiang); eyelid closure difficulty plus EX-HN5 (Taiyang); and pain behind the ear mastoid process Ex-HN17 (Yifeng). All acupoints will be carefully selected according to the clinical experience and the literature. After the acupuncture operation, the needle will be retained for 30 min before removal. The treatment will be performed once a day, 5 times as a course of treatment, with 2 days rest among the courses, for a total of 4 courses (weeks). The acupuncture group will be combined with the medicine therapy based on acupuncture treatment. The acupuncture control group will be treated with acupuncture only. The acupuncture points and methods are summarized in Table 2.

The electroacupuncture group

The acupuncture points and the treatment course of this group will be the same as those of groups A and AC, and four acupoints will be connected to an electroacupuncture device and treated with electroacupuncture. The needles on GB14 (Yangbai), SI18(Quanliao), ST4 (Dicang), and ST6 (Jiache) will be connected to the SDZ-II Acupuncture Stimulating Instruments (Suzhou Medical Supplies Factory Co., LTD., China) with 2-Hz frequency and the varying amplitude according to the comfort of the participants, ranging from 2 to 5 mA to enhance the sensation of acupuncture. The needles will be kept for 30 min and then removed.

The sham acupuncture group

Patients in this group will be treated with sham acupuncture at the following five non-meridian and non-acupoint stimulation points, and the specific location is shown in Table 3. The location of acupoints can be avoided by referring to the 2006 National Standard of the People's Republic of China (GB/T 12346-2006) *name and location of acupoints*. Patients will be placed in the supine position, their skin will be disinfected, and the Streitberger placebo needle (0.30 × 30 mm) will be used (24). When the needle is attached to the skin through a plastic ring, the patient might feel a tingling sensation, mimicking a puncture to the skin. However, when the needle is pressed against the skin, it does not penetrate the skin but instead retracts into the handle. The frequency, course, and time of acupuncture will be the same as those of the acupuncture group.

The blank control group

Except for the medicine therapy, no electropuncture, acupuncture, or sham acupuncture will be carried out during the whole experiment in this group.

Outcome measures

The outcome evaluation will be conducted at 6 time points, including the baseline, days 5, 10, and 20, and weeks 8 and 12 of

treatment. In addition, SFGS and HBGS will be evaluated before each treatment to evaluate the recovery rate. Safety measures will be assessed at the baseline and day 20 of the treatment. The evaluation schedule is shown in Table 1.

Primary outcome measures

The primary outcome is the effectiveness rate after the intervention period, which will be evaluated immediately at the end of treatment on the 20th day. Combined with the results of SFGS and HBGS, the efficacy evaluation criteria have been formulated according to the *Evaluation and efficacy standard of Integrated Chinese and Western Medicine for peripheral facial nerve palsy (draft)* by Yang et al. (25) as shown in Table 4. The effectiveness rate is calculated by dividing the sum of the number of cured, efficacious, and effective patients in each group by the number of patients in each group. The Sunnybrook facial grading system (SFGS) is composed of three distinct areas that generate a comprehensive score describing the overall static and dynamic state of the face. Final score = free movement points − static points − linkage points. SFGS score can range between 0 and 100, and the higher the score is, the better facial nerve function (26). The House-Brackmann facial nerve grading system (HBGS) is a scale for assessing the severity of Bell's palsy, which can potentially classify facial nerve injury into six grades (27). Grade I indicates normal function, grade II mild dysfunction, grade ≤ IV moderate palsy, and grade ≥ V severe palsy (27). SFGS and HBGS scores will be evaluated prior to each treatment until the end of the study and during the follow-up periods of 8 and 12 weeks of treatment.

- Recovery speed: the patient's recovery will be evaluated daily through SFGS and HBGS until the patient is assessed as "cure" according to the evaluation criteria for curative effect (Table 4). The period from baseline to this time is considered the recovery time. If the patient's recovery time is shorter, it will be considered that the recovery speed is faster.
- The diameter of the facial nerve: bilateral nerve color Doppler ultrasonography will be conducted by a board-certified neurosonologist in the Department of Ultrasound of CMU1H. The diameter of the main trunk and five branches of the facial nerve on both sides of the face will be measured three times, and the average value will be taken.
- Echo intensity and thickness of facial muscles: the thickness and recovery strength of the frontalis muscle, the orbicularis oculi muscle, the orbicularis oris muscle, the depressor anguli oris muscle, the depressor labii inferioris, and the mentalis muscle will be measured using a diagnostic ultrasound system. The determination of maximum muscle thickness has been reported to be orthogonal to the direction of muscle fibers (19). Thus, gray analysis will be used to quantify the echo intensity of each muscle (19). The results of three independent measurements for each muscle will be averaged to minimize the differences.
- Blood flow parameters of facial artery: color Doppler ultrasound will be used to measure and record the systolic peak velocity (Vs), end-diastolic velocity (Vd), and resistance index (RI) of bilateral facial artery, inferior labial artery, and superior labial artery. All data will be measured three times and thereafter averaged.
- The serum inflammatory level: at the baseline; 5, 10, and 20 days of treatment; 8 and 12 weeks of treatment; the count of neutrophils, lymphocytes, platelets; and the levels of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) will be measured to assess the levels of immune inflammation.
- Safety evaluation: the various safety indicators will be measured at the baseline and the end of treatment, including blood routine (the count of neutrophils, lymphocytes, platelets, monocytes, and hemoglobin content), the liver function (alanine aminotransferase and aspartate aminotransferase), and the kidney function (blood urea nitrogen and serum creatinine).
- Adverse events: acupuncture can exhibit potential adverse events, such as pain, hematoma, and infection, and the participants will be clearly informed about all these adverse events before signing informed consent. We will also provide appropriate medical care for the commonly observed adverse reactions. Any adverse events will be recorded by CRF. In case of serious adverse events, treatment will be terminated, and a detailed report will be made to researchers and the ethics committee within 24 h of the occurrence. The ethics committee will make recommendations and decide whether the patient can continue the treatment. We will give them proper compensation for their medical expenses.

TABLE 4 Evaluation criteria for curative effects.

Curative effect	HBGS	SFGS
Cure	Grade I	≥ 90
Efficacious	Grade II	70–89
Effective	Grade III	50–69
Ineffective	Grade IV and above	< 50

Data collection

The CRF will be completed by the clinical investigator. Clinical investigators will have to ensure accuracy, completion, and timely loading of data into CRF while preserving the original records. The completed CRF and other scales will be reviewed by the clinical supervisor and transferred to the data manager. To reduce shedding and increase study compliance, the investigator and data collector will remind the subjects about this procedure 1 day before the scheduled visit date.

Data management

There will be two data administrators entering and proofreading the data to ensure accuracy. If any problem is detected with the data, the data supervisor will ask the researcher for clarification. After the study, the clinical researchers, data managers, and statistical analysts will carefully review the established database. After a blind audit and confirmation of the correctness of the established database, principal researchers and statistical analysts will lock the data. The locked data files will remain unchanged. The data will only be used for this specific research project.

Confidentiality

All information collected during the study will be kept confidential and held by the investigator. The various researchers, members of the ethics committee, and relevant management departments have the right to review the information records of the participants to the extent permitted by the law. The personal information of the participants will not be independently disclosed in any research report or publications related to the project.

Patients and public involvement

Patients and the public will not participate in the analysis and evaluation of the results of this study. The results will be disseminated through publication in peer-reviewed journals.

Statistical analysis

The statistical analysis of this trial will use SPSS 26.0 software. To include the data of the participants who might withdraw later from the trial, all statistical analyses were based on the intention-to-treat population of all randomly assigned patients. Missing data will be analyzed using multiple imputations using the Markov chain Monte Carlo. The continuity data will be described as mean ± standard deviation (SD) or median and interquartile spacing. The classified data will be described with the frequency and percentage (*N*, %). The assessment of the difference between groups will use repeated measure analysis of covariance (ANCOVA) and trend chi-square, and the mixed effect model will also be used to evaluate the efficacy based on adjusting possible covariates. For results that require a comparison between multiple groups, Bonferroni will be used for multiple corrections. An interim analysis will be performed when half of the participants have completed the main outcome measurement.

Quality control

The participants involved in the implementation will be trained in a unified manner, using unified recording methods and judgment standards. We will formulate and implement rigorous, detailed, and feasible relevant standard operating procedures (SOP), and clinical supervisors and the data supervisors will carefully supervise the whole process of investigation according to the SOP. The investigator shall accurately and carefully record all the contents in CRF according to the filing requirements of the case report form so as to ensure the authenticity and reliability of the case report form. All observations and findings in the trial will be verified to ensure the reliability of the data and to ensure that all conclusions in the clinical trial have been derived from the original data.

Data monitoring and trial steering committee

The data and safety monitoring of this trial will be entrusted to the data monitoring committee (DMC) and the Data and Safety Monitoring Committee (DSMB) of CMU1H, which are independent of the sponsors and the research group and have no competitive interests. The main function of DMC will be to monitor the treatment and integrity of the trial data and conduct interim analysis to confirm whether the trial confirms the principles of this protocol. DSMB consists of five renowned experts in different fields and monitors the performance and safety of the trial every 6 months. It will have the right to obtain the various interim results of the trial, reveal a participant's allocated intervention, and make the final decision on whether to terminate the trial.

The modification of the protocol

Any modifications to the protocol will require the formal approval of the ethics committee of CMUIH and the Chinese clinical trial registry.

Post-trial care

This study does not plan to provide any post-trial care.

Trial status

The version number of this protocol is 2.0, dated 1 June 2021. The clinical trial is currently underway. The recruitment started on 1 October 2021 and is scheduled to be completed by the end of 2025.

Discussion

A number of studies have shown the effectiveness and safety of acupuncture in the treatment of Bell's palsy, and acupuncture has been widely used in the non-drug alternative treatment of Bell's palsy. However, it is still not clear whether acupuncture can be applied to patients in the acute phase, especially electroacupuncture.

The main controversy is whether acupuncture is beneficial to facial edema in the acute stage of Bell's palsy (28, 29). To the best of our knowledge, this clinical trial is the first study planned to analyze the effect of facial edema in patients with Bell's palsy in the acute phase by using facial nerve color Doppler ultrasound. The main purpose of this trial is to present a well-designed parallel randomized sham-control trial to evaluate the potential efficacy of different acupuncture modalities on acute Bell's palsy patients and its effect on facial nerve edema. It also aims to preliminarily explore its mechanism through inflammatory and immune indicators to provide a reference for the selection of clinical acupuncture treatment opportunities.

First, we have designed two observation groups and three control groups. These groups have been allocated adequately to completely compare the effects of acupuncture, electroacupuncture, and medicine treatment on patients with Bell's palsy in the acute phase. To determine whether real acupuncture or placebo effect might be responsible for the treatment, non-point and non-transdermal operation of overlapping blunt needles will be performed as sham acupuncture control.

Second, to achieve better therapeutic effects, we have chosen a semi-standardized acupoint selection scheme of core acupoints and additional acupoints according to the guidelines (12) and the clinical

experience of acupuncturists in the department, and light stimulation will be given according to the principle of "shallow needling and less needling in acute stage." For the selection of acupoints in the SA group, non-meridian and non-acupoint stimulation will also be selected to eliminate the interference of meridians and acupoints.

Third, the combination of HBGS and SFGS will be used as the evaluation standard of curative effect. HBGS is a scale for assessing the severity of Bell's palsy, recommended by AAN and AAO-HNSF (2). HBGS has emerged as the most commonly used and reliable scale in clinics and has been widely used. However, its practicality is significantly limited due to observations of only large-scale effects. SFGS has gradually attracted the attention of researchers at home and abroad in recent years. A number of researchers have indicated that SFGS is the best scoring system for facial palsy and have recommended it as a supplement to the longitudinal grading score of HBGS (30, 31). The system is sensitive to the facial improvement evaluation and can display a higher value for follow-up (32). Therefore, the combination of HBGS and SFGS can be used to comprehensively evaluate the degree of facial paralysis and facial nerve functions.

Fourth, in addition to the diameter of the trunk, the acquisition of color Doppler ultrasound of the facial nerve also includes the diameter and echo intensity of the five branches to completely determine the situation of facial nerve edema. For the facial blood flow information, Vs, Vd, and RI of the facial artery will be collected by ultrasonic Doppler to observe the potential effect of acupuncture on facial blood flow in patients with Bell's palsy in the acute phase. The thickness and echo intensity of five different facial muscles, such as the frontal muscles, will be measured to observe the effect of acupuncture on the facial muscles in patients. This will aid us to observe the possible improvement of facial blood circulation and muscle activity in patients with acute Bell's palsy by acupuncture.

Fifth, although the pathogenesis of Bell's palsy is not completely clear, inflammation plays an important role in this condition. Most researchers agree that an abnormal immune response caused by viral infection is closely related to the occurrence and development of facial nerve palsy. Thus, strategies to control the degree of neuroinflammatory response can prove to be beneficial to the outcome of the disease by functionally regulating the immune function of the body (33). The neutrophil-to-lymphocyte (NLR) ratio has been recognized as a new potential marker to determine inflammation, which is routinely measured in peripheral blood and plays a vital role in evaluating Bell's facial palsy (34, 35). The guidelines for the management of acute Bell's palsy, published by the French Society of ENT and Head and Neck Surgery (SFORL) in 2020, also recommended that a complete blood count screen for neutrophil/lymphocyte ratios should be conducted, as elevated levels might suggest a poor prognosis (8). The measurements of the serum samples from patients with Bell's palsy showed significantly higher levels of IL-6, IL-8, and TNF-α in patients with Bell's palsy compared to controls (36). In addition, a previous study aimed at understanding the mechanism of EA in the treatment of patients with lumbar disc herniation, which is also a neuro edema disease, and found that EA can effectively reduce the levels of IL-2, TNF-α, and IL-6 contents (37).

Meanwhile, this trial might face some potential challenges that must be solved. First of all, since patients with Bell's palsy will be recruited within 3 days of onset, the number of patients may be small. Thus, we have made widespread use of the internet and community publicity to increase awareness, and at the same time, we will provide free examination and treatment for patients to draw attention from patients. Second, to completely ensure blindness in the four groups besides the BC group, the treatment will be conducted in a separate room or a curtain will be used to cover the bed, while patients will be wearing an eye mask. Third, to improve compliance and reduce the rate of loss to follow-up, the researchers will remind the patient 1 day before the examination, and the patient will be accompanied by a special person.

Although there are many difficulties associated with this study, we will strive to conduct research according to the research norms and to ensure the research quality meets the highest standard. This is the first clinical observation using facial nerve color ultrasound to explore the potential therapeutic effect and the recovery of facial nerve edema of different acupuncture modalities on patients with Bell's palsy in the acute phase and to initially explore its possible mechanisms. The results of this study will help to provide novel visual evidence for applications of different acupuncture modalities in the treatment of patients with Bell's palsy in the acute phase.

Ethics statement

The studies involving humans were approved by evidence-based capacity building project for basic Chinese medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZW: Investigation, Writing – original draft. JZ: Funding acquisition, Software, Writing – review & editing. ZZ: Investigation, Methodology, Visualization, Writing – review & editing. YL: Investigation, Methodology, Writing – review & editing. SR: Project administration, Supervision, Writing – review & editing. HS: Data curation, Formal analysis, Writing – review & editing. DM: Investigation, Software, Writing – review & editing. RL: Investigation, Validation, Writing – review & editing. YZ: Conceptualization, Project administration, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1327206/full#supplementary-material

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Glossary

SFGS	Sunnybrook facial grading system
HBGS	House-Brackmann facial nerve grading system
MRI	Magnetic resonance imaging
RCT	Randomized controlled trial
CMU1H	First Affiliated Hospital of China Medical University
TCM	Traditional Chinese medicine
CONSORT	Consolidated Standards of Reporting Trials
STRICTA	Standards for Reporting Intervention in Controlled Trials of Acupuncture
A	Acupuncture
EA	Electroacupuncture
SA	Sham acupuncture
BC	Blank control
AC	Acupuncture control
AAN	American Academy of Neurology
AAO-HNSF	American Academy of Otolaryngology-Head and Neck Surgery Foundation
Vs	Systolic peak velocity
Vd	End-diastolic velocity
RI	Resistance index
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
TNF-α	Tumor necrosis factor-α
CRF	Case Report Form
SD	Standard deviation
ANCOVA	Analysis of covariance
SOP	Standard operating procedures
NLR	Neutrophil-to-lymphocyte
SFORL	French Society of ENT and Head and Neck Surgery

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Acupuncture therapy on myofascial pain syndrome: a systematic review and meta-analysis

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Purpose: Traditional Chinese medicine (TCM) therapies, especially acupuncture, have received increasing attention in the field of pain management. This meta-analysis evaluated the effectiveness of acupuncture in the treatment of myofascial pain syndrome.

Methods: A comprehensive search was conducted across a number of databases, including PubMed, Cochrane Library, WOS, CNKI, WANFANG, Sinomed, and VIP. Furthermore, articles of studies published from the inception of these databases until November 22, 2023, were examined. This systematic review and meta-analysis encompassed all randomized controlled trials (RCTs) on acupuncture for myofascial pain syndromes, without language or date restrictions. Based on the mean difference (MD) of symptom change, we critically assessed the outcomes reported in these trials. The quality of evidence was assessed using the Cochrane Risk of Bias Tool. The study is registered with PROSPERO under registration number CRD42023484933.

Results: Our analysis included 10 RCTs in which 852 patients were divided into two groups: an acupuncture group (427) and a control group (425). The results of the study showed that acupuncture was significantly more effective than the control group in treating myofascial pain syndromes, which was reflected in a greater decrease in VAS scores (MD=−1.29, 95% [−1.65, −0.94], $p<0.00001$). In addition, the improvement in PRI and PPI was more pronounced in the acupuncture group (PRI: MD=−2.04, 95% [−3.76, −0.32], $p=0.02$) (PPI: MD=−1.03, 95% [−1.26, −0.79], $p<0.00001$) compared to the control group. These results suggest that acupuncture is effective in reducing myofascial pain. It is necessary to further study the optimal acupoints and treatment time to achieve the best therapeutic effect.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42023484933.

KEYWORDS

acupuncture, myofascial pain syndrome, complementary and alternative therapies, pain, traditional Chinese medicine

Background

The traditional definition of myofascial pain syndrome (MPS) suggests that regional pain originates from hyperirritable spots located within the taut band of skeletal muscle, referred to as myofascial trigger points (MTrPs) (1). Myofascial pain syndrome (MPS) is regarded as one of the most prevalent chronic musculoskeletal pain syndromes. The prevalence of MPS may be as high as 85% in pain clinics (2). Common causes of MPS and dysfunction may include direct or indirect trauma, spinal pathology, exposure to cumulative and repetitive strain, postural dysfunction, and physical disorders (3, 4). The pharmacological management of myofascial pain predominantly involves analgesics and muscle relaxants, with nonsteroidal anti-inflammatory drugs (NSAIDs) being the most frequently prescribed medications. Despite the widespread use of oral NSAIDs, there is a dearth of randomized controlled trials (RCTs) specifically assessing their efficacy for myofascial pain syndrome (MPS). Consequently, there exists a paucity of robust evidence regarding the effectiveness of anti-inflammatory drugs in treating MPS. Moreover, caution should be exercised regarding the prolonged use of oral NSAIDs due to potential gastrointestinal, renal, and antiplatelet adverse effects (5).

Over the past few decades, there has been a notable rise in clinical and scientific attention toward using acupuncture to treat myofascial pain syndrome (MPS). Many clinical studies, especially randomized controlled trials (RCTs), have explored acupuncture's potential as an intervention for MPS. These studies have consistently demonstrated positive effects of acupuncture in alleviating pain. Several clinical trials and systematic evaluations have indicated that acupuncture can effectively reduce both pain and irritability associated with MPS (6, 7). While the precise mechanism of acupuncture for myofascial pain syndrome (MPS) remains to be fully elucidated, mechanistic studies have concentrated on both peripheral and central aspects. Nevertheless, research indicates that acupuncture can suppress pain transmission by reducing substance P (SP) levels and enhancing the release of endogenous opioids (8, 9). A recent study revealed that acupuncture enhances strength, function, and locomotor activity in a rat model of muscle pain syndrome through its antioxidant effects (10). Additionally, another study demonstrated that acupuncture at trigger points modulated gene expression in muscle tissue, consequently promoting muscle regeneration. Regarding the central aspect, some scholars advocate the notion that acupuncture can activate supraspinal and higher centers engaged in pain processing (11).

Despite the increasing wealth of clinical evidence on the management of myofascial pain in recent years, there is a noticeable absence of more recent meta-analyses focusing on the overall efficacy of acupuncture for this condition. This gap highlights the need for more focused meta-analyses, especially as clinical trials advance. Our proposed meta-analysis aims to fill this void by assessing acupuncture's effectiveness for myofascial pain using clearly defined outcome measures. The goal of our meta-analysis is to provide valuable insights and information for future clinical treatment strategies, which will be especially helpful for physicians seeking effective approaches to manage myofascial pain.

Methods

Search strategy and data mining

For our systematic review and meta-analysis, we searched various literature databases, including PubMed, Cochrane Library, WOS, CNKI, WANFANG, Sinomed, and VIP. The search aimed to identify randomized controlled trials (RCTs) on the effects of acupuncture for myofascial pain syndromes from the inception of each database to November 22, 2023. For the searches, we performed separate searches for acupuncture and myofascial pain, and then combined the results of both searches. We independently conducted a comprehensive review of all relevant published meta-analyses and their reference lists, without imposing any specific limitations on article types. Based on our knowledge, there have been no recent updates on this topic, which supports our claim. The search strategies used in this study are extensively detailed in Supplementary File 1.

Literature selection

Our inclusion criteria for the retrieved studies were as follows: (1) Diagnosis of "myofascial pain syndrome" based on clear diagnostic (inclusion) criteria (12–14). The patient's diagnosis was not influenced by other co-morbidities. (2) In these trials, the treatment modality in the experimental group was acupuncture added to the control group. The manipulation and specific acupuncture points used in research are not limited. (3) Any type of control group can be considered as a control group, including traditional western medicine control group, routine care control group and blank control group. (4) Outcomes: Evaluation of the quality of pain management should include at least one of the following scales: 1. Pain Rating Index (PRI). 2. Present Pain Intensity (PPI). 3. Visual Analog Scale (VAS) scores. 4. Efficacy of diagnostic and therapeutic criteria for TCM syndromes. 5. Efficacy of clinical research guidelines for TCM (new medicines) or other meta-analyses referring to extrapolable data on myofascial pain syndromes. 6. The validity of the analysis. Exclusion criteria: patients with one or more other types of pain in addition to myofascial pain syndrome; other interventions such as moxibustion, transcutaneous electrical nerve stimulation, acupoint injections, etc. were used in the study; the paper was only an abstract or review; the study did not have outcome indicators; or the complete literature was not available.

Data collection

All exclusion and inclusion criteria will be discussed and determined by all researchers prior to the start of the study. At the formal start of the screening phase, each of the two researchers will independently review all study titles and abstracts according to the criteria discussed beforehand, exclude obviously irrelevant literature, and then read the full text of the screened articles. After further screening, the final literature for inclusion was identified, and then the basic information of the articles was extracted along with the data for the set endpoints without knowledge of each other's review. Finally, the results were cross-checked. When the results of two researchers conflicted, a third researcher stepped in to resolve the disagreement.

In the extraction of basic information and data, we mainly recorded the authors of the article and the time of the study, the age of the samples included in the study, the duration of myofascial pain, the number of samples, the measures of the intervention and the control group, the site of pain and the time of application of acupuncture. For the outcome indicators, the values of the primary and secondary outcome indicators were extracted and recorded.

Quality assessment

We assessed bias in the randomized controlled trials included in the review by means of the Revised Cochrane Risk of Bias Tool (RoB-2) (15). We scored high, medium and low risk based on the risk entries after reading the full text of the included studies, and the specific criteria for each score will refer to Cochrane's meta-analysis criteria, and then presented the results of our comprehensive bias assessment through the use of Revman 5.4 software, which graphically and clearly depicts the possible bias in these trials, helping us to clearly understand the specific quality and potential risk of the included articles.

Statistical analysis

Revman software for meta-analysis. Visualization was achieved through forest plots. Statistical analyses were performed using mean difference (MD), and heterogeneity was assessed using the I^2 index. When the effects showed heterogeneity ($I^2 > 50\%$), the analysis was performed using a random-effects model; when the data showed homogeneity, the analysis was performed using a fixed-effects model (16).

Results

Search results

Initially, a total of 6,234 potential research articles were identified through our search using the designated terms. We then excluded 2,876 duplicate studies using EndNote 20 software. After reviewing titles and abstracts, we identified 2,690 articles that were not relevant to the study and excluded them. In addition, we excluded 300 articles because they were reviews or conference materials. We then thoroughly examined the full text of the remaining 367 articles. Of these, 357 articles were excluded for reasons such as being retrospective studies or not related to acupuncture for myofascial pain symptoms. Ultimately, after careful review, a total of 10 clinical studies met the criteria and were deemed suitable for inclusion in the meta-analysis (17–26) (Figure 1).

Characteristics of the included studies

A total of 852 patients were included in the 10 trials, including 427 in the acupuncture group and 425 in the control group (17–26). Of the 10 studies, seven groups were treated with direct acupuncture (17, 19, 21–25), and three studies used acupuncture and massage (18, 20, 26). In five studies, the control group used medication for oral treatment (18–21, 26). Several other studies one used rehabilitation (17), one used lidocaine injections (22), one used McKenzie therapy. The remaining two studies control group was treated with herbal medicine (23, 24). For the diagnosis of myofascial pain syndrome, 3 studies used the Pain Science (19, 21, 22). The diagnostic criteria were: the diagnostic criteria were categorized into major and minor criteria, and five major criteria and at least one minor criterion were met to diagnose MPS. Primary criteria: (1) complaints of regional pain; (2) sensory abnormalities in the area of expected distribution of the complaints of pain or trigger point tenderness; (3) palpable tension zone in the affected muscle; (4) intense point tenderness at a point within the tension zone; (5) some degree of restriction of movement during measurement. Secondary criteria: (1) repetition of the complained clinical pain or sensory abnormality at the pressure point; (2) localized twitch response induced by lateral grasping or needle insertion into the trigger point of the band; (3) relief of pain by stretching the muscle or injecting the trigger point. Three studies used the Criteria for Diagnosis and Efficacy of Diseases in Traditional Chinese Medicine (19, 22, 25), and four studies used other criteria such as the Guiding Principles for Clinical Research of New Traditional Chinese Medicines, and Surgical Treatment of Cervical Spine Disease (17, 23, 24, 26). Six of the 10 studies treated neck and shoulder myofascial pain (17–20, 25, 26) and four studies were on low back myofascial pain (21–24). Table 1 shows the main characteristics of the included studies: including the sample sizes of the two groups, the ages of the included patients, the treatments used in the treatment group, the treatments used in the control group, and the duration of myofascial pain syndrome. Regarding the efficacy criteria of the included studies, eight studies assessed the VAS (17–23, 26), four studies assessed the PPI and PRI scores (19, 20, 22, 23), and nine studies assessed the efficacy of the treatments using the treatment criteria of TCM evidence (17–25). Table 2 shows the outcome indicators of the included studies.

Quality assessment

The methodological assessment results are depicted in Figure 2. Out of the 10 studies employing random allocation methods, 9 were appraised as low risk due to the utilization of a randomized table of numbers (17, 19–26), while 1 study was deemed to have an unclear risk of bias due to inadequate information (18). None of these studies provided sufficient detail about the allocation concealment process to warrant a clear risk of bias judgment. Similarly, none of them involved blinding of subjects or administrators due to notable discrepancies in acupuncture treatment utilization between the treatment and control groups. All studies were found to have complete outcome data with a low risk of bias (17–26). Six studies were classified as having a low risk of bias for selective reporting (17–19, 21–23), as they reported all prespecified endpoints. Conversely, four studies were identified as having a high risk of bias for selective reporting due to poor endpoint reporting (20, 24–26). Additionally, insufficient data were available in the 10 studies to assess other risks of bias.

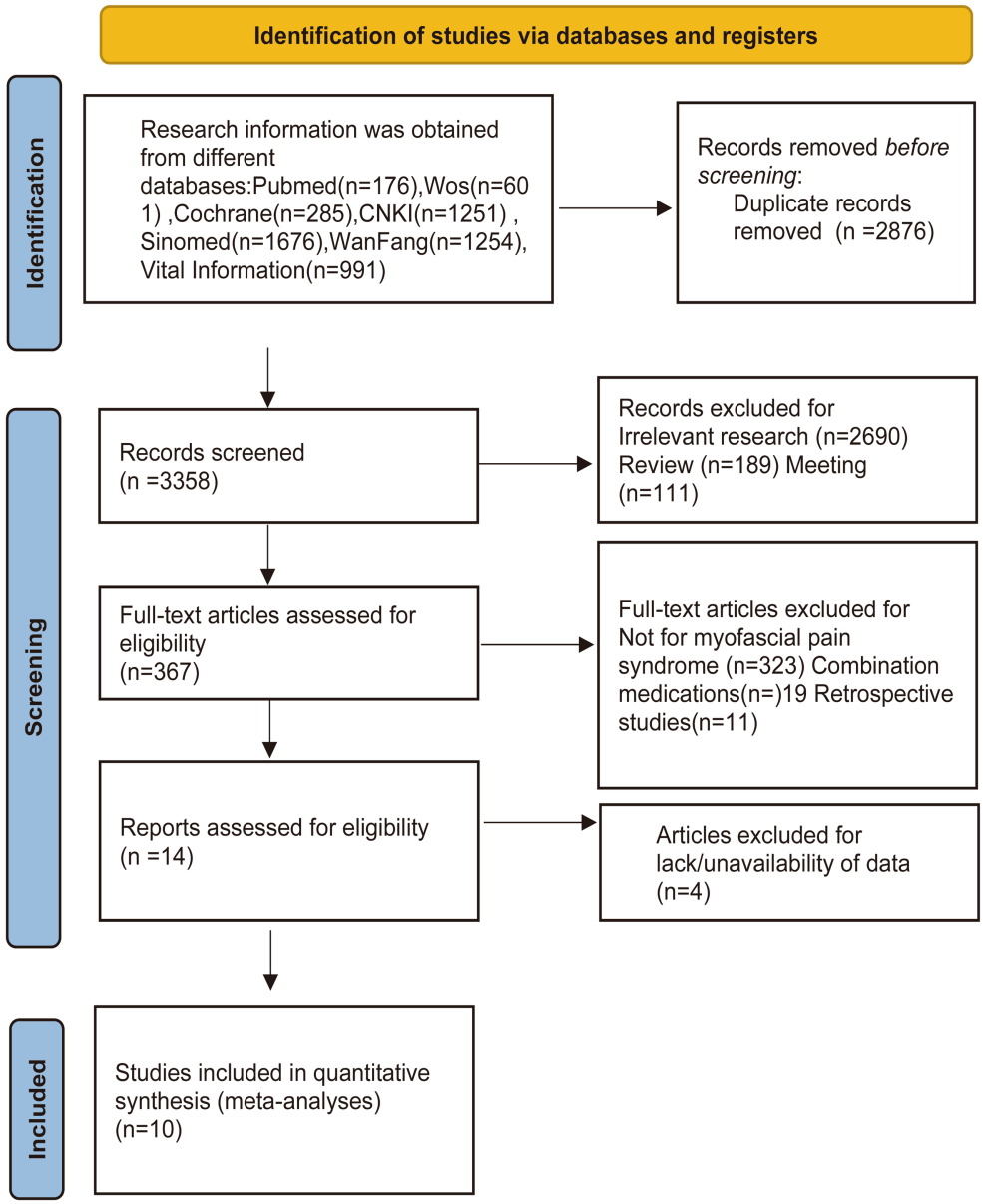

FIGURE 1
Flow diagram showing the screening and selection process of reports to be included in the meta-analysis.

Results of individual studies

Main outcome indicators

Visual analog scale (VAS)

The Visual Analog Scale (VAS) is a commonly used tool for assessing pain intensity. It consists of a horizontal or vertical line, usually 10 centimeters in length, with anchor points at each end representing the extremes of pain intensity (e.g., "no pain" to "worst pain imaginable"). Patients are asked to mark on the line the point that best represents their current level of pain. The distance from the "no pain" end of the line to the patient's mark is measured and recorded, providing a numerical value that represents the intensity of the pain experienced by the patient. The VAS score can range from 0 to 10 or from 0 to 100, with higher scores indicating greater pain intensity. A total of 8 articles assessed VAS scores in 694 patients, 348 in the acupuncture group and 346 patients in the control group (17–23, 26). Notably, VAS values were significantly lower in patients who underwent acupuncture treatment than in the control group. Due to substantial heterogeneity among these studies ($I^2 = 98\%$, $p < 0.00001$), we employed a random-effects model. The combined results, as depicted in Figure 3, revealed a statistically significant difference in VAS scores (MD = −1.29, 95% CI [−1.65, −0.94], $p < 0.00001$). These findings indicate that the acupuncture treatment group exhibited greater improvement in myofascial pain compared to the control group To ensure the stability of our findings, we excluded each study and observed the changes in the combined results after exclusion. We found that the results showed consistency after the exclusion of each study, which demonstrated the stability of our conclusion that the acupuncture group had a

TABLE 1 Characteristics of included studies.

Author	Age (years)	Duration of disease (years)	Number of acupuncture group	Number of control group	Acupuncture group	Control group	Location of pain	Frequency of acupuncture	Outcome indicator
Chen et al. (17)	Acupuncture group:57.73 ± 9.81 control group:58.49 ± 10.87	Acupuncture group:0.2 ± 0.08 control group:0.19 ± 0.09	30	30	Control group+acupuncture	Convalescent training	Neck and shoulder	5 times per week for 1 month	Clinical efficacy, VAS
Xiaolu (18)	Acupuncture group:63.32 ± 2.76 control group:63.35 ± 2.73	Acupuncture group:2.11 ± 0.06 control group:2.09 ± 0.05	56	56	Control group+acupuncture and massage	Celecoxib	Neck and shoulder	Every two days for one month	Clinical efficacy, VAS
Xi-liang (19)	Acupuncture group:45.17 ± 5.09 control group:45.87 ± 5.23	Acupuncture group:1.04 ± 0.23 control group:1 ± 0.22	46	45	Control group+acupuncture	Indomethacin + Tizanidine Hydrochloride	Neck and shoulder	Every two days for 14 days	Clinical efficacy, VAS, PPI, PRI
Kang (20)	Acupuncture group:45.72 ± 4.80 control group:45.13 ± 5.04	NA	30	30	Control group+acupuncture and massage	Tizanidine	Neck and shoulder	NA	Clinical efficacy, VAS, PPI, PRI
Hongliang et al. (21)	Acupuncture group:42.96 ± 8.22 control group:43.65 ± 8.62	Acupuncture group:1.94 ± 0.72 control group:1.71 ± 0.73	46	46	Control group+acupuncture	Paracetamol	Lower back	Once a day for 14 days	Clinical efficacy, VAS
Xiongjiang et al. (22)	Acupuncture group:43.96 ± 8.42 control group:44.65 ± 8.72	NA	48	48	Control group+acupuncture	Lidocaine injection	Lower back	Every two days for 20 days	Clinical efficacy, VAS, PPI, PRI
Wang (23)	Acupuncture group:49.58 ± 2.74 control group:49.43 ± 2.89	Acupuncture group:5.98 ± 1.01 control group:5.78 ± 1.09	42	41	Control group+acupuncture	Massage	Lower back	6 times per week for 21 days	Clinical efficacy, VAS, PPI, PRI
Zhijuan etal (24)	Acupuncture group:34.10 ± 9.55 control group:34.12 ± 9.54	Acupuncture group:3.25 ± 1.05 control group:3.24 ± 1.02	49	49	Control group+acupuncture	Hot compress with Chinese medicine	Lower back	1 time per week for 2 weeks	VAS
Yuxia (25)	NA	NA	30	30	Control group+acupuncture	McKenzie therapy	Neck and shoulder	Every two days.	VAS
Hongsheng et al. (26)	Acupuncture group:62.39 ± 5.92 control group:63.51 ± 6.37	Acupuncture group:2.36 ± 5.28 control group:2.41 ± 4.94	50	50	Control group+acupuncture and massage	Celecoxib	Neck and shoulder	Three times a week for one month	Clinical efficacy

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TABLE 2 Data on outcome indicators included in the study.

Author	Number of acupuncture group	Number of control group	VAS	Clinical efficacy	PPI	PRI
Chen et al. (17)	30	30	Acupuncture group:1.78 ± 0.81 control group:4.66 ± 1.72	Acupuncture group:20(significant efficiency)28(efficiency) control group:14(significant efficiency)25(efficiency)	NA	NA
Xiaolu (18)	56	56	Acupuncture group:1.44 ± 0.08 control group:1.98 ± 0.21	Acupuncture group:52(significant efficiency)55(efficiency) control group:45(significant efficiency)47(efficiency)	NA	NA
Xi-liang (19)	46	45	Acupuncture group:3.52 ± 0.49 control group:4.79 ± 0.52	Acupuncture group:31(significant efficiency)44(efficiency) control group:18(significant efficiency)39(efficiency)	Acupuncture group:1.16 ± 0.12 control group:1.99 ± 0.16	Acupuncture group:1.57 ± 0.16 control group:2.01 ± 0.18
Kang (20)	30	30	Acupuncture group:1.18 ± 0.32 control group:4.79 ± 0.52	Acupuncture group:18(significant efficiency)28(efficiency) control group:10(significant efficiency)21(efficiency)	Acupuncture group:1.10 ± 0.26 control group:2.45 ± 0.47	Acupuncture group:0.48 ± 0.08 control group:1.09 ± 1.20
Hongliang et al. (21)	46	46	Acupuncture group:2.33 ± 0.22 control group:3.43 ± 0.20	Acupuncture group:31(significant efficiency)40(efficiency) control group:24(significant efficiency)38(efficiency)	NA	NA
Xiongjiang et al. (22)	48	48	Acupuncture group:2.33 ± 0.51 control group:2.67 ± 0.42	Acupuncture group:31(significant efficiency)42(efficiency) control group:29(significant efficiency)43(efficiency)	Acupuncture group:0.83 ± 0.11 control group:1.54 ± 0.24	Acupuncture group:6.48 ± 1.01 control group:9.79 ± 1.08
Wang (23)	42	41	Acupuncture group:2.24 ± 0.80 control group:4.31 ± 0.82	Acupuncture group:31(significant efficiency)41(efficiency) control group:21(significant efficiency)35(efficiency)	Acupuncture group:0.92 ± 0.30 control group:2.21 ± 0.50	Acupuncture group:6.31 ± 1.14 control group:10.14 ± 1.22
Zhijuan et al. (24)	49	49	NA	Acupuncture group:42(significant efficiency)48(efficiency) control group:28(significant efficiency)41(efficiency)	NA	NA
Yuxia (25)	30	30	NA	Acupuncture group:10(significant efficiency)28(efficiency) control group:7(significant efficiency)26(efficiency)	NA	NA
Hongsheng et al. (26)	50	50	Acupuncture group:1.24 ± 0.32 control group:3.12 ± 0.84	NA	NA	NA

significantly lower VAS than the control group after treatment. Therefore, we can state that for myofascial pain, acupuncture treatment is effective in reducing the pain level of patients compared to the control group.

To ensure the accuracy of the results, we performed subgroup analyses for the different acupuncture interventions in the treatment groups (acupuncture, acupuncture combined with massage) (Figure 4). Acupuncture combined with massage treatments were mainly based on rubbing and pressing on the affected acupoints on the basis of acupuncture, and crossing the hands to squeeze and knead the patient's painful areas of the tendons in front of and behind the muscles. The results showed that there was a statistical effect of both acupuncture and acupuncture combined with massage on the outcome of myofascial pain ($p < 0.00001$) and there was no heterogeneity between the two groups ($I^2 = 0\%$). To further investigate the treatment of myofascial pain with acupuncture, we performed a subgroup analysis of patient age and pain site, which showed that differences in patient age and pain site did not affect the results, and there was no heterogeneity between the different subgroups. The results of the subgroup analysis showed the robustness of the results of acupuncture for myofascial pain.

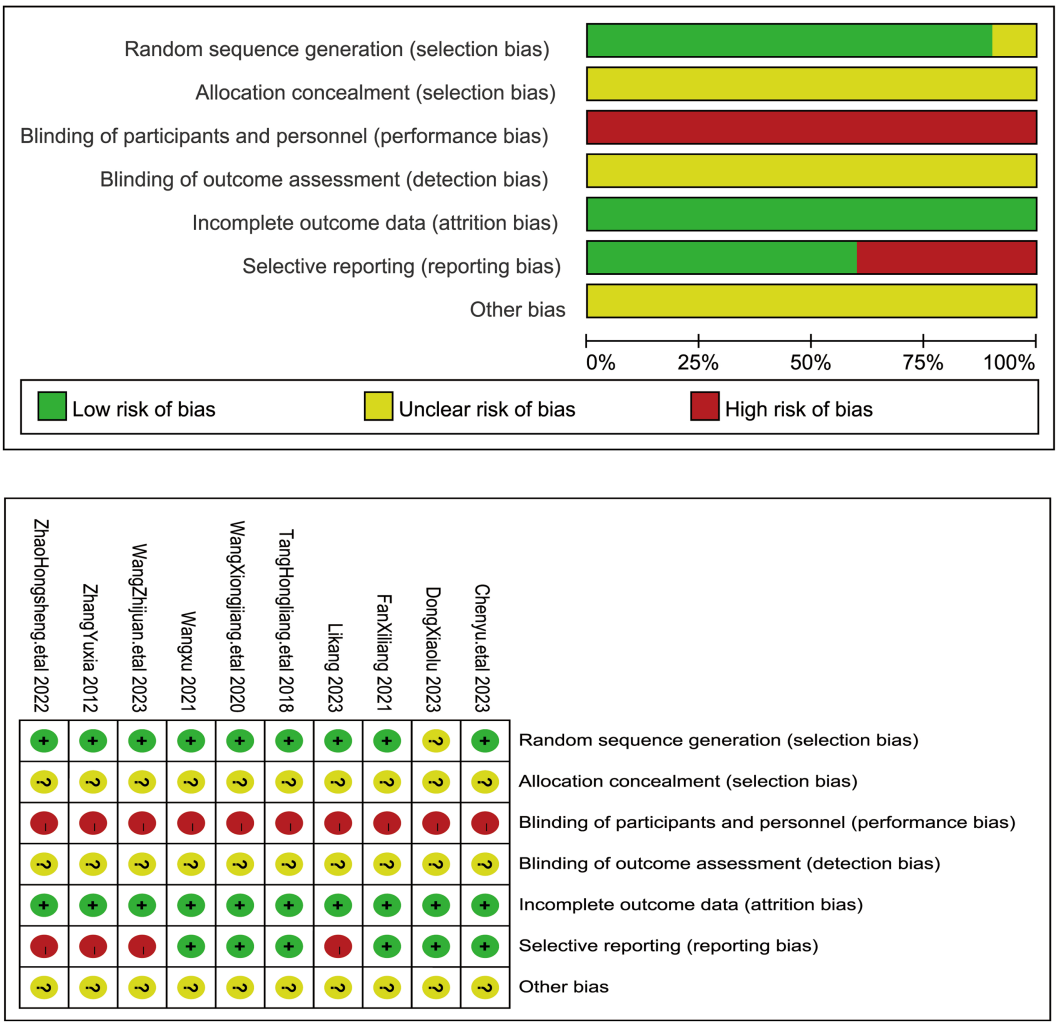

FIGURE 2
The figure represents the risk of bias assessment for the studies selected in the meta-analysis.

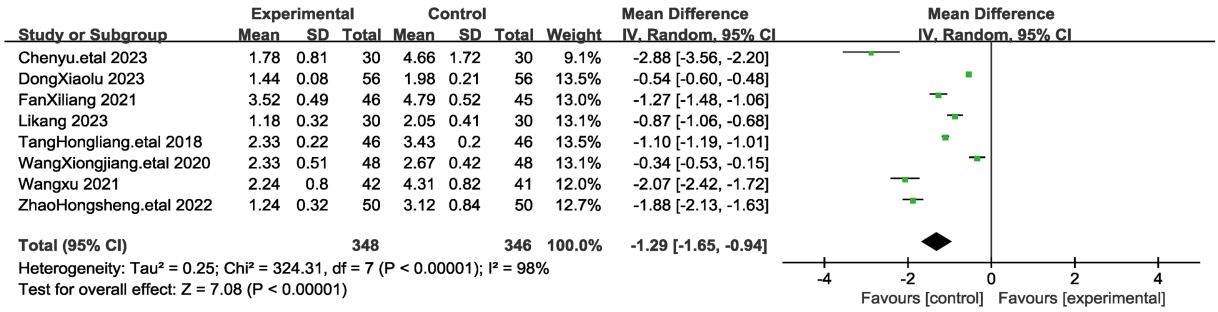

FIGURE 3
The figure represents a forest plot of the meta-analysis for Visual analog scale (VAS). Each row represents a study and lists the name of the study, the mean systolic blood pressure and standard deviation for the acupuncture and control groups, the sample size, and the mean difference and its 95% confidence interval.

Secondary outcome indicators

Pain rating index (PRI)

The Pain Rating Index (PRI) is a component of the McGill Pain Questionnaire, a widely used tool for assessing the quality and intensity of pain. The PRI consists of 78 pain descriptors divided into 20 groups, each representing a different quality of pain (such as throbbing, shooting, stabbing, etc.). Patients are asked to indicate which words best describe their pain, and each selected word is assigned a numerical value based on its rank in the group (e.g., the

first word selected is assigned a value of 1, the second word a value of 2, and so on). The PRI score is calculated by summing the numerical values of all selected words, providing a measure of the overall intensity of pain descriptors chosen by the patient. A total of 4 articles evaluated PRI scores in 330 patients, 166 in the acupuncture group and 164 patients in the control group (19, 20, 22, 23). Notably, PRI values were significantly lower in patients who underwent acupuncture treatment than in the control group. Due to the significant heterogeneity between these studies ($I^2 = 99\%$, $p < 0.00001$), we used a random effects model for the analysis. The results of the combined analysis showed (Figure 5) that there was a significant difference in PRI between the acupuncture group and the control group (MD = −2.04, 95% CI [−3.76, −0.32], $p = 0.02$), suggesting that acupuncture treatment was more effective in improving myofascial pain. To ensure the stability of our findings, we excluded each study and observed the changes in the combined results after exclusion. We found that the results showed consistency after the exclusion of each study, which demonstrated the stability of our conclusion that the acupuncture group had a significantly lower PRI than the control group after treatment. Therefore, we can state that for myofascial pain, acupuncture treatment is effective in reducing the pain level of patients compared to the control group.

Present pain intensity (PPI)

Present Pain Intensity (PPI) is a scale used to assess the current level of pain experienced by an individual. It is commonly used in clinical settings and research studies to quantify pain intensity at a specific point in time. The PPI scale typically ranges from 0 to 10, with 0 indicating no pain and 10 indicating the worst possible pain. Patients are asked to rate their current pain level on the PPI scale, providing a subjective measure of their pain intensity. This rating can be used to monitor changes in pain over time, assess the effectiveness of pain management interventions, and guide treatment decisions. A total of 4 articles evaluated PPI scores in 330 patients, 166 in the acupuncture group and 164 patients in the control group (19, 22, 23). Notably, PPI values were significantly lower in patients who underwent acupuncture treatment than in the control group. Due to the significant heterogeneity between these studies ($I^2 = 95\%$, $p < 0.00001$), we used a random effects model for the analysis. The results of the combined analysis showed (Figure 6) that there was a significant difference in PPI between the acupuncture group and the control group (MD = −1.03, 95% CI [−1.26, −0.79], $p < 0.00001$), suggesting that acupuncture treatment is more effective in improving myofascial pain. To ensure the stability of our findings, we excluded each study and observed the changes in the combined results after exclusion. We found that the results showed consistency after the exclusion of each study, which demonstrated the stability of our conclusion that the acupuncture group had a significantly lower PPI than the control group after treatment. Therefore, we can state that for myofascial pain, acupuncture treatment is effective in reducing the pain level of patients compared to the control group.

Diagnostic efficacy criteria for Chinese medicine diseases

Nine studies evaluated the efficacy of acupuncture treatment involving 752 patients (17–25), and the efficacy was assessed according to the Criteria for Diagnosis and Efficacy of Traditional Chinese Medicine (TCM) Conditions for Myofascial Pain Syndrome. Cure: Symptoms and signs disappear and the patient is able to return to normal work. Significant effect: disappearance of signs and symptoms, no limitation of activity, only pain and discomfort. Effective: improvement of symptoms, reduction of pain, mild limitation of activity; Ineffective: no improvement of symptoms and signs. We combined the cure rate and the significant efficiency rate into the significant efficiency rate. In terms of significant efficacy, we used a fixed-effects model given the low heterogeneity that existed between these studies ($I^2 = 14\%$, $p = 0.32$). The results indicate (Figure 7A) that the combined treatment shows a significant statistical difference compared to the control group (RR = 1.35, 95% CI [1.21, 1.51], $p < 0.0001$). There was no significant heterogeneity among the studies in terms of overall efficacy ($I^2 = 0\%$, $p = 0.52$), and we employed a fixed-effect model for analysis. The results show (Figure 7B) that the combined results also exhibit significant statistical significance compared to the control group (RR = 1.12, 95% CI [1.06, 1.18], $p < 0.0001$). The efficacy rates and overall effectiveness indicate that the acupuncture treatment group is more effective in treating myofascial pain compared to the control group.

Discussion

Acupuncture stands as one of the commonly utilized alternative therapies. Despite its unclear mechanism of action, the prevailing consensus suggests that acupuncture elicits systemic responses, particularly within the nervous system, through physical stimulation of specific points on the body's surface. This stimulation regulates bodily functions, ultimately yielding therapeutic effects (27, 28). The publication of various controlled trials has demonstrated acupuncture's significant efficacy in managing pain syndromes, including acute and chronic low back pain, osteoarthritis of the knee, headaches, myofascial pain, neck pain, and fibromyalgia. Numerous studies have indicated that acupuncture analgesia can be initiated through the stimulation of high-threshold, small-diameter nerves in the muscles (29). These nerves are able to send messages to the spinal cord, which then activates neurons in the spinal cord, brainstem (the gray area around the aqueduct), and hypothalamus (arcuate), which in turn triggers the endogenous opioid mechanism (30–32). A study has shown that pressure-point acupuncture has an analgesic effect and that the intensity of the stimulus may depend on various parameters, such as the procedure, needle size and insertion site. Pressure-point insertion of needles affects sensitized injury receptors, whereas non-pressure-point insertion does not. Pressure pain points are sites where injury receptors (e.g., multimodal receptors) are sensitized by various factors. Moxibustion stimulation of pressure points activates the sensitized multimodal receptors, thereby relieving pain (33). It is also because of its role in myofascial pain that acupuncture is recommended as a treatment option for myofascial pain (34). The results of our meta-analysis showed that acupuncture significantly outperformed the treatment regimen in the control group. This superiority was reflected in lower VAS scores, lower PRI and PPI scores, and higher treatment efficacy in the acupuncture group, and these differences were statistically significant. In order to compare acupuncture therapy and drug efficacy in more depth, we performed a subgroup analysis based on the differences between the treatment

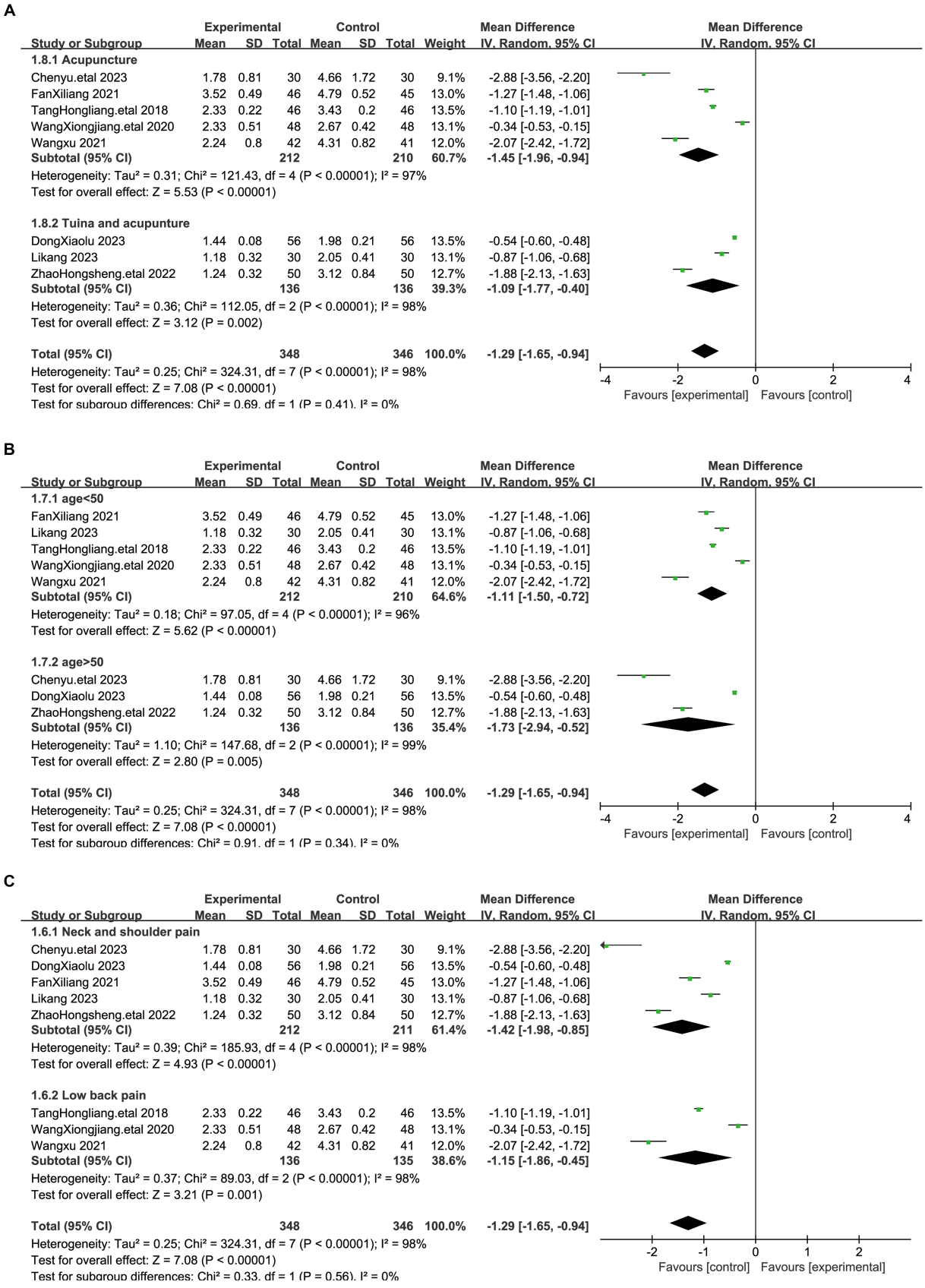

FIGURE 4
Figure shows a forest plot of subgroup analyses of the visual analog scale (VAS). **(A)** Subgroup analyses regarding different interventions. **(B)** Subgroup analyses of patient age. **(C)** Subgroup analyses of different pain sites.

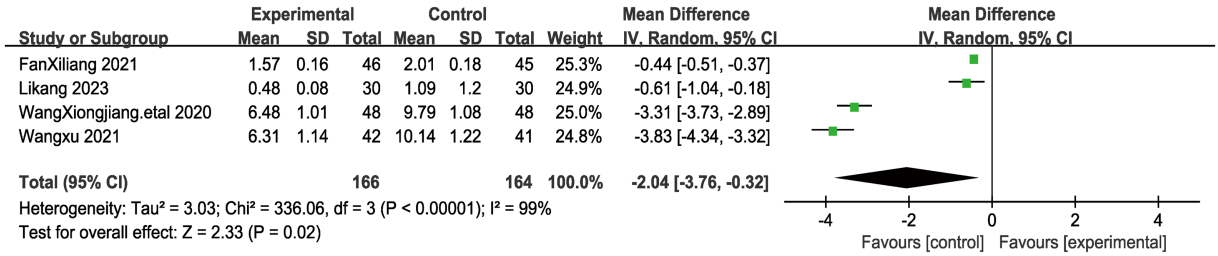

FIGURE 5
The figure represents a forest plot of the meta-analysis for Pain rating index (PRI).

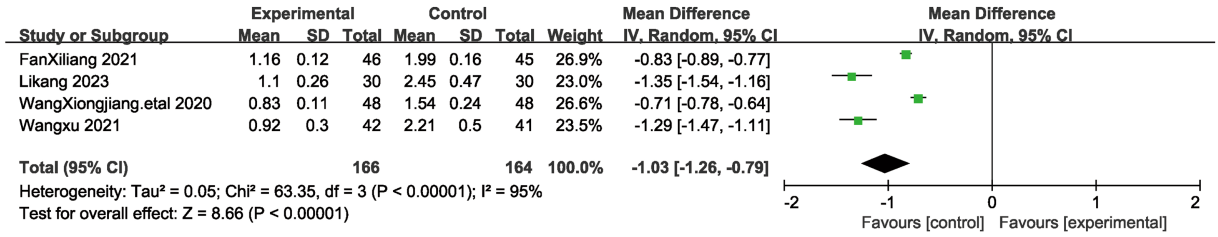

FIGURE 6
The figure represents a forest plot of the meta-analysis for Present pain intensity (PPI).

protocols of the control group and the acupuncture group, a step taken to explore whether the differences in the treatment groups would affect the reliability of the results, which showed that the different interventions demonstrated good therapeutic effects. Subsequently, subgroup analyses were performed according to the age and pain site of the patients in the different studies. In terms of safety, it is noteworthy that no serious adverse effects were reported in any of the studies, which highlights the fact that acupuncture treatment has a good safety record (35).

While our research findings suggest that the combination of acupuncture and medication is more effective than medication alone for myofascial pain, it is important to acknowledge the limitations of our study. There is significant heterogeneity among the included studies, likely due to differences in the implementation of clinical trials, such as variations in acupuncture point selection, treatment duration and techniques, as well as differences in the types and dosages of medication used in control groups. To comprehensively assess the clinical efficacy of acupuncture in alleviating myofascial pain, future studies should prioritize large-sample, multicenter randomized controlled trials using recognized reliable study designs. We also observed that adverse effects were not systematically studied and documented in the included studies, highlighting the need for future research to verify efficacy. Furthermore, these studies should standardize acupoint selection and treatment methods based on evidence-based principles of traditional Chinese medicine to enhance comparability between treatment studies and facilitate more effective treatments. Additionally, efforts are needed to develop clinical acupuncture treatment protocols that are both efficacious and feasible. This will contribute to the development of evidence-based clinical practice guidelines. Finally, it is important to note that due to the many limitations present in this paper, an updated meta-analysis will be necessary in the future as more clinical trials are conducted. Incorporating higher-quality original studies can provide results with a higher degree of confidence.

Conclusion

Our study revealed an important finding: the acupuncture group showed significant improvements in VAS scores, PPI and PRI scores, and treatment efficiency compared to treatment with medication alone. This finding provides a solid theoretical basis for the treatment of myofascial pain syndrome with acupuncture. Nevertheless, given the limitations of the existing literature, there is an urgent need for more rigorous and reliable clinical trials to further validate this finding. It may be necessary to conduct an in-depth analysis of different acupoints and intervention times to better explore the factors affecting efficacy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

JX: Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. XZ: Writing – original draft, Methodology, Formal analysis, Data curation. XL: Writing – original draft, Validation, Project administration, Methodology, Data curation. XG: Writing – original draft, Investigation, Data curation. LJ: Writing – original draft, Investigation, Conceptualization. QL: Writing

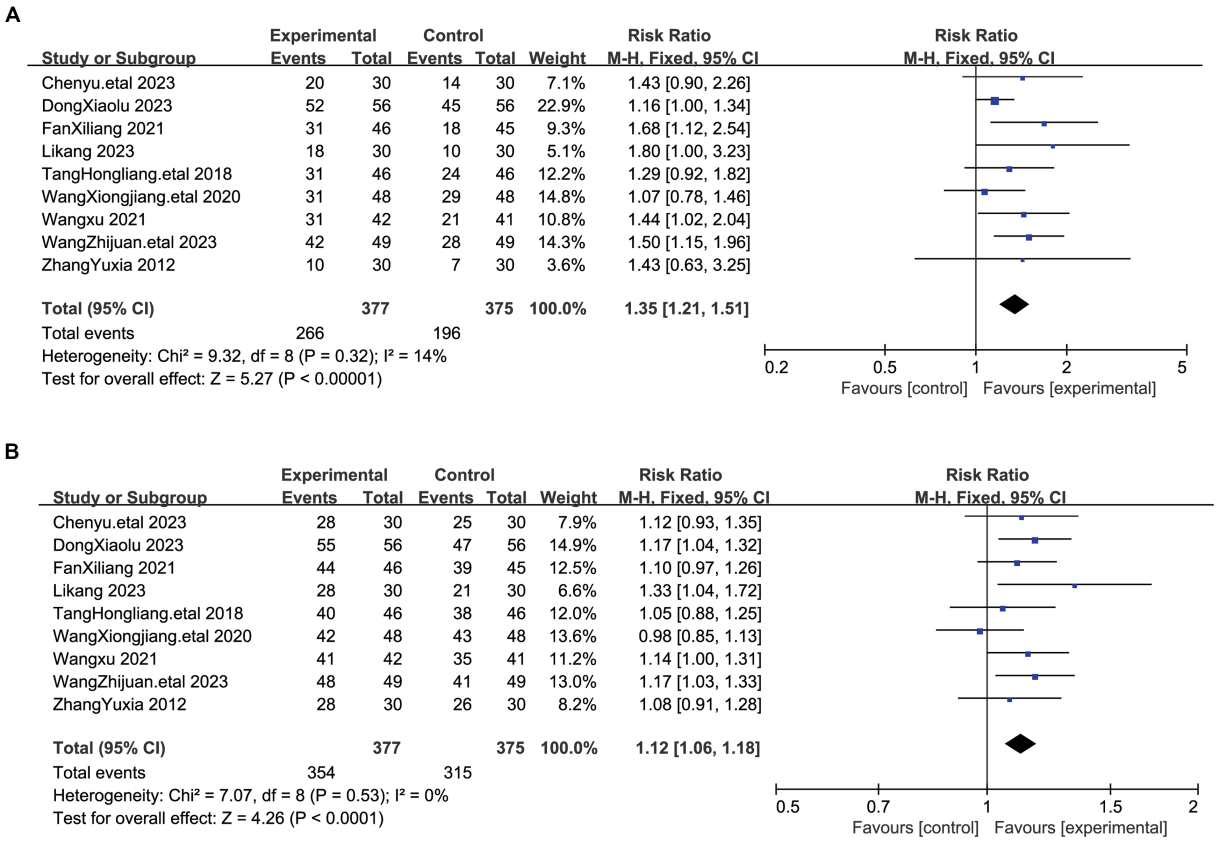

FIGURE 7
(A) The graph shows a forest plot of significant efficacy rates. **(B)** The graph shows a forest plot of total efficacy rates for the treatment of myofascial pain syndromes.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1374542/full#supplementary-material

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New perspectives on migraine treatment: a review of the mechanisms and effects of complementary and alternative therapies

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Migraine is a prevalent and disabling neurovascular disorder, with women being more susceptible, characterized by unilateral throbbing headache, often accompanied by nausea and vomiting, and often associated with various comorbidities such as brain and cardiovascular diseases, which can have a serious impact on quality of life. Although nonsteroidal anti-inflammatory drugs (NSAIDs) are the main first-line medications for the treatment of pain, long-term use often leads to side effects and drug addiction, which emphasizes the need to investigate alternative pain management strategies with fewer adverse effects. Complementary and alternative medicine is a viable pain intervention often used in conjunction with traditional medications, including acupuncture, herbs, moxibustion, transcutaneous electrical stimulation, bio-supplements, and acupressure, which offer non-pharmacological alternatives that are now viable pain management options. This review focuses on the mechanistic doctrine of migraine generation and the role and potential mechanisms of Complementary and Alternative Therapies (CAT) in the treatment of migraine, summarizes the research evidences for CAT as an adjunct or alternative to conventional therapies for migraine, and focuses on the potential of novel migraine therapies (calcitonin gene-related peptide (CGRP) antagonists and pituitary adenylyl cyclase-activating peptide (PACAP) antagonists) with the aim of evaluating CAT therapies as adjunctive or alternative therapies to conventional migraine treatment, thereby providing a broader perspective on migraine management and the design of treatment programs for more effective pain management.

KEYWORDS

migraine, pain management, alternative therapy, acupuncture, complementary therapy

1 Introduction

Migraine is a recurrent neurovascular disorder clinically characterized by unilateral throbbing moderate to severe headaches, often accompanied by other symptoms such as nausea and vomiting, and sensitivity to light and sound (1). According to epidemiologic studies, the incidence is 12–15% in the general population, and women are more commonly affected than men, especially in the most fertile age group, 25 to 55 years (2). Migraine, as the second most disabling neurological disorder, has co-morbid relationships with a variety of brain disorders (e.g., cerebral infarction, cerebral hemorrhage), cardiovascular disease, and epilepsy, and is a significant cause of disability (3). Migraine arises from a series of intracranial and extracranial changes due to neuronal dysfunction and carries the risk of changing from episodic migraine to chronic migraine, especially as the frequency of attacks increases and acute care medications are overused (4, 5).

Traditional treatments for migraine include a variety of acute care options (e.g., over-the-counter pain relievers (sometimes in combination with caffeine), nonsteroidal anti-inflammatory drugs, opioids) and migraine-specific medications (e.g., tretinoin and ergot) (6). Recent advances include the approval of CGRP antagonists for migraine prophylaxis in adults, such as erenumab, fremanezumab, and galcanezumab (7). While these therapeutic agents are effective in many individuals, they may not be appropriate for all patients, and some have contraindications or potential side effects (6). In addition, overuse of acute medications can lead to chronicity of migraine (8, 9).

Complementary and alternative therapies (CAT) are being explored as potential alternative treatments. They are becoming more widely recognized as a viable option for pain management because of their ability to relieve stressful effects, reduce recurrence and prevent chronic pain (10). CATs encompass a variety of forms including, but not limited to, transcutaneous electrical stimulation, herbs, acupuncture, acupressure, moxibustion, qigong, tai chi, yoga, and meditation (10, 11). These therapies include non-pharmacological options such as electrical nerve stimulation devices and magnetic stimulation devices that target various nerves such as the trigeminal, vagus and occipital nerves (12). Behavioral medicine techniques, such as biofeedback training and positive thinking, have also been used for some time to help manage migraines (13). These alternative therapies can provide more options for patients seeking relief from migraine symptoms, especially those who have not responded well to traditional therapies or are looking for non-pharmacological treatments. Research indicates that in the treatment of migraine, these alternative therapies demonstrate significant advantages that cannot be overlooked. For instance, acupuncture, a common form of CAT, not only matches the efficacy of mainstream pharmacological treatments but also offers a lower risk of side effects, providing patients with a safer and more appealing treatment option (14). Consequently, as our understanding of CAT deepens, these therapies not only offer a diverse array of treatment options for migraine sufferers but also drive innovation in chronic pain management, contributing to enhanced treatment outcomes and improved quality of life for patients.

2 Mechanisms of action of migraine

2.1 Migraine mechanisms in neurobiological and physiological perspective

Despite the fact that the pathogenesis of migraine is not clearly understood, there have been several theories that attempt to explain its cause, including vascular dysfunction, aseptic inflammatory response in the dura mater, and magnesium deficiency (15–17) (Figure 1A). Not only that, but there is evidence to support that migraine with aura is associated with cortical spreading depression (CSD), in which depolarizing waves generated by neurons and glial cell membranes in the cerebral cortex diffuse themselves along the cortex, leading to activation of trigeminal afferent pathways (18, 19). In particular, the caudal subnucleus of the spinal trigeminal nucleus (STN) sends out nociceptive-sensitive nerve fibers that transmit information about perceptual stimuli to the thalamus, leading to sensitization of tertiary neurons. During the diffusion of signals from the cerebral cortex, CSD may be associated with large potassium (K^+) efflux, sodium (Na^+) voltage-sensitive channel opening, and glutamate release (20).

In addition, most scholars now believe that activation of the trigeminal vascular system (TGVS) better explains the cause of migraine. Migraine attacks begin with triggers, especially migraine-inducing factors that alter central excitability, such as stress, sleep deprivation, fasting, and sound (21). Under these stimuli, the trigeminal nervous system is sensitized, which in turn induces the trigeminal ganglion (TG) to release a variety of neuropeptides, including CGRP, substance P (SP), and pituitary adenylate cyclase-activating polypeptide (PACAP) to participate in the neuroinflammatory response. At the same time, as TGVS is in a chronically activated state, it leads to a series of other changes, including mast cell degranulation and changes in meningeal vasodilatation. More interestingly, CSD can alter the permeability of the blood–brain barrier through activation and upregulation of matrix metalloproteinases (22, 23).

Considering that CGRP, as a key peptide, plays an important role in pain signaling, it has been demonstrated that CGRP release can be inhibited using herbs (24). The transient receptor potential ankyrin (TRPA) mediates CGRP release in neurogenic inflammation, and the study by Benemei et al. (25) demonstrates that Petasin inhibits CGRP signaling, achieving this through desensitization of TRPA. New studies have recently found that the PACAP pathway is independent of the CGRP pathway, and there are findings suggesting that frequent headache-induced reductions in PACAP and subsequent up-regulation of PACAP receptors play an important role in migraine progression (26–28). Therefore, PACAP antagonists may be a new therapeutic option for patients who are insensitive to CGRP antagonists (28). Perhaps, in the therapeutic regimen for migraine, CAT may play a role by inhibiting the PACAP signaling pathway. In addition, when treating chronic migraine and hyperparathyroidism (PTH), it may be more effective to consider combined inhibition of the CGRP and PACAP signaling pathways rather than inhibition of a single one of these signaling pathways (29).

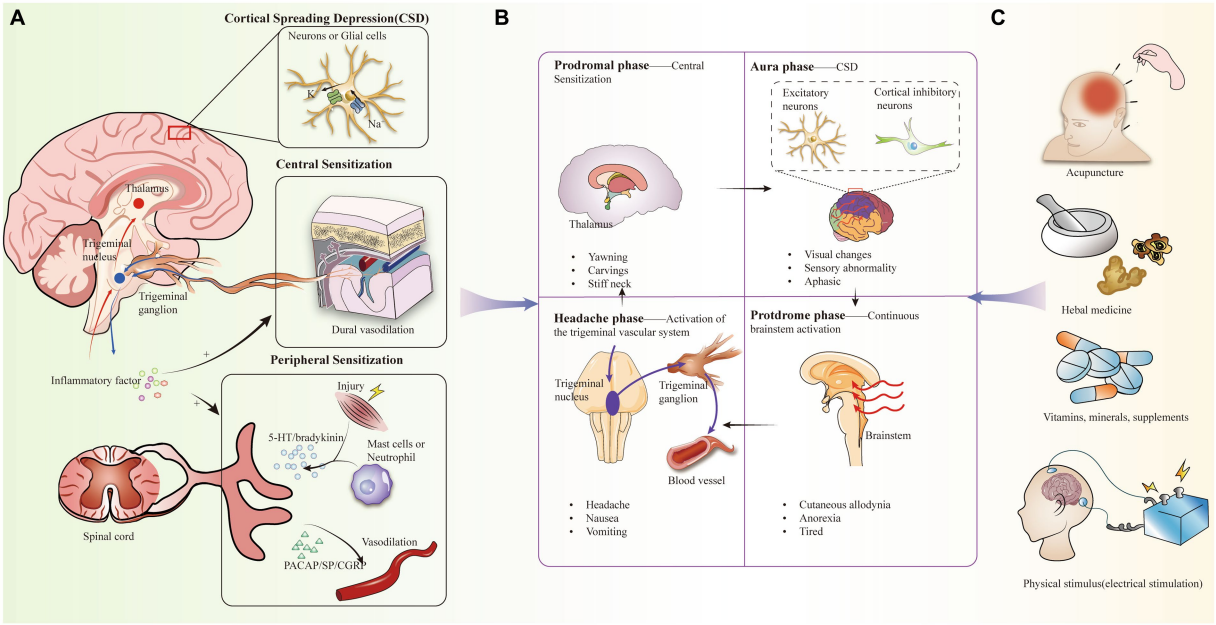

FIGURE 1
(A) Pathogenesis of migraine, including activation of the trigeminal vascular system, central and peripheral sensitization, cortical spreading inhibition, inflammation. **(B)** Clinical manifestations of the four periods of migraine and the corresponding mechanistic doctrines. **(C)** Complementary alternative therapies for migraine headaches.

2.2 Inflammation and migraine

Epidemiologic studies have found that 2.5–3% of patients with episodic migraine (EM) transition to chronic migraine (CM) in the second year (21, 30). The mechanism of its chronicity may be closely related to peripheral sensitization of primary afferent nerve fibers, secondary neurons in the STN, and central sensitization of higher neurons such as the thalamus (31, 32). In addition, the inflammatory response is closely related to peripheral sensitization and increased central sensitivity (33, 34). When activation of injury receptors occurs, primary afferent neurons, mast cells, and eosinophils in local tissues release a variety of chemicals, such as 5-hydroxytryptamine (5-HT) and bradykinin, which promotes neuroinflammation and modulates pain (35, 36). Among them, 5-HT 1F receptor agonists (e.g., Lasmiditan) are already in clinical trials (37). In addition, the introduction of CGRP as a target has been an important advance in migraine medication (38). CGRP levels increase when migraine attacks occur and decrease after treatment, thereby attenuating the vasodilating potency and central sensitizing effects of the pro-inflammatory neuropeptide CGRP, which has been confirmed in numerous studies to be a key neurotransmitter involved in migraine attacks (39, 40). A range of CGRP receptor antagonists and monoclonal antibodies to CGRP are currently in clinical trials, opening up new possibilities for migraine treatment drugs (41).

3 Applications and research evidences of cat in migraine management

Migraine is categorized into a prodromal symptomatic phase, an aura phase, a headache phase, and a late headache phase, with headache phase symptoms manifesting as recurrent pain, nausea, and vomiting (32, 42–44). Currently, tretinoin, a 5-hydroxytryptamine 5-HT1B/1D receptor agonist, is the migraine-specific acute treatment of migraine during the headache phase, but it is not suitable for every patient, while the prophylactic effect is not good, and in recent years, the more promising alternative for acute-phase treatment has been complementary alternative therapies (CAT) (45) (Figure 1B). CAT has been used in the treatment of a wide range of pains, including mind–body interventional therapies (e.g., meditation), biologic based therapies (e.g., taking herbs and vitamins, dietary supplementation), physical therapy, and manual therapies including acupuncture (41, 46) (Figure 1C). Despite some methodological challenges, the effectiveness of these CAT modalities is supported by several studies (47) (Table 1).

Migraine may be associated with electrolyte disturbances, and magnesium deficiency may induce migraine by affecting cortical inhibition or leading to abnormalities in glutamatergic neurotransmission, which is seen as a potential mechanism for the magnesium-migraine association (53). Magnesium is involved in the regulation of the nervous system through multiple pathways, not only regulating vasodilatation by affecting mitochondrial metabolism, neurotransmitter release, and substance P release, but also attenuating neuroinflammation by inhibiting the nuclear factor κB pathway in pro-inflammatory cells (54, 55). Given the close link between inflammation and migraines, employing magnesium as a supplement emerges as a potent approach for the mitigation or prophylaxis of migraine episodes. In CAT, there have been several randomized clinical controlled trials supporting the use of magnesium as a supplement for the prevention of migraine attacks; however, most of the studies have been combination treatments in conjunction with other vitamins or bioorganic molecules (56). Using a randomized, multicenter, double-blind controlled trial, Gaul et al. demonstrated

TABLE 1 Clinical evidence for CAT in the treatment of migraine.

Statistical methods	Types of CAT	Research and intervention groups	Interventions	Results	Conclusions	Limitations	Reference
Multicenter, Randomized, Controlled, Blinded	Acupuncture	150 Acupuncture Primary Treatment of Migraine Patients with Episodic Migraine without Aura	20 sessions of complementary acupuncture treatment	Patients who underwent acupuncture therapy in the experimental group had a significant reduction in the number of migraine attacks at weeks 13–20 and a significant reduction in the frequency of migraine attacks at weeks 17–20	Preventing migraine attacks without aura with 20 treatments of hand acupuncture is superior to sham acupuncture and usual care	The lack of baseline prophylaxis is not typical; the time frame of the study was not long enough	(48)
Randomized, Controlled	Acupuncture	48 participants: 10 controls and 38 migraineurs	Two sessions of 5 days each, 1 day between sessions (11 days total)	VAS, PSQI, and MSQ were medically statistically significant in patients treated with acupuncture	Acupuncture is effective in relieving migraine symptoms	The psychological assessment scale lacked assessment of pain status	(49)
Double-blind, Randomized, Controlled	REN	Sixty-five migraine patients underwent multifocal rTMS	Dot-burst stimulation at 67 Hz, 85% RMT, and 8 s column-to-column spacing	Migraine patients treated with real rTMS had a lower average number of migraine days per month; the rate of reduction in migraine attack frequency was higher	Multifocal rTMS is an effective and well-tolerated prophylactic treatment for episodic migraine patients	5 patients withdrew, with missing data and loss to visit bias	(50)
Randomized, Controlled	REN	CM patients (18–55 years old) with International Classification of Headache Disorders, Third Edition (ICHD-3) β-criteria	10 Hz rTMS applied with a figure-of-eight magnetic stimulation coil three times a month, one day apart, for three months	More than 50% reduction in the number of headache days and 50% reduction in headache severity at 3 months in group II compared with group I	rTMS combined with amitriptyline is safer and more effective in treating CM than rTMS alone	Approximately 50% of patients in group I are transferred to group II due to inadequate headache relief	(48)
Prospective controlled clinical trial	Massage Therapy	16 female patients with migraine	Eight female migraineurs underwent 12 sessions of CTM for four weeks.	Significant changes in pain, concomitant symptoms (except vomiting), medication use, Headache Impact Test-6, and Disability with Migraine Disability Assessment Scale (DMDAS) scores in the CTM group compared with the control group	CTM can be considered a non-pharmacologic and complementary therapy for migraine	Only female patients were tested, there was selection bias; the sample size was too small, the reproducibility and representativeness of the study results were poor, and false-negative or false-positive conclusions may be drawn	(70)
Randomized, Controlled	Reflexology	48 women (33–58 years old) with migraine for 2–10 years admitted from November 2013 to November 2015	The RG group received two 10-treatment sessions per week; the SMG group received three 15-treatment sessions per week.	All variables (VAS, IA, FA, DA) within the RG and SMG were reduced from baseline values at 3 months after treatment	Reflexology and segmental massage offer a safe alternative to pharmacologic treatment of migraine. Migraineurs derive significant health benefits from foot reflexology	Short follow-up period; small sample size	(71)

(Continued)

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TABLE 1 (Continued)

Statistical methods	Types of CAT	Research and intervention groups	Interventions	Results	Conclusions	Limitations	Reference
Double-blind, Placebo-controlled	Ginger	107 patients (18–60 years old) with episodic migraine, not taking any prophylactic medications	3 capsules of 200 mg of dried ginger extract (5% active ingredient) or placebo (cellulose) each time	The number of days of severe pain, analgesic use for acute migraine, and duration of migraine attacks were reduced in both groups, but there were no significant differences between groups	Ginger has no greater benefit in the prophylactic treatment of migraine compared to placebo	High placebo response; lack of pharmacologic evaluation of ginger capsules	(51)
Randomized, Single-center, Double-blind, Parallel, Controlled	Magnesium	260 migraineurs (18–65 years old) one month of no prophylaxis, 3 months of therapy	Randomized to 3 intervention groups receiving oral sodium valproate tablets, magnesium sodium valproate tablets, and magnesium oxide tablets twice daily for 12 weeks	All migraine characteristics were significantly reduced in all three groups compared with those reported at baseline; MIDAS and HIT-6 scores were significantly lower in Groups A, B, and C, and these changes were more pronounced in Groups A and B than in Group C	Magnesium enhances the antimigraine properties of valproate in combination therapy and reduces the dose of valproate required for migraine prophylaxis	Some participants did not participate in blood collection; lack of complete data on serum magnesium levels limited the analysis of the correlation between serum magnesium levels and treatment efficacy in the three groups of patients	(54)
Cross-sectional	Magnesium	3,626 participants (20–50 years old) in the 2001–2004 National Health and Nutrition Examination Survey (NHANES)	Dietary magnesium intake determined by 24-h retrospective method and supplemental magnesium intake determined by dietary supplement interviews	Mean dietary magnesium intake was below the RDA in both migraine and control groups; In the adjusted model, dietary and total magnesium intake were associated with lower odds of migraine in the lowest Q	Inadequate Magnesium Intake Linked to Migraine in U.S. Adults 20–50 Years of Age	Cannot explain temporal relationship between magnesium ingestion and migraine; residual confounding after adjusting for modeling; single question for assessing migraine	(52)
Randomized, Multicenter, Double-blind, Placebo-controlled	Magnesium, CoQ10 and Riboflavin	130 adult migraineurs (18-65 years) with ≥ 3 migraine attacks per month	2 capsules of a proprietary supplement containing magnesium, riboflavin and coenzyme Q10 were taken orally in the morning and evening for 3 months	Migraine frequency decreased and intensity was significantly lower in the supplement group	Treatment with supplements containing magnesium, riboflavin, and coenzyme Q10 reduced migraine frequency; the Migraine symptoms and disease burden significantly reduced in dietary supplementation group	Unblinding patients in the verum group due to chromaturia	(56)

REN, Remote Electrical Nerve Stimulation; VAS, visual analogue scale; PSQI, Pittsburgh sleep quality index; MSQ, MinnesotaSatisfaction Questionnaire; rTMS, Repetitive Transcranial Magnetic Stimulation; CTM, connective tissue massage; IA, intensity of attacks; FA, frequency of attacks; DA, duration of attacks; MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test-6; RDA, recommended dietary allowance; RG, reflexology group; SMG, segmental massage group.

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that treatment with supplements containing magnesium, riboflavin, and coenzyme Q10 reduces the frequency of migraine attacks, their clinical symptoms, and the burden of disease (56). Among these, riboflavin may protect nerves by reducing inflammation and anti-oxidative stress properties, suggesting its potential as a migraine preventive agent (57).

Herbal treatment has the advantages of holistic conditioning, multi-targeting, and long-lasting effects, which are conducive to individualized and fine-tuned treatment for migraine patients (58–60). In 22 years, Yang et al. (61) showed that in a rat model of nitroglycerin (NTG)-induced migraine, the Chinese herbal formula Xiongshao Zhitongfang (XZR) regulated NO, 5-HT, CGRP, and SP to normal levels, while inhibiting mast cell degranulation and the release of inflammatory factors, which resulted in attenuation of migraine symptoms. In addition, in a homozygous rat model, rhubarb extract from the traditional Chinese medicine *Rheum palmatum* also down-regulated the inflammatory response and alleviated migraine via the cGMP-PKG pathway (62). However, there is not much research available on how herbs can holistically condition the body and its long-term effects in treating migraines.

In addition to the commonly used pharmacological complementary alternative therapies, non-pharmacological treatments such as Remote Electrical Nerve Stimulation (REN), massage therapy, due to fewer adverse events, then it may be a more promising mode of treatment for migraine (63, 64). In randomized controlled trials, the frequency of migraine attacks was reduced in patients treated with rTMS therapy; also, rTMS was safer and more effective in treating chronic migraine (CM) when combined with amitriptyline (50, 65). The mechanisms involved may be related to the regulation of central and peripheral sensitization by rTMS (66).

From the perspective of qi and yin and yang concepts of Chinese medicine, acupuncture is based on meridians placing needles or pressing on specific locations on the patient's skin to achieve therapeutic effects; from the perspective of physiology, the stimulation of high-threshold and tiny nerve fibers can transmit signals to specific brain regions mirrored by acupuncture points, leading to the release of endogenous opioids to achieve analgesic effects (67). Functional magnetic resonance imaging (MRI) data support that areas of brain activity in migraine patients who undergo acupuncture include the limbic system and the default mode network, as well as pain processing areas. The increased ALFF (Amplitude of Low-Frequency Fluctuation) values in these areas suggest that acupuncture may enhance spontaneous brain activity in patients with migraines (49). Acupuncture has been shown to be superior to sham surgery and placebo (68, 69). Meta-analyses have been performed to show that acupuncture reduces the frequency of migraine attacks more than pharmacologic prophylaxis and is less likely to result in withdrawals and reports of adverse effects due to adverse reactions (68).

4 Limitations of research on the use of cat for migraine treatment

Despite the large number of randomized controlled trials showing the benefits of complementary alternative therapies for migraine treatment, most studies have limitations, focusing mainly on methodological challenges (47). Common reasons for this include short follow-up time, small sample size, and patient loss, which leads to poor reproducibility and representativeness of the study results (70, 71). The limited availability of diagnostic criteria is also a challenge. Current diagnostic criteria do not adequately capture the heterogeneity of migraine, including underlying genetic and neurobiological factors. For example, a controlled trial of acupuncture treatment was unable to hypothesize a link between psychological and pain states because the Psychological Assessment Scale lacked an assessment of pain states (49). In addition, a recent meta-analysis showed a trend toward higher placebo responses in migraine prevention trials over the last 30 years (72). Another promblem is the impact of differences in patterns of regional culture. In Asian cultures, herbal treatments and tai chi are widely popular. However, these non-mainstream medical approaches may limit acceptance and application in non-Asian populations (73, 74).

5 Discussion

Migraine is a mechanistically complex disorder caused primarily by neurovascular disorders, and its pathologic and physiologic processes are evolutionary and do not consist of a single mechanistic doctrine (75). Genetic and epigenetic susceptibility may also explain the development of migraine (76–78). Large genome-wide association studies have shown that genetics may contribute to altered brain morphology in individuals at high risk for migraine. Although genome-wide association studies have identified many susceptibility variants, including genetic factors shared with comorbidities, more in-depth studies exploring the overall susceptibility loci for migraine are needed to understand the cellular phenotypes resulting from migraine gene variants (26).

The design of future studies of complementary alternative treatments for migraine should ensure methodological rigor, reproducibility, and safety. 0Incorporation of CAT into migraine treatment should take into account the frequency of visits, the patient's expectations of the treatment, and the psychological response to the treatment setting in order to avoid a high placebo response (26). Although most treatments are well tolerated with limited adverse effects, the possible risk of death due to carotid artery entrapment with high-speed chiropractic and hepatotoxicity of pyrrolizidine alkaloids in butterbur cannot be ignored (47, 79, 80). In addition, key areas of migraine research include further exploration of molecular markers and the use of imaging techniques to identify key mechanisms and triggers. In a longitudinal neuroimaging study, the duration of the aura phase of a spontaneous human migraine attack was found to be 48 h using MRI, and hypothalamic activation may serve as a potential marker for this staging (75, 81). In summary, the potential of CAT in migraine treatment is remarkable, offering a range of pharmacological and non-pharmacological options that can be tailored to the therapeutic needs of individual patients. While current research supports the efficacy of various CAT modalities, it is clear that more rigorous studies are needed to fully understand the mechanisms and optimize their integration into clinical practice.

Author contributions

XS: Conceptualization, Writing – original draft, Writing – review & editing. QZ: Data curation, Writing – original draft. LaS:

Conceptualization, Writing – original draft. LeS: Writing – original draft. HC: Data curation, Writing – original draft. YY: Writing – original draft. ML: Methodology, Writing – original draft. XX: Writing – original draft. BL: Data curation, Writing – original draft. ZL: Data curation, Writing – original draft. JY: Data curation, Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effectiveness of acupuncture in treating patients with pain and mental health concerns: the results of the Alberta Complementary Health Integration Project

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Background: This study presents real-world evidence on the clinical outcomes of the Alberta Complementary Health Integration Project (ABCHIP), which utilized acupuncture to address pain and mental health issues in two vulnerable populations in Alberta: youth (aged 24 and below) and elderly (aged 55 and above).

Methods: Over 282days, a total of 606 patients received 5,424 acupuncture treatments. Tailored to each patients' specific pain and mental health concerns, an individualized treatment plan was selected, following a standard treatment protocol lasting 1 to 3 months. Patients were evaluated at least twice: initially and upon completing therapy. Primary treatment outcomes were assessed using various measures, including the Brief Pain Inventory (BPI), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire 9 (PHQ9), PROMIS Anxiety 8a and its pediatric form PROMIS Anxiety-Pediatric, PROMIS Short Form v1.0 Fatigue 8a and its pediatric counterpart PROMIS Pediatric Short Form v2.0 Fatigue 10a, PROMIS Short Form v1.1 Anger 5a and its version PROMIS SF v2.0 5a, and EQ-5D-5L. These measures gauged pain reduction, improved sleep quality, reduced depression, anxiety, fatigue, anger, and quality of life, respectively.

Results: Analysis of data from 500 patients who received at least 6 acupuncture sessions through ABCHIP showed statistically significant improvements in clinical outcomes. Among this group, the subgroup of 235 patients who received at least 12 sessions demonstrated the most favorable treatment outcomes, including an 75.5% reduction in pain severity, a 53.1% improvement in sleep quality, a 78.4% drop in depression, a 41.1% decline in anxiety, a 43.7% decrease in fatigue, a 38.2% decrease in anger, and a 42.6% improvement in overall quality of life.

Conclusion: Integrating acupuncture with usual care demonstrates promise in enhancing mental health, alleviating chronic and general pain, and improving overall quality of life. The findings suggest that integrative programs, such as ABCHIP, present an effective approach to addressing pain and mental health concerns in vulnerable populations, providing valuable insights for future healthcare interventions.

KEYWORDS
acupuncture, integrative medicine, pain, mental health, clinical outcomes

1 Introduction

Following the global outbreak of COVID-19, the prevalence of mental health problems has surged due to the broader societal impact and public health responses, including infection control, physical distancing, and quarantine (1, 2). Concerns about mental health and psychosocial well-being, encompassing depressive symptoms, anxiety, stress, post-traumatic stress symptoms, sleep problems, and other psychological disorders, have grown during the COVID-19 pandemic (3). The pandemic's direct consequences, such as fear of transmission and a sense of danger, have contributed to these issues. Moreover, economic and financial hardships have indirectly impacted mental health (4, 5). The economic shutdowns resulting from the pandemic have had a disastrous impact on global economies, especially in nations with frequent domestic epidemics, inadequate healthcare systems, and high economic vulnerability (6).

Furthermore, chronic pain following an acute COVID-19 infection has exacerbated the situation. There are speculations that the infection might have caused neuroinflammation, a peripheral and central inflammatory response potentially causing persistent musculoskeletal issues and cognitive impairment (7, 8). Chronic weariness, decreased physical ability, and muscle weakness are just a few of the enduring clinical consequences associated with both Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (9). A general decline in the quality of life has been observed long after significant coronavirus epidemics (7–9).

Interest in acupuncture has been steadily growing as individuals and healthcare professionals explore additional ways to manage pain, mental health, addiction, and various chronic health issues. Acupuncture, well-established as a safe and effective adjunct intervention, has been found to significantly improve people's quality of life and promote overall wellness when integrated with conventional treatments (10–12). Following a holistic approach, acupuncture not only helps alleviate various issues such as chronic pain, mental stress, anxiety, depression, and non-medicated pain relief but also serves as a powerful preventive form of care, strengthening immunity (13–17).

Funded by the government of Alberta, the ABCHIP project provided free acupuncture to address pain, mental health, and addiction issues for youth and elderly in Alberta. Aimed at promoting psychosocial well-being and resilience for these vulnerable populations, ABCHIP sought to mitigate, prevent, and treat pain, mental health, and behavioral issues arising from the COVID-19 pandemic. The project also aimed to reduce dependence on habit-forming pharmaceuticals and promote the integration of acupuncture to deliver patient-centered care.

2 Materials and methods

2.1 Hypothesis and objective of the study

The study tested the following hypothesis: Patients who received acupuncture would experience improved mental and physical well-being, as well as a higher quality of life.

The objectives of the study were as follows: (1) to measure pain severity before and after the course of treatment; (2) to examine changes in pain interference and physical function; (3) to assess changes in the psychosocial well-being of participants.

2.2 Participants

Inclusion criteria were: (1) Youth (aged 24 and below) and the elderly (aged 55 and above), experiencing mental health issues; (2) Those who have any of the following concerns or conditions: mental health concerns and/or conditions (e.g., sleep disorders, anxiety, depression, oppositional defiant disorder, developmental disorders, eating disorders, cognitive impairment and dementia, digestive complaints, etc.); (3) Chronic pain or pain management issues; (4) Addiction (drugs and others).

Exclusion criteria included: (1) Participants refusing to provide their consent; (2) Children whose parents or guardians refused to offer their consent; (3) Patients who revoked their consent; (4) Patients not accessible or comfortable receiving treatment; (5) No-shows without giving notice twice or more.

2.3 Recruitment

The study, conducted at the Alberta College of Acupuncture & Traditional Chinese Medicine (ACATCM)—Huatuo Clinic, recruited participants through various channels. Primary care physicians, Alberta Health Services (AHS) mail-out services, and public outreach initiatives served as referral sources. The study also collaborated with primary care doctors to improve patient referrals.

To broaden outreach, the AHS mail-out service, in partnership with the AHS/SPOR group at the Center for Health Informatics (CHI) at the University of Calgary, was utilized. The Enterprise Data Warehouse (EDW) within Alberta Health Services helped identify potential participants in the youth and elderly categories with mental health issues. Advertisements, including project flyers and roadside posters in English, Chinese, and Korean, were employed to attract participants. Individuals could opt for self-referral or receive recommendations from medical professionals.

For recruitment and information dissemination, the study maintained an updated website at http://www.abchip.ca and utilized social media platforms, including Facebook. This multi-faceted recruitment strategy aimed to maximize outreach and ensure diverse participation in the study.

In all the recruiting channels, individuals interested in participating in ABCHIP were directed to submit their applications on the study website. The applications were then reviewed by the project coordinator. All applicants who fit the selection criteria were admitted into ABCHIP to ensure maximum autonomy. Given the limited timeframe of the CHIP program and its nature as a community service program, the recruitment was not done on a random basis. We continued to admit applicants until the end of the one-year program.

Instead of pre-determining a sample size, we continued to admit applicants into ABCHIP throughout the one-year period of this program for the following two reasons:

First, according to our power calculation, the minimum sample size needed for an observational study with 50 predictors would be 450–500 to reach 80% power and a 0.05 significance level. We used this as a minimum threshold for ABCHIP recruitment.

Second, CHIP was a community service program funded through the Government of Alberta's investment aimed at enhancing mental health and addiction support for Albertans during the COVID-19 pandemic. Maximizing the number of individuals served in the program, subject to the project budget, was one of the program objectives.

At the end of our study, a total of 606 individuals were admitted into CHIP.

2.4 Treatment

Patients received effective and complimentary acupuncture treatments from licensed and experienced practitioners with 5–15 years of practice. The primary goal of these treatments was to improve patients' mental health and well-being by addressing concerns such as pain management, sleep quality, dietary habits, anxiety, and depression. The acupuncture treatment protocols in this study were designed based on established evidence and clinical expertise from local and international leading experts in our team, ensuring that only standard, proven acupuncture treatments were provided, without any experimental procedures.

During the initial consultation, practitioners engaged in discussions with patients and their family members to understand their expectations and treatment goals. Subsequently, they formulated individualized treatment plans for each patient, drawing upon gathered information and discussions, while also referring to established treatment protocols. This approach aligns with the ABCHIP's guiding principle of providing accountable and patient-centered care. By delivering tailored acupuncture treatments that address the unique needs of each patient, the program aims to offer holistic care for overall health improvement.

Treatment plans were customized based on the patient's condition and severity, typically lasting 1 to 3 months. Given the community service nature of the project, the goal was to assist as many participants as possible while maintaining a reasonable level of treatment effectiveness. The treatment was conducted twice a week, a frequency proven crucial for optimal results, especially in addressing chronic pain and mental health issues (18–21). In each treatment, a minimum of six acupuncture sessions was the standard. The duration of treatment varied based on the types and severities of patients, with the majority completing their acupuncture regimen within 12 sessions. Some complex cases required additional sessions, but the total did not exceed 18 sessions. Participants could conclude their treatment after the sixth session if they felt their treatment goals were achieved.

2.5 Data collection

Patients were evaluated at least twice throughout the study: once at the beginning and once after completion of therapy.

Questionnaires included instruments to measure pain, sleep quality, depression, anxiety, fatigue, anger, and general quality of life, along with demographic questions (age, gender, race/ethnicity, income, etc.) in the baseline surveys. The secure web program REDCap (Research Electronic Data Capture) was utilized for creating and administering online surveys and databases to collect and preserve this data.

After every three treatment sessions, participants were asked to respond to questions from an online questionnaire on REDCap. Information on chronic pain, mental health, and quality of life was again collected for the purpose of treatment effect monitoring and outcome evaluation.

2.6 Outcome measures

2.6.1 Pain

The degree of pain and its impact on functioning were evaluated using the Brief Pain Inventory (BPI). The severity of pain was determined by averaging responses to four questions on pain intensity—pain at its "worst" in the previous week, pain at its "least" in the previous week, pain at its "average" in the previous week, and current pain. Pain interference was quantified by averaging responses to seven questions that assessed how much pain affected daily activities: general activity, mood, walking capacity, normal work (both inside and outside the home), relationships, sleep, and enjoyment of life. A higher score on the scale, which ranged from 0 to 10, indicated greater pain severity (22). A scoring system was used, averaging responses to pain severity or interference sections on the BPI. A score of less than 2 indicated none to mild pain, 2–5 indicated moderate pain, and 6 or greater indicated severe pain (23).

2.6.2 Sleep

The Pittsburgh Sleep Quality Index (PSQI) was utilized to assess sleep quality. Component scores, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction, were derived from 19 questions according to scoring instructions. The global sleep quality score, representing the sum of these seven components on a scale of 0 to 21, indicated overall sleep quality. PSQI scores exceeding five indicate poorer sleep (24).

2.6.3 Depression

The level of depression was evaluated using the Patient Health Questionnaire 9 (PHQ9). A PHQ9 score was computed by summing responses to nine questions that assessed the frequency of depressive symptoms. A higher PHQ9 score indicated more severe depression, with scores ranging from 0 to 27. A PHQ-9 score of 5 or less indicated no or minimal depression, 5 to 9 indicated mild depression, 10 to 14 indicated moderate depression, and 15 or more indicated severe depression (25).

2.6.4 Anxiety

To measure anxiety in adults, PROMIS Anxiety 8a was employed, while PROMIS Anxiety-Pediatric was utilized for assessing anxiety in children. A final score, ranging from 8 to 40, was derived by summing up eight questions on fear, anxious misery, and hyperarousal. A higher score indicated more severe anxiety. For anxiety scores, values between 0 and 17 indicated no to minimal anxiety, between 17 and 21

suggested mild anxiety, between 22 and 31 indicated moderate anxiety, and scores of 32 and higher were indicative of severe anxiety (26).

2.6.5 Fatigue

The PROMIS Short Form v1.0 Fatigue 8a assessed fatigue in adults, while PROMIS Pediatric Short Form v2.0 Fatigue 10a evaluated fatigue in minors. The total of questionnaire responses produced a fatigue score up to 40, with a higher score indicating greater fatigue. Fatigue values of less than 22 indicated none to slight fatigue, 22–27 suggested mild fatigue, 27–36 indicated moderate fatigue, and a score greater than 36 signified severe fatigue (27).

2.6.6 Anger

Adults were assessed using PROMIS Short Form v1.1 Anger 5a, while minors were assessed using PROMIS SF v2.0 5a. The total score, ranging from 5 to 25, was calculated by summing responses to five questions, with a higher score indicating more intense anger. Scores less than 13 indicated none to slight anger, 13–15 suggested mild anger, 16–20 indicated moderate anger, and a score greater than 21 signified severe anger (28).

2.6.7 Overall quality of life

Overall quality of life was assessed using EQ-5D-5L. This survey explores patients' mobility, self-care, daily activities, pain/discomfort, and anxiety/depression levels. A health utility score, ranging from slightly under zero (worse than death) to one (complete health), is derived from the responses to these five aspects, with a higher score indicating better health (29).

2.7 Data analysis

Data management and analyses were completed using STATA statistical software (College Station, TX). Demographic characteristics of participants were reported using descriptive statistics. Short-term outcomes were assessed using information from participant questionnaires administered at the beginning (baseline) and completion of the treatment (post-treatment). Mean scores for each treatment outcome were described at baseline and post-treatment with associated 95% confidence intervals (CIs). Patients were evaluated at least twice throughout the study: once at the beginning and once after completion of therapy, the overall mean of individual differences in outcome scores from baseline to post-treatment was reported for each outcome with associated 95% CIs. In addition, percent changes in mean values from baseline to post-treatment were also reported for the overall cohort and stratified by group. Additionally, an economic evaluation of ABCHIP has been conducted, and the results are reported in a companion paper (28).

3 Results

3.1 Study sample

As depicted in Figure 1, a total of 606 individuals underwent at least one acupuncture session through ABCHIP. Data from 15 patients were excluded due to incomplete questionnaire responses, making interpretation challenging. Furthermore, 91 individuals were excluded as they had undergone fewer than the required minimum of six acupuncture treatments. The majority of patients completed their acupuncture therapy within 12 sessions, except for a few more severe cases that necessitated up to 18 sessions. This yielded a valid sample size of 500.

The participants were categorized into three groups based on the total number of acupuncture treatments (Tx) received (Figure 2):

Group A = patients who received a total of 12 or more treatments.
Group B = patients who received a total of 9–11 treatments.
Group C = patients who received a total of 6–8 treatments.

3.2 Descriptive characteristics

Table 1 provides a comprehensive overview of the demographic composition of the study sample. Notably, females constitute the majority, representing 73.2% of all respondents. The age cohort from 55 to 74 years up 74.6% of the total. Regarding racial and ethnic backgrounds, East Asians comprise the largest group at 55.4%, followed by Whites at 36.4%. In terms of income distribution, a substantial proportion of respondents fall within the <$13,311 and >$37,801 brackets, accounting for 22.8% and 19%, respectively. Examining marital status, married or common-law individuals form the largest segment, representing 56.2%. Looking at educational attainment, 35.2% of respondents have no post-secondary education, while others hold diverse educational backgrounds, including bachelor's degrees (16.8%), non-university certificates (12.8%), and graduate degrees (11.6%). Lastly, the findings indicate a significant presence of immigrants in the studied population, with 61.4% identifying as immigrants.

3.3 Baseline conditions and treatment outcomes

Distributions of outcome severity and mean outcome scores at baseline and post-treatment are reported in Table 2. Mean individual differences and percent changes in treatment outcomes from baseline to post-treatment are reported in Table 3.

3.3.1 Pain severity

The majority of patients experienced moderate to severe pain before undergoing treatment in ABCHIP. Approximately 73% of patients identified pain as their primary health concern, with 90% reporting moderate to severe pain severity at baseline. Overall, mean BPI scores fell from 4.45 (95% CI: 4.27, 4.63) at baseline to 1.52 (95% CI: 1.37, 1.67) post-treatment with an average individual difference of −2.93 (95% CI: −3.12, −2.74) and a percent reduction of −65.8%. Participants in Group A (receiving 12 or more acupuncture treatments) experienced the largest reduction in pain severity of 75.5% while participants in Group C (6–8 treatments) experienced the smallest reduction of 51.0% (Table 3).

3.3.2 Pain interference

Overall, 80% of patients reported moderate to severe pain interference at baseline while only 17% of patients reported moderate to severe pain post-treatment. Pain interference was significantly reduced by 3.29 points (95% CI: 3.09, 3.49) on the BPI scale from baseline (BPI: 4.19; 3.98, 4.40) to treatment (BPI: 0.90; 0.76, 1.04),

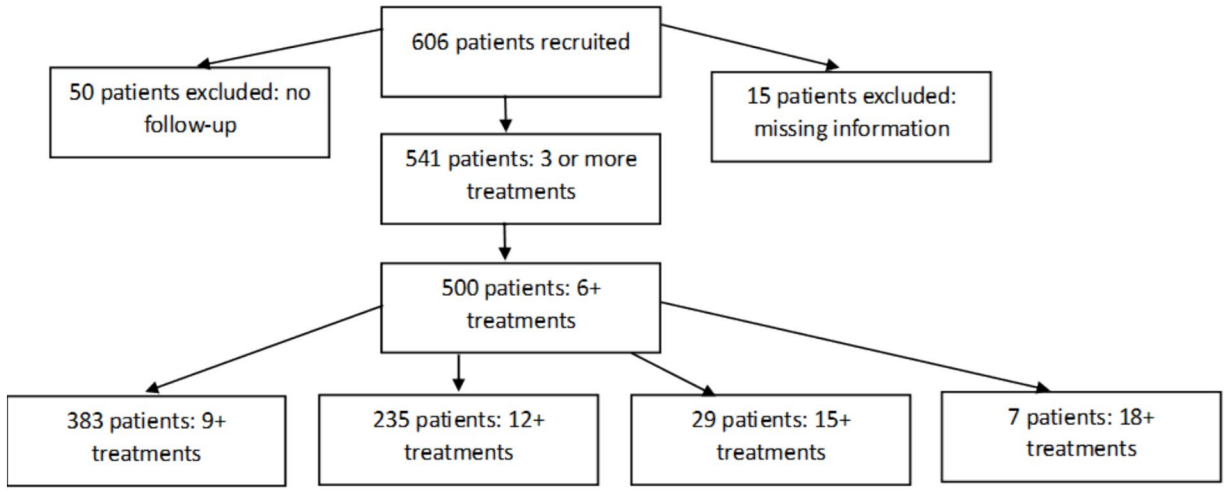

FIGURE 1
ABCHIP sample.

corresponding to a percent change of 78.5% for the overall cohort (Table 3). Similarly, pain interference was most reduced for Group A, and least reduced for Group C, although all groups reported a significant reduction in pain interference, underscoring acupuncture's effectiveness in substantially enhancing patients' quality of life by alleviating pain-related challenges.

3.3.3 Depression

17% of patients expressed overall concern about depression, with 52% reporting moderate to severe depression at baseline and a mean PHQ-9 score of 10.28 (95% CI: 9.69, 10.87). Following treatment, only 7.6% of individuals reported moderate to severe depression with a mean PHQ-9 of 3.08 (95% CI: 2.68, 3.48). PHQ-9 scores were reduced by an average of 7.20 (95% CI: 6.73, 7.67) points following treatment, corresponding to a 70.0% overall decrease (Table 3). Groups A, B, and C experienced 78.4, 68.5, and 57.7% decreases, respectively; all decreases were statistically significant.

3.3.4 Anxiety

18% of patients reported an anxiety disorder, with 40% of participants experiencing moderate to severe anxiety at baseline (mean score: 18.62; 95% CI: 17.83, 19.41). Only 10.4% of participants reported moderate to severe anxiety after treatment (mean score: 11.75; 95% CI: 11.23, 12.28). Anxiety scores significantly decreased for the overall cohort by 36.9% and for each individual treatment group (Table 3).

3.3.5 Sleep quality

Approximately 74% of ABCHIP patients reported poor sleep quality at baseline, while 35.4% reported poor sleep quality post-treatment. For the overall cohort, PSQI scores dropped significantly by 4.13 (95% CI: 4.46, 3.79); there was a 45.6% decrease from PSQI scores at baseline (9.03; 8.63, 9.44) to post-treatment (4.91; 4.61, 5.20). Groups A, B, and C reported 53.1, 41.7, and 34.9% reductions in PSQI scores, respectively. All decreases were statistically significant.

3.3.6 Fatigue

Approximately 67% of patients experienced moderate to severe fatigue at baseline, reporting at mean PROMIS fatigue score of 21.15 (95% CI: 20.34, 21.97). Post-treatment, only 7% of patients reported moderate to severe fatigue and the mean score was 13.07 (95% CI: 12.46, 13.69). Overall fatigue scores dropped by 38.2%; mean differences were significantly negative for the overall cohort (−8.08; 95% CI: −8.80, −7.36) and all treatment groups.

3.3.7 Anger

While 21.2% of participants reported moderate to severe anger scores at baseline, only 3.4% reported following treatment. Anger scores decreased from 11.28 (95% CI: 10.84, 11.72) to 7.44 (95% CI: 7.12, 7.75), corresponding to a 34.0% decrease. The mean individual decrease was by 3.84 points (95% CI: 3.46, 4.22) for the overall cohort; decreases were significantly for all treatment groups.

3.3.8 Overall quality of life

The average EQ5D-5L score for pain, depression, and anxiety patients was 0.63 (95% CI: 0.62, 0.65) at baseline, lower than the average EQ5D-5L score for Albertans in 2018, which was 0.85 (30). However, the mean EQ5D-5L score was significantly higher post-treatment at 0.87 (95% CI: 0.86, 0.88), corresponding to a percent increase of 38.1%. The average individual increase in EQ5D-5L was 0.24 (95% CI: 0.22, 0.25); this increase was significantly for all treatment groups.

4 Discussion

Analysis of data from 500 patients who received at least 6 acupuncture sessions through ABCHIP showed statistically significant improvements in clinical outcomes. Among this group, the subgroup of 235 patients who received at least 12 sessions demonstrated the most favorable treatment outcomes, including an 75.5% reduction in pain severity, a 53.1% improvement in sleep quality, a 78.4% drop in

depression, a 41.1% decline in anxiety, a 43.7% decrease in fatigue, a 38.2% decrease in anger, and a 42.6% improvement in overall quality of life.

This study has certain limitations. Firstly, ABCHIP is not a randomized controlled trial; instead, it focuses on providing community services and real-world evidence. Secondly, all data used

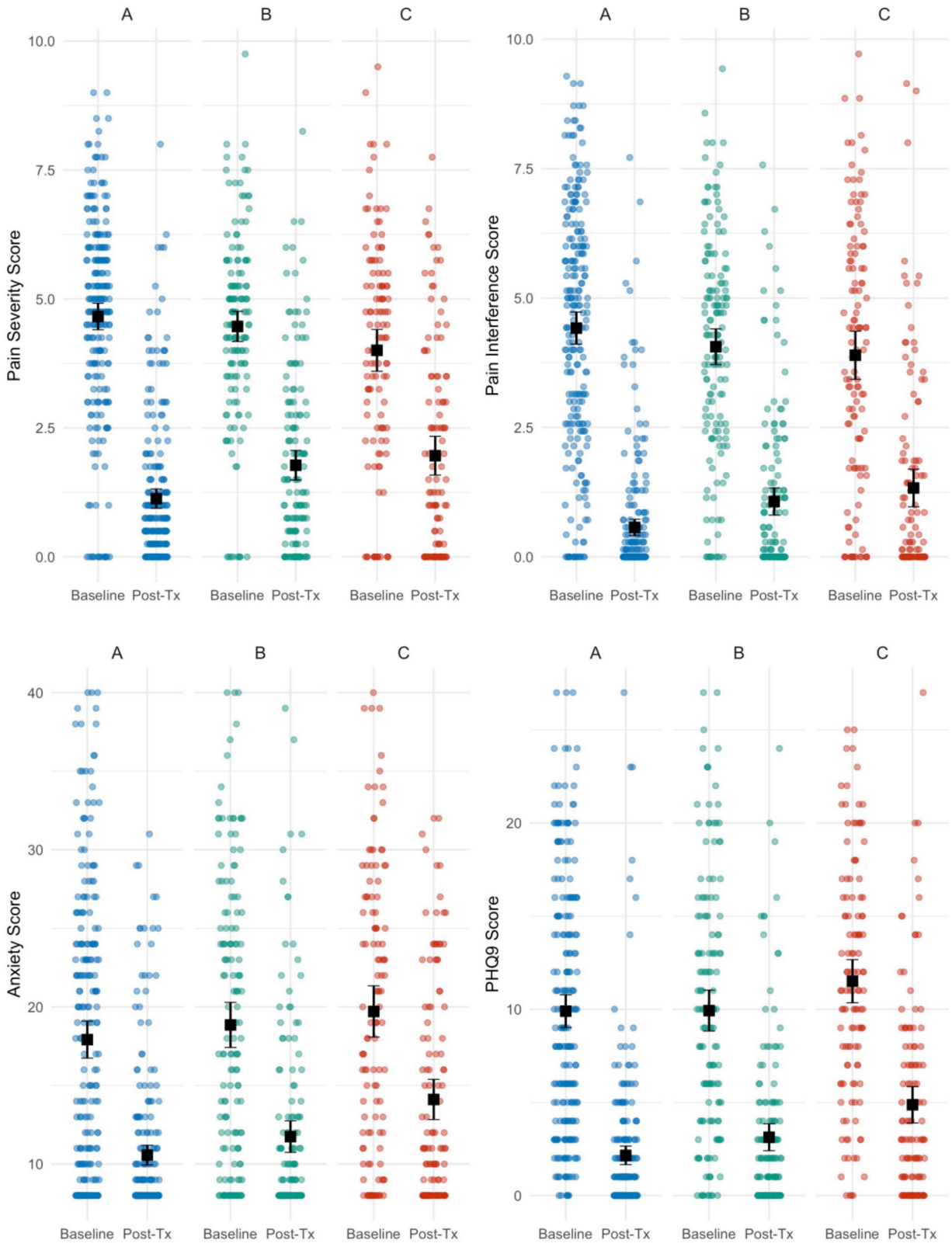

FIGURE 2 (continued)

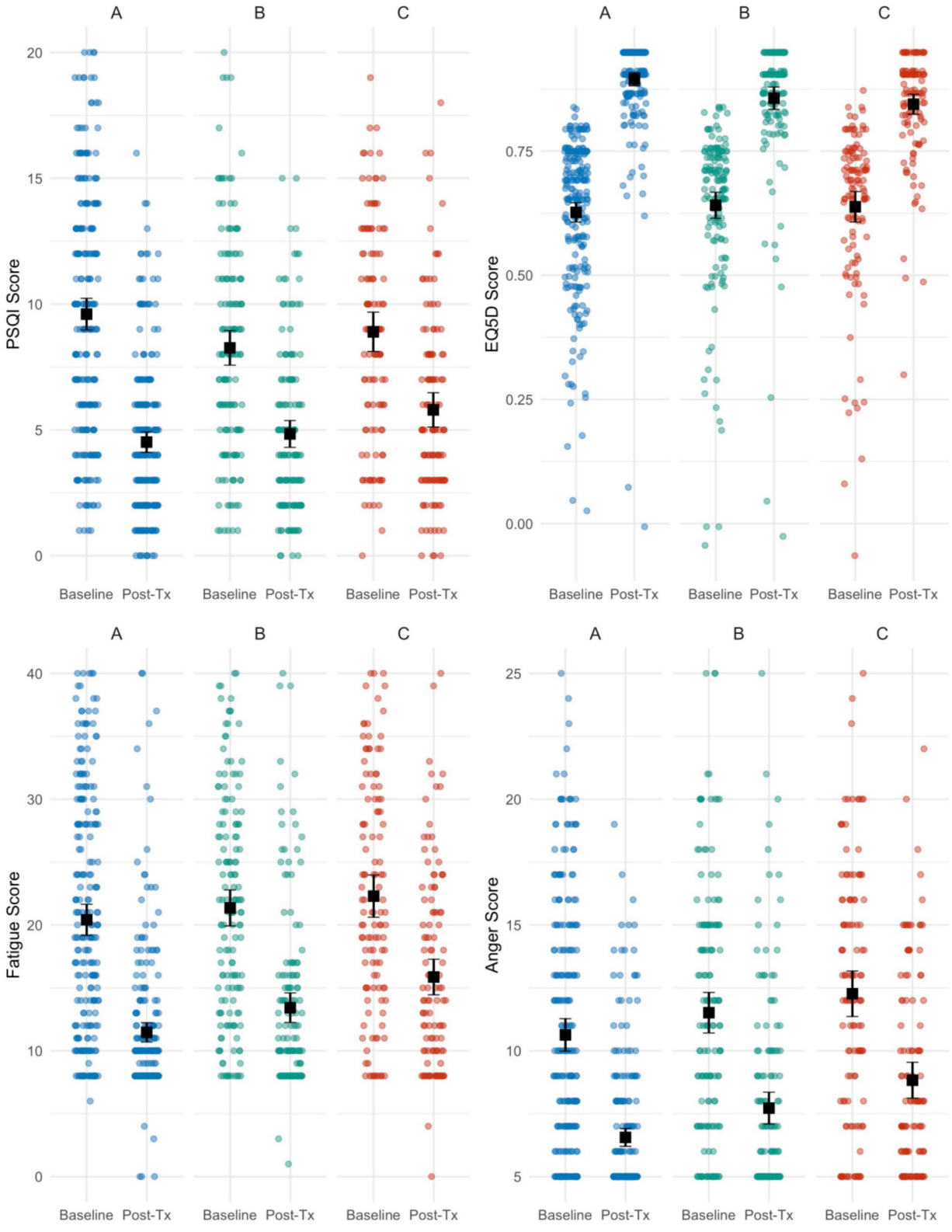

FIGURE 2
Distribution of scores at baseline and post-treatment by treatment group for each treatment outcome. Black points represent mean value and black error bars represent 95% CIs.

for constructing outcome measures and conducting treatment evaluations are self-reported. Despite using instruments with high validity and reliability, these measures are still subject to reporting errors.

TABLE 1 ABCHIP patient sample demographic characteristics.

Characteristic	Frequency, *n* (%)
Gender	
Female	366 (73.2%)
Male	129 (25.8%)
Other	5 (1.0%)
Age	
<18 y/o	23 (4.6%)
18–24 y/o	37 (7.4%)
55–64 y/o	222 (44.4%)
65–74 y/o	162 (32.4%)
75+ y/o	36 (7.2%)
No response	20 (4.0%)
Race/Ethnicity	
East Asian	277 (55.4%)
White	182 (36.4%)
Mixed Race	12 (2.4%)
South Asian	8 (1.6%)
Southeast Asian	6 (1.2%)
Latin American	5 (1.0%)
Metis	4 (0.8%)
Black	1 (0.2%)
Arab	1 (0.2%)
First Nations	1 (0.2%)
No response	3 (0.6%)
Income	
<$13,311	114 (22.8%)
$13,111–$22,628	76 (15.2%)
$22,628–$26,621	53 (10.6%)
$26,621–$37,801	40 (8.0%)
>$37,801	95 (19.0%)
Marital status	
Married/Common Law	293 (58.6%)
Single	87 (17.4%)
Divorced/Separated	87 (17.4%)
Widowed	33 (6.6%)
Highest education	
No post-secondary education	176 (35.2%)
Bachelor's degree	84 (16.8%)
Non-university certificate	64 (12.8%)
Graduate degree	58 (11.6%)
Trade/vocational school	44 (8.8%)
Post-secondary cert/diploma	33 (6.6%)
No response	4 (8.2%)
Student status	
Junior high	4 (0.8%)
Senior high	19 (3.8%)
University/College	19 (3.8%)
No response	458 (91.6%)
Immigrant status	
Immigrant	307 (61.4%)
Non-immigrant	191 (38.2%)
No response	2 (0.4%)
Main complaint	
Back pain	99 (19.8%)
Shoulder pain	70 (14.0%)
Neck pain	55 (11.0%)
Knee pain	54 (1.08%)
Depression and anxiety	54 (10.6%)
Sciatica	44 (8.8%)
Anxiety	36 (7.2%)
Depression	30 (6.0%)
Hip pain	16 (3.2%)
Headache	15 (3.0%)
Wrist pain	6 (1.2%)
Leg pain	3 (0.6%)
Osteoarthritis (hand)	3 (0.6%)
Lateral epicondylitis	3 (0.6%)
Addiction	3 (0.6%)
ADHD	2 (0.4%)
Concussion	1 (0.2%)
PTSD	1 (0.2%)

Nevertheless, the findings from ABCHIP suggest that integrating acupuncture with usual care demonstrates promise in enhancing mental health, alleviating chronic and general pain, and improving overall quality of life. Integrative programs, such as ABCHIP, offers a holistic approach to addressing both physical symptoms and psychological well-beings. This approach is particularly beneficial in vulnerable populations where conventional treatments may have limitations.

The findings from ABCHIP underscore the potential of integrative medicine to provide comprehensive support for patients experiencing pain and mental health challenges. By integrating acupuncture, a therapy known for its stress-reducing and pain-relieving effects, into conventional care, the program not only addresses symptoms but also promotes overall quality of life. This integrative approach aligns with the principles of psychosomatic medicine, which recognizes the intricate interplay between mental and physical health.

Moreover, our study highlights the importance of personalized and patient-centered care approaches in healthcare interventions. By tailoring treatments to individual needs and incorporating therapies that address both mind and body, healthcare providers can better support patients facing complex health challenges.

TABLE 2 Distribution of baseline and post-treatment outcomes for all ABCHIP patients.

Outcomes	Baseline frequency, *n* (%)	Baseline mean (95% CI)	Post-Tx frequency, *n* (%)	Post-Tx mean (95% CI)
BPI group (pain severity)				
None to mild pain (<2)	52 (10.4%)	4.45 (4.27–4.63)	342 (68.4%)	1.52 (1.37–1.67)
Moderate pain (2–5)	295 (59.0%)		134 (26.8%)	
Severe pain (6+)	153 (30.6%)		24 (4.8%)	
BPI (pain interference)				
None to mild pain (<2)	96 (19.2%)	4.19 (3.98–4.40)	415 (83.0%)	0.90 (0.76–1.04)
Moderate pain (2–5)	244 (48.8%)		73 (14.6%)	
Severe pain (6+)	160 (32.0%)		12 (2.4%)	
PHQ-9 (depression)				
None (0–4)	124 (24.8%)	10.28 (9.69–10.87)	380 (76.0%)	3.08 (2.68–3.48)
Mild (5–9)	117 (23.4%)		82 (16.4%)	
Moderate (10–14)	120 (24.0%)		17 (3.4%)	
Moderately severe (15–19)	76 (15.2%)		13 (2.6%)	
Severe (20–27)	63 (12.6%)		8 (1.6%)	
PROMIS anxiety				
No to minimal anxiety (0–17)	231 (46.2%)	18.62 (17.83–19.41)	415 (83.0%)	11.75 (11.23–12.28)
Mild anxiety (17–21)	69 (13.8%)		33 (6.6%)	
Moderate anxiety (22–31)	148 (29.6%)		48 (9.6%)	
Severe anxiety (32+)	52 (10.4%)		4 (0.8%)	
PSQI (sleep quality)				
Good (0–5)	130 (26.0%)	9.03 (8.63–9.44)	323 (64.6%)	4.91 (4.61–5.20)
Poor (>5)	370 (74.0%)		177 (35.4%)	
PROMIS fatigue				
No to slight fatigue (<22)	273 (54.6%)	21.15 (20.34–21.97)	438 (87.6%)	13.07 (12.46–13.69)
Mild fatigue (22–27)	67 (13.4%)		32 (6.4%)	
Moderate fatigue (27–36)	118 (23.6%)		21 (4.2%)	
Severe fatigue (36+)	42 (8.4%)		9 (1.8%)	
PROMIS anger				
None to slight (<13)	301 (60.2%)	11.28 (10.84–11.72)	440 (88.0%)	7.44 (7.13–7.75)
Mild (13–15)	93 (18.6%)		43 (8.6%)	
Moderate (16–20)	92 (18.4%)		14 (2.8%)	
Severe (21+)	14 (2.8%)		3 (0.6%)	
EQ-5D-5L quality of life	—	0.63 (0.62–0.65)	—	0.87 (0.86–0.88)

In conclusion, the findings from ABCHIP provide valuable insights into the benefits of integrative programs in addressing pain and mental health issues. This study not only supports the integration of complementary therapies into clinical practice but also underscores the relevance of psychosomatic considerations in healthcare delivery. Future research and healthcare interventions can build upon these insights to further optimize patient care and outcomes in diverse patient populations.

Data availability statement

The datasets presented in this article are not readily available because data requests are subject to ethics approval by the University of Calgary Conjoint Health Research Ethics Board (CHREB). Requests to access the datasets should be directed to CHREB, chereb@ucalgary.ca.

Ethics statement

The studies involving humans were approved by the University of Calgary Conjoint Health Research Ethics Board (CHREB) (Ethics ID: REB 21-0086). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

TABLE 3 Mean individual differences and percent change in outcome values from baseline to post-treatment timepoints, stratified by treatment group.

Outcome	Group	Mean difference (95% CI)	Percent change
BPI (pain severity)	Group A	−3.53 (−3.80, −3.26)	−75.5%
	Group B	−2.69 (−3.01, −2.37)	−60.5%
	Group C	−2.04 (−2.41, −1.67)	−51.0%
	Overall	−2.93 (−3.12, −2.74)	−65.9%
BPI (pain interference)	Group A	−3.85 (−4.14, −3.55)	−87.0%
	Group B	−2.99 (−3.32, −2.66)	−73.9%
	Group C	−2.56 (−2.97, −2.15)	−65.8%
	Overall	−3.29 (−3.49, −3.09)	−78.6%
PHQ9 (depression)	Group A	−7.74 (−8.45, −7.03)	−78.4%
	Group B	−6.80 (−7.62, −5.98)	−68.5%
	Group C	−6.63 (−7.63, −5.63)	−57.7%
	Overall	−7.20 (−7.67, −6.73)	−70.1%
PROMIS anxiety	Group A	−7.35 (−8.32, −6.38)	−41.1%
	Group B	−7.11 (−8.25, −5.97)	−37.9%
	Group C	−5.60 (−6.92, −4.27)	−28.4%
	Overall	−6.87 (−7.51, −6.22)	−37.0%
PSQI (sleep quality)	Group A	−5.09 (−5.62, −4.55)	−53.1%
	Group B	−3.43 (−3.95, −2.92)	−41.7%
	Group C	−3.10 (−3.74, −2.46)	−34.9%
	Overall	−4.13 (−4.46, −3.79)	−45.8%
PROMIS fatigue	Group A	−8.94 (−10.00, 7.89)	−43.7%
	Group B	−8.03 (−9.31, −6.75)	−37.7%
	Group C	−6.43 (−8.02, −4.83)	−28.8%
	Overall	−8.08 (−8.80, −7.36)	−38.2%
PROMIS anger	Group A	−4.07 (−4.64, −3.50)	−38.2%
	Group B	−3.79 (−4.47, −3.11)	−33.1%
	Group C	−3.44 (−4.18, −2.69)	−28.0%
	Overall	−3.84 (−4.22, −3.46)	−34.1%
EQ5D-5 L (quality of life)	Group A	0.27 (0.25, 0.29)	42.6%
	Group B	0.22 (0.19, 0.24)	33.7%
	Group C	0.21 (0.18, 0.23)	32.4%
	Overall	0.24 (0.22, 0.25)	37.5%

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SS: Visualization, Writing – original draft, Writing – review & editing. YT: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. XX: Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. GoY: Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. YC: Validation, Writing – original draft, Writing – review & editing, Investigation. GuY: Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. JJ: Investigation, Project administration, Writing – original draft, Writing – review & editing. YX: Data curation, Formal analysis, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. LP: Data curation, Formal analysis, Software, Visualization, Writing – original draft, Writing – review & editing. BX: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. JQ: Formal analysis, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Fire needle therapy for the treatment of cancer pain: a protocol for the systematic review and meta-analysis

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Background: Cancer patients frequently suffer pain as one of their symptoms. It includes acute and chronic pain and is one of the most feared symptoms for patients. About one-third of adults actively undergoing cancer treatment suffer from pain related to their condition. Cancer pain control remains suboptimal due to a lack of assessment, knowledge, and access. Fire needle therapy, a traditional Chinese medicine, offers a potentially beneficial addition to current pain management approaches. This protocol outlines a systematic review and meta-analysis to compile evidence and examine the pain-relieving effects and safety of fire needle therapy for cancer patients.

Methods and analysis: We will systematically search China National Knowledge Infrastructure (CNKI), Wanfang Database, China Biology Medicine disc (CBM), China Science and Technology Journal Database (CSTJ or VIP), PubMed, Web of Science, Embase, Cochrane Central Registry of Controlled Trials (CENTRAL), Chinese Clinical Trial Registry (Chictr), Opengrey, Worldcat, and Scopus from inception through July 2023. Random control trials (RCTs) include all types of cancer patients (age ≥ 18 years) complaining of pain. The primary outcome will be changes in pain intensity measured by Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Neuropathic Pain Scale (NPS), or Brief Pain Inventory (BPI). Secondary outcomes include quality of life (EORTC QLQ-C30 and GCQ), performance status (KPS), times of burst pain, treatment response rate, the dose reduction of analgesic drugs, and side effects rates. Utilizing the Cochrane risk bias measurement tool: Risk of Bias 2 (RoB 2), the trials' quality will be evaluated, and meta-analysis will be performed using RevMan software (version 5.4).

Discussion: This systematic review will be the first comprehensive review of the literature to provide a meta-analysis of fire needle therapy for cancer pain, including only Random control trials (RCTs). For the sake of transparency and to avoid future duplication, the publication of this protocol offers a clear illustration of the procedures utilized in this evaluation. The results of our future studies may provide a new approach and theoretical basis for the treatment of cancer pain by medical oncology professionals.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42023418609.

KEYWORDS

fire needle therapy, cancer pain, protocol, systematic review, complementary and alternative medicine, efficacy, safety

1 Introduction

Pain is a prevalent symptom among cancer patients (1). It includes acute pain and chronic pain (2). Cancerous tumors can cause pain by pressing on nerves, bones, or organs, and releasing chemicals that can cause pain (2, 3). The cancer's destruction of surrounding tissue can also lead to pain (2). Around one-third of adults undergoing active cancer treatment suffer from pain related to their condition (4). Cancer pain can have a significant effect on a patient's day-to-day activities as well. Cancer pain can lead to sleep disturbances (5), fatigue, nausea, and vomiting (6), all of which can make it difficult to carry out normal activities and enjoy life. Pain can also contribute to feelings of depression and anxiety, further affecting a patient's quality of life (7). In addition to the physical toll cancer pain takes on patients, it can also have a significant economic burden (8). The cost of pain medications and other treatments can be quite high, and patients may also incur additional expenses related to managing their pain, such as travel to medical appointments or modifications to their home or workplace. This can place a strain on patients and their families, both emotionally and financially (9).

There are many treatments available for pain such as pharmacological agents, nerve blocks, psychological therapies, physiotherapy, alternative remedies, and surgery (10–12). What's more, a new treatment option, contextual effects (placebo and nocebo effects), should be in the spotlight (13). It has been identified to modulate chronic pain as well as musculoskeletal pain (14, 15). Pain patients use the contextual effect to explain the effects of treatment, while it has been applied in the fields of rehabilitation, physical therapy, and nursing (16–19). For the treatment of cancer pain, the WHO proposed three-step analgesic approach is a major part of this (20). For mild pain, non-opioid analgesics like paracetamol or ibuprofen are used in the first stage; for moderate pain, weak opioids like codeine or tramadol are used in the second step; and for severe pain, strong opioids like morphine or fentanyl are used in the third step (21).

However, there are several restrictions and disadvantages to this strategy. First, due to inadequate opioid prescription or therapy, many patients do not experience sufficient pain relief (22, 23). Second, opioids have serious adverse effects, including addiction, constipation, nausea, drowsiness, and respiratory depression (11, 24). Third, due to supply problems and regulatory restrictions, opioids are frequently unavailable or unaffordable in low- and middle-income nations (25). Consequently, other treatments have been explored and created to decrease reliance on opioids. Fire needle therapy is one of them.

By burning a specific needle till it becomes red and immediately penetrating the skin at the body's acupuncture point, fire needle therapy is a form of traditional Chinese medicine that heals illnesses (26). Fire needle therapy, which combines acupuncture, direct moxibustion, and needling into one method, is known for its simplicity, practicality, efficiency, and quickness (27, 28). Fire needle therapy has the significant efficacy in treating pain and has sufficient theoretical basis for treating cancer pain (29). According to studies, the use of a fire needle eliminates or improves pathological alterations such as local tissue edema, hyperemia, exudation, and adhesion by stimulating the illness site and reflex point. This boosts metabolism and blood flow while reducing inflammation (30). Fire needle therapy can reduce the levels of pain transmitters in the central and peripheral nerve systems, including substance P and 5-hydroxytryptamine (31, 32). In particular, TNF(tumor necrosis factor) and interleukin-1 levels can both be decreased with fire needle therapy (33). Additionally, it can encourage the body to release more of a vascular endothelial growth factor that is necessary for damage recovery (34). In terms of Traditional Chinese medicine, the acupoints targeted by the fire needle therapy may help to regulate the flow of qi (life force energy) in the body, which could have a positive effect on pain perception (27).

As a result, based on the most recent research, we designed this study to evaluate the efficacy and safety of fire needle therapy in the management of pain in cancer patients. We will also look into the efficient fire needle points and treatment regimens to recommend more usable therapies for clinical care.

2 Methods

2.1 Study registration

This review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42023418609. Reporting standard followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols (See Supplementary material).

2.2 Eligibility criteria for study inclusion

2.2.1 Type of study

Only RCTs with cancer pain patients treated with fire needle therapy are eligible for inclusion, and there will be no language restrictions during the search process.

2.2.2 Type of intervention

The treatment group will receive fire needle therapy without any restrictions on the depth, frequency, intensity, or area of application of needling. Fire needle therapy either used alone or combined with other therapies (e.g., modern medicine, other acupuncture methods) will be included. RCTs compared fire needle therapy directly with different types of TCM (e.g., herbal decoction, another form of acupuncture) will be excluded from this study.

2.2.3 Type of controls

All the active therapies will be part of the control group. Sham fire needling, no treatment, usual care, oral analgesics, and other active

therapies may be included. Placebo, blank controls will be considered for inclusion.

2.2.4 Type of outcome measure

Considering that the population of our study is cancer patients presenting with pain, the results of the evaluation of pain-related scales will be chosen as our primary outcome indicators for analysis, including visual analog scale (VAS), numerical rating scale (NRS), Neuropathic Pain Scale (NPS) and Brief Pain Inventory (BPI). Secondary outcome indicators such as Karnofsky performance status (KPS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30), the General Comfort Questionnaire (GCQ), times of burst pain, treatment response rate, the dose reduction of analgesic drugs, and side effect rates will be included for analysis. If trials involved any of the above outcome indicators will be included in the analysis.

2.2.5 Type of exclusion criteria

- Duplicate studies;
- Studies that report only abstracts but not complete data;
- Articles with obvious statistical or logical errors.

2.3 Search methods for identification of studies

2.3.1 Electronic data sources

The following databases will be searched from their inception through July 2023: China National Knowledge Infrastructure (CNKI), Wanfang Database, China Biology Medicine disc (CBM), China Science and Technology Journal Database (CSTJ or VIP), PubMed, Web of Science, Embase, Cochrane Central Registry of Controlled Trials (CENTRAL), Chinese Clinical Trial Registry (Chictr), Opengrey, Worldcat, and Scopus.

2.3.2 Searching other resources

Any eligible studies potentially overlooked will also be manually identified by scanning the reference lists of related systematic reviews and conference proceedings.

2.3.3 Search strategy

See Supplementary material for details.

2.4 Data collection and analysis

2.4.1 Selection of studies

Duplicates were found and eliminated using Zotero software after gathering the search results from these databases. Then, two independent reviewers (JN Z and YH R) will browse the titles and abstracts of the studies, and studies that do not meet the eligibility criteria based on the titles and abstracts will be excluded. The remaining studies' complete texts will be located and reviewed for the last round of selection. The arbiter (WZ W) shall resolve any differences of opinion on the data selection. The method for finding and screening studies will be depicted in a PRISMA flow diagram (see Figure 1).

2.4.2 Data extraction and management

Two reviewers JN Z and YH R will use a standardized data extraction form to extract the following information for each included RCT:

- Basic information about the RCT: such as title, authors, date of publication, and number of subjects involved;
- Criteria for inclusion of subjects: such as restrictions on demographic information, diagnostic criteria for disease, age, sex, ethnicity, the severity of disease, and duration of disease;
- Details of interventions and controls: such as the method of fire needle therapy, site of acupuncture, dose, duration of treatment, and combined intervention regimen;
- Outcome indicators: names, definitions, and results of outcome indicators;
- Methodology entries: randomized methods, blinded methods (including blinding of physicians, patients, and outcome assessors), allocation concealment, missing data, selective reporting.

A third investigator (WZ W) will make judgments about any differences and questions. Following a transfer of data, the synthesis will be performed using RevMan software (version 5.4, Cochrane Collaboration, Oxford, United Kingdom) (36).

2.4.3 Assessment of risk of bias in the included studies

Two authors (JN Z and YH R) will independently evaluate the risk of bias using the Cochrane risk bias measurement tool: Risk of Bias 2 (RoB 2). The following biases will be assessed. The tool consists of the following 5 domains, randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The authors classified studies as low risk of bias, some concerns or high risk of bias.[1] The arbiter (WZ W) will resolve any disagreements regarding the bias assessment. The quality assessment results will be illustrated in a risk-of-bias graph and a risk-of-bias summary table.

2.4.4 Data synthesis

Data synthesis for the meta-analysis will be accomplished using the RevMan version 5.4 software. Referring to Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions,[2] we chose to use a fixed-effects model or a random-effects model based on the magnitude of heterogeneity. When heterogeneity was significant (I square $\geq$ 50%, or $p < 0.05$), a random-effects model was used; when it was not significant (I square < 50% and $p \geq 0.05$), a fixed-effects model was used. A 95% confidence interval (CI) will be used to determine the mean difference (MD) for continuous data. The risk ratio (RR) with 95% confidence interval (CI) will be utilized for dichotomous data. Weighted mean difference (WMD) will be used in subgroup analyses comparing different treatments, and standardized mean difference (SMD) will be used in subgroup analyses comparing the efficacy of the same treatment in different populations.

1 https://training.cochrane.org/handbook/current/chapter-08

2 training.cochrane.org/handbook/current/chapter-10

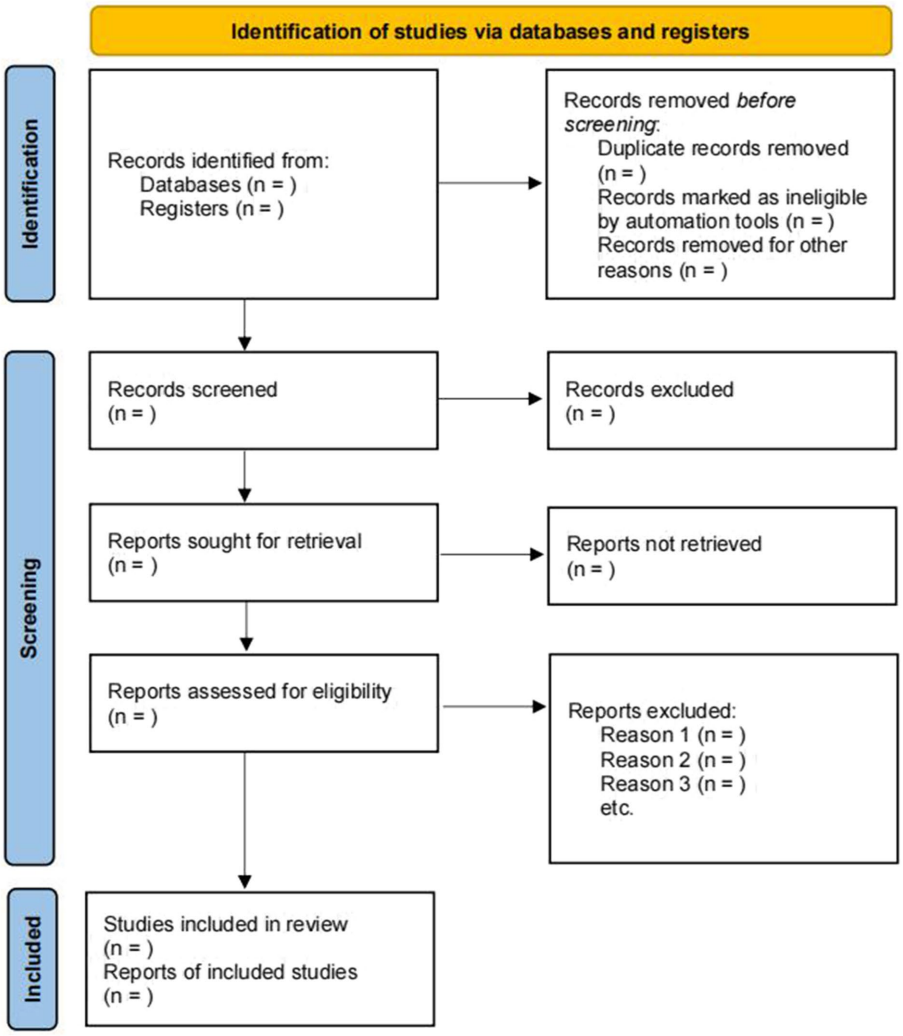

FIGURE 1
Flowchart of the literature review and selection process (35).

2.4.5 Dealing with missing data

If the full text of an article is not available, the reviewers will attempt to contact the author to obtain it. If the author cannot be contacted, this article will be excluded from the analysis. The state of relevant articles for which the authors were contacted will be reported in the study results and provide a descriptive summary of the main results of the relevant articles.

2.4.6 Assessment of heterogeneity

For heterogeneity among the outcomes of the included studies, the Chi2 test will be used. The following I^2 thresholds will be applied in this study:

- I^2:0–40%: probably not significant;
- I^2:30–60%: possibly moderate heterogeneity;
- I^2:50–90%: possibly significant heterogeneity;
- I^2:75–100%: possibly substantial heterogeneity.

The statistical value of I^2 will depend on the magnitude of its influence factors and the strength of evidence of heterogeneity (such as the p-value of the Chi^2 test). The effects of clinical and statistical heterogeneity will be addressed when examining the analysis results (37).

A random-effects model will be applied if significant statistical heterogeneity is discovered; otherwise, a fixed-effects model will be applied. Also, we will assess clinical heterogeneity, including study population, study design, and treatment protocols. The results of the synthesis will be visualized in the form of a forest plot. If heterogeneity is too great, quantitative analysis will be abandoned in favor of qualitative analysis.

2.4.7 Assessment of publication biases

If over 10 RCTs are included in the meta-analysis, publication bias will be evaluated using funnel plots. If there are less than 10 RCTs in the meta-analysis, we will employ Egger's test and Begg's test for publication bias.

2.4.8 Subgroup analysis

If the data permits, we will perform the following subgroup analyses:

- The depth, frequency, and intensity of different piercings;
- Cancer pain of the patient (different cancers).

2.4.9 Sensitivity analysis

To assess the impact of study design, sample size, and methodological quality, a sensitivity analysis will be performed and, where possible, the robustness of the data synthesis will be determined.

2.5 Grading the quality of evidence

Considering the type of study we included as a randomized controlled trial, randomized controlled trials should be initially rated as high-quality evidence according to the GRADE approach. However, due to limitations in five aspects, the quality of evidence may be downgraded to some extent. These five aspects include: study design limitations (downgrade 1–2 levels), inconsistency of results (downgrade 1–2 levels), indirectness (downgrade 1 level), imprecision (downgrade 1 level), and publication bias (downgrade 1 level). The degree of the downgrade will be determined with reference to the Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions* (38), and related literature (39).

2.6 Patient and public involvement

This meta-analysis data processing phase will utilize published clinical trial data without direct patient or public participation.

2.7 Dissemination and ethics

Because the data used in the study are not individualized, ethical approval is not required for this study. Necessary protocol revisions will be documented in a comprehensive review. The study findings will be published in peer-reviewed journals and potentially presented at applicable conferences.

3 Discussion

In recent years, due to changes in living environment, the incidence of cancer continues to rise and about 69% of patients suffer cancer pain, including pain caused by cancer, cancer-related, lesions and anti-cancer treatment (40). Cancer pain can occur at any stage from early to late stage of cancer, seriously affecting patients' treatment and daily life (41). The WHO's three-step analgesic ladder for cancer pain control is the primary approach for managing cancer pain, with opioids as the core component of the analgesia. However, long-term use of opioids can cause adverse reactions such as constipation, nausea, and vomiting, as well as many problems such as addiction, dependence, and poor tolerance (42). Compared with Western medicine, acupuncture therapy in the treatment of cancer pain is not only effective but also has the advantages of safety, simple operation, small adverse reactions, no dependence, and addiction (43).

Research has shown that pain relief from acupuncture is associated with neuro-humoral factors (44), which can relieve pain by encouraging the release of endogenous opioid peptides, increasing local endorphin levels and peripheral opioid receptor activity during inflammatory responses, and suppressing the synthesis of endogenous pain (45, 46). The stimulation amount of fire needle is much greater than that of traditional acupuncture (29). Thus, fire needle therapy may be able to treat pain that cannot be relieved by ordinary acupuncture (47). Several studies have found that fire needle alone or combined with Western medicine can significantly relieve the pain symptoms of cancer pain patients and reduce the NRS score (47, 48). Compared to using only Western medicine, fire needling alone or in combination with Western medicine demonstrates higher efficacy and lower incidence of adverse effects (48–51). In conclusion, fire needle is an appropriate treatment for cancer pain and should be gradually promoted in clinical practice.

There are some limitations of fire needle therapy. Firstly, there is a fearfulness in patients and a poor reception of that. Secondly, the efficacy and safety of fire-needle therapy need further research and proof. Thirdly, there are potential risks including pain, skin lesions, allergy, and other adverse reactions (52, 53).

This review aims to present information on the different acupuncture points and fire needle therapy that can be used to treat pain in cancer patients. It will cover more than just the effects of fire needling on symptoms in patients with cancer pain. This study may have practical implications for utilizing fire needle therapy in oncology. It could help guide the application of fire needling as an alternative treatment for cancer pain management, thus helping clinicians determine whether fire needle therapy is an effective option to incorporate into pain management programs for cancer patients.

3.1 Limitations

However, this study has many limitations. Additional factors that could influence the results include the participants' experience and expectations with acupuncture, the potential diversity of individualized treatments, and the minimization of inclusion and exclusion criteria (54). In addition, the current study may have some methodological or research quality problems, which may lead to the fact that the exactness of the evidence that we end up with in our study may not be very high. To solve the above problems, we will set strict inclusion and exclusion criteria in the literature screening and data extraction stage, and try to select only the higher quality-studies. Quality assessment will be conducted to differentiate the quality of studies. We will also improve the certainty of evidence by designing and implementing high-quality original studies when conditions permit. In the meantime, we will call for more high-quality studies of RCTs, pending further evidence accumulation.

Author contributions

JZ: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. YR: Software, Writing – original draft, Writing – review & editing. WW: Data curation, Writing – original draft, Writing – review & editing. YY: Writing – original draft, Writing – review & editing. JW: Writing – review & editing. YT: Writing – review & editing. YZ: Writing – review &

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Economic evaluation of acupuncture in treating patients with pain and mental health concerns: the results of the Alberta Complementary Health Integration Project

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Background: The COVID-19 pandemic and its economic impact have heightened the risk of mental health and pain-related issues. The integration of acupuncture with conventional medicine shows promise in improving treatment outcomes for these conditions. The Alberta Complementary Health Integration Project (ABCHIP) aimed to provide acupuncture to youth (aged 24 and under) and seniors (aged 55 and above) experiencing chronic pain, pain management issues, mental health issues, and/or related conditions. The program aimed to promote integrative care, assess the effectiveness and cost-effectiveness of these therapies, and deliver patient-centered care.

Design: ABCHIP provided acupuncture to address pain, mental health, and addiction issues at no cost to two vulnerable populations in Alberta: youth and the older adult. A total of 606 patients aged 14–65 received 5,424 acupuncture treatments. Outcome measures included pain interference, pain severity, sleep quality, depression, anxiety, fatigue, anger, and quality of life. Short-term outcomes were assessed through questionnaires completed at the beginning and completion of the treatments, while long-term benefits were estimated using these outcome indicators and existing literature on the economic cost of illnesses.

Result: The cost-effectiveness analysis revealed the following ratios per Quality-Adjusted Life Year (QALY): CND12,171 for the overall sample, CND10,766 for patients with pain, CND9,331 for individuals with depression, and CND9,030 for those with anxiety. The cost–benefit analysis demonstrated annual cost savings ranging from CND1,487 to CND5,255, with an average of CND3,371.

Conclusion: The study findings indicate that ABCHIP's treatment for pain, depression, anxiety, and sleep issues is cost-effective, leading to substantial cost savings and improved quality of life for patients. The program's cost per Quality-

Adjusted Life Year (QALY) is significantly lower than benchmarks used in other countries, demonstrating high cost-effectiveness and value. Patients receiving 12 treatments experienced significant improvements across all measures, with estimated economic benefits surpassing treatment costs. In summary, ABCHIP offers a cost-effective and economically efficient therapy choice for individuals dealing with pain and mental health issues.

KEYWORDS

acupuncture, integrative medicine, pain, mental health, economic evaluation

1 Background

Existing risk factors for mental health and pain-related issues have been amplified due to the COVID-19 pandemic. The combination of lockdown measures, physical distancing, and the uncertainty surrounding the pandemic has led to social isolation, loss of income, limited access to services, increased substance abuse, and decreased social support, particularly among vulnerable populations such as the older adult and youth (1–3). The economic crisis resulting from the pandemic has further impacted the quality of life, physical and mental health, and access to healthcare, especially in insurance-based systems (3). These economic conditions can exacerbate existing mental health issues and contribute to the development of new ones. Furthermore, mental health problems can intensify pain-related disorders. Psychosocial stressors and unique biological factors can contribute to or worsen chronic pain, which may be more prevalent in individuals with a weakened stress response system. The prolonged stresses associated with the COVID-19 pandemic have the potential to increase the prevalence of chronic pain (4, 5). The anticipated economic recession following the pandemic is likely to widen healthcare disparities and disproportionately affect socially disadvantaged individuals with limited access to care (6, 7). Consequently, there is a pressing need for healthcare services to address pain and mental health issues related to COVID-19. Policy briefs from the United Nations and calls from international agencies such as the World Health Organization emphasize the importance of investing in mental health and psychosocial support as part of the COVID-19 response (8, 9). However, the economic recession triggered by the pandemic may pose challenges to implementing an effective mental health response.

Acupuncture is an ancient form of Chinese medicine that can help manage chronic pain, insomnia, stress, anxiety, and depression. The effectiveness of acupuncture has been extensively studied by researchers and clinicians worldwide. Rigorous scientific studies have found acupuncture to be a safe and effective complementary therapy, often used alongside conventional medical care to manage chronic pain and mental health conditions (10–19). As an increasing number of top institutions and clinics integrate acupuncture into their services, the crucial questions for healthcare policymakers are: is it cost-effective to incorporate acupuncture into the current healthcare system? Would it bring cost savings to the healthcare system and society? In other words, what is the value of investing in complementary therapies such as acupuncture?

Conceptually, the overall benefits of integrating Complementary & Alternative Medicines (CAM) such as acupuncture into the healthcare system for pain and mental health management include both short-term and long-term gains. As illustrated in Figure 1, these benefits are three-folded. First, health benefit: improvements in health status, which leads to cost savings from reducing overall healthcare utilization and expenditures, as well as improvements in quality of life, which translates into population welfare gain. Second, harm reduction: improvement in pain management could reduce patients' exposure to addictive substances. Third, lifelong productivity: for younger populations, CAM can enhance school performance and lead to long-term productivity gains. Research suggests that adverse childhood experiences (ACEs) can increase the likelihood of developing physical and mental illnesses, including addiction, later in life, as well as negatively impacting academic and employment performance (20, 21). The integration of acupuncture could potentially provide lifelong benefits by assisting individuals in managing ACEs, improving academic achievement, and enhancing school attendance, thereby increasing overall productivity.

In recent years, a growing body of literature has examined the cost-effectiveness of acupuncture treatment (22–28). Many studies find acupuncture to be cost-effective in managing chronic pain and mental health conditions. The integration of acupuncture with conventional medicine offers a unique approach that shows promise in enhancing both mental and physical health while also generating cost savings.

To address the increased risk of mental health and pain-related issues caused by COVID-19, the Alberta Complementary Health Integration Project (ABCHIP) was launched. ABCHIP aims to prevent and treat pain and mental health issues related to COVID-19 while delivering accountable and patient-centered care. This paper contributes to the growing literature on the economic evaluation of complementary therapies such as acupuncture. Our study focuses on the economic evaluation of the ABCHIP project, emphasizing the importance of investigating the direct and indirect benefits associated with these therapies to determine their efficiency and effective utilization of limited healthcare resources. Our results provide insights into improving the efficiency of resource allocation in the healthcare system.

2 Materials and methods

This research has been reviewed and approved by the University of Calgary's Conjoint Health Research Ethics Board (CHREB) under Ethics ID: REB 21–2050. All participants provided informed consent to participate in the study. The first ABCHIP acupuncture treatment

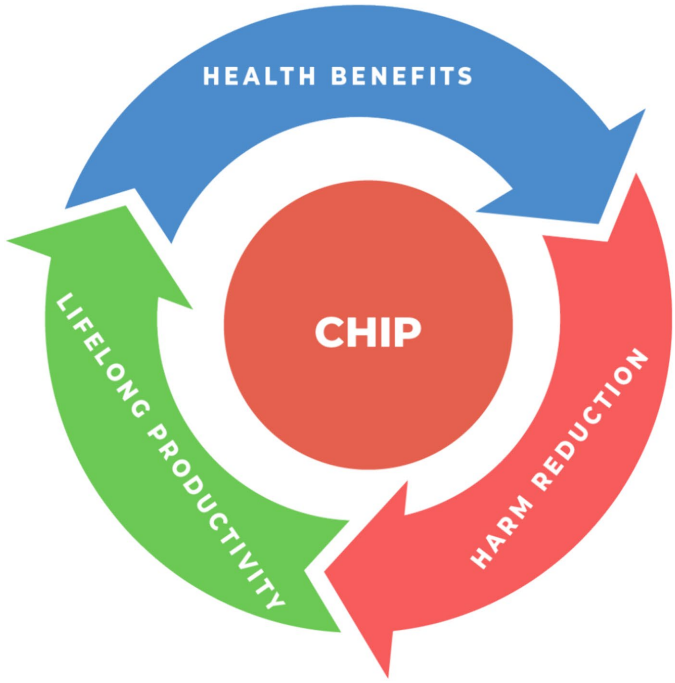

FIGURE 1
Overall benefits of CHIP (Complementary Health Integration Program).

was performed on May 25, 2021. The final ABCHIP acupuncture treatment was performed on March 03, 2022.

2.1 Patients

To be eligible for inclusion in the study, patients had to meet the following criteria: age $\leq$ 24 or age $\geq$ 55 and have any of the following concerns or conditions: mental health concerns and/or conditions (such as sleep disorders, anxiety, depression), chronic pain, or pain management issues. Patients who did not provide consent or withdrew their consent, including children whose parents or guardians did not give consent, as well as participants who were not available or comfortable with receiving these treatments, were excluded from the study.

Patients were recruited through public outreach campaigns, mail-out services provided by Alberta Health Services (AHS), and referrals from primary care doctors (28). Out of the 606 patients who received the services, 72% were female, 27% were male, and 1% identified with other genders. These patients received a total of 5,424 acupuncture treatments (29).

2.2 Interventions

All interventions provided in the study were offered free of charge. Certified and registered acupuncturists provided acupuncture treatments. To support patients with mental health issues, an onsite social worker was recruited as part of the study. Participants were encouraged to meet with the social worker for an initial hour-long visit and a follow-up 30-min meeting during their participation in the project, whenever they felt the need for assistance.

The objective of the study was to evaluate the performance of acupuncture in combination with conventional medicine. Each patient received personalized acupuncture care, and the frequency of treatment was determined based on the patient's condition and treatment goals. Patients were also allowed to pursue any additional conventional treatment they deemed necessary while receiving services from ABCHIP.

During the initial session, practitioners gathered information about the patient's diet, sleep schedule, and lifestyle. They conducted a comprehensive examination of physical issues, including observing painful areas on the body, examining the coating, color, and form of the tongue, assessing the color of the face, and evaluating the intensity, rhythm, and quality of the wrist pulse. Based on this information and the treatment goals of the patients, individualized treatment plans were created, referring to the ABCHIP acupuncture treatment protocols (28).

ABCHIP acupuncture treatment protocols in this study were developed based on established evidence and clinical expertise from local and international leading experts in our team. Only standard, proven acupuncture treatments were provided, and no experimental procedures were undertaken (28).

A typical treatment plan in ABCHIP lasted 1 to 2 months and included one or two treatments per week, with a minimum of six total visits and the actual number of visits adjusted based on the severity and treatment goals of each patient. Treatment progress was tracked after each set of three treatments using the same survey. Among patients who had received six or more treatments, which is necessary

to observe noticeable effects, the study found that satisfactory outcomes were achieved within 6–18 acupuncture sessions (28, 29).

2.3 Data collection

Patient surveys were conducted at the initial visit and after every three treatments. The survey questionnaires included various well-validated and commonly used instruments to assess pain conditions, pain intensity, depression, anxiety, sleep quality, fatigue, and overall quality of life (please refer to Outcome Measures for details). These data were collected and stored securely online using a dedicated application called Research Electronic Data Capture (REDCap). Baseline surveys also included demographic questions such as age, gender, race/ethnicity, income, and more.

Data collectors underwent extensive training on survey items and effective communication with patients experiencing mental health issues. This ensured efficient and patient-centered survey conduct. Measures were also taken to ensure participants were well-prepared and informed about the survey process, as well as aware of the available support from the project team during data collection if any discomfort or concerns arose. This information was explicitly stated in the patient consent form provided upon enrollment in the study.

2.4 Outcome measures

ABCHIP employed a diverse range of well-validated and widely used instruments to measure various health aspects. Pain and its impact were evaluated with the Brief Pain Inventory (BPI), depression with the Patient Health Questionnaire-9 (PHQ-9), anger with the PROMIS Short Form v1.1 Anger 5a (for adults) and PROMIS SF v2.0 5a (for minors), anxiety with the PROMIS Anxiety 8a for adults and PROMIS Anxiety-Pediatric for minors, sleep quality with the Pittsburgh Sleep Quality Index (PSQI), fatigue with the PROMIS Short Form v1.0 Fatigue 8a (for adults) and PROMIS Pediatric Short Form v2.0 Fatigue 10a (for minors), and overall quality of life with the EQ-5D-5L instrument (28, 29).

The Quality-Adjusted Life Year (QALY) was used as a measure of health benefit in this economic evaluation study. QALY considers not only the duration of life but also the quality of life experienced during that time, encompassing the intangible costs of illnesses. The EQ-5D instrument assessed the quality of life based on five dimensions: mobility, self-care, pain, usual activities, and psychological status. Each dimension was categorized as no problems, minor problems, or major problems. By comparing respondents' scores to national standards, EQ-5D offered a reliable assessment of overall health and quality of life. The EQ-5D score ranges from 0 to 1, with 1 representing the highest attainable quality of life and 0 indicating a quality of life worse than death. A higher EQ-5D score signifies better health outcomes.

2.5 Economic evaluation

To determine the benefits of the treatment, the improvements observed in pain, depression, anxiety, sleep quality, and quality of life were translated into economic gains, encompassing both direct and indirect benefits. Direct benefits include reduced healthcare utilization, such as decreased hospitalization, emergency room visits, and medication costs. Indirect benefits encompass increased productivity, improved functioning, and reduced absenteeism from work or school.

Cost-effectiveness analysis (CEA) and cost–benefit analysis (CBA) were employed to evaluate the economic impact of the ABCHIP program. Per-patient costs were used for both CEA and CBA. The study also assessed the long-term benefits by utilizing short-term indicators and estimates of the economic cost of diseases from previous literature.

CEA was conducted using quality-adjusted life years (QALYs) as the measure of health benefit. The CEA ratio was calculated by dividing the *per capita* cost of the intervention by the average improvement in the quality-of-life measure. A lower CEA ratio indicates higher cost-effectiveness, while a higher ratio suggests lower cost-effectiveness.

For CBA, data from the Economic Burden of Illness literature was utilized to project cost savings. The study measured improvements in various clinical outcomes, such as pain, depression, anxiety, and sleep quality, based on the number of acupuncture treatment sessions received by patients (12, 9–11, and 6–8). The Economic Burden of Illness literature was then used to estimate the economic benefits of these treatment improvements, considering reductions in both direct costs (e.g., hospital, physician, medication, and institutional care expenses) and indirect costs (e.g., reduction in quality of life, productivity loss due to disability, and premature mortality).

The per-patient cost of the ABCHIP program was compared to the per-person reduction in economic burden to calculate the per-patient cost savings. Economic burden of illness studies assess the societal opportunity cost of illness or injury by translating their impact into direct and indirect costs. References to the Economic Burden of Illness literature are provided in Table 1 to support the evaluation of these economic benefits.

Table 1 provides the sources of Economic Burden of Depression, Anxiety, Pain, and Sleep Issues in Canada, which were utilized in this study to estimate the direct and indirect costs associated with these conditions. The table also indicates the factors that were considered in their calculations. It is worth mentioning that these findings are based on the best available data and methodologies, and are considered scientifically reliable.

Economic burden of illness studies take into account both direct and indirect costs of illnesses. The direct costs are associated with hospital treatment, prescription medication, and physician care. Indirect costs include lost productivity due to illness, such as missed workdays, reduced work capacity, and long-term disability. Together, these costs provide a comprehensive view of the financial impact of a disease on both the healthcare system and society as a whole. To estimate the economic burden of depression, we referred to The Economic Burden of Illness in Canada, 2010 (30) and the Mental Health Commission of Canada (31), for pain we referred to the Canadian Pain Task Force Report from 2019 (32) and the Canadian STOP-PAIN project 2010 (33), for anxiety we referred to conference board of Canada report 2016 (34), and finally the RAND 2016 report on the economist costs of insufficient sleep (35).

We gathered estimates from these sources and adjusted all values to 2022 Canadian dollars, as reported in Table 1. According to these studies, the per-person direct and indirect costs of depression range from a lower bound of CAD 4,991 to an upper bound of CAD 13,898. The per-person cost of anxiety is CAD 2,653. For pain, the costs range from CAD 9,197 to CAD 20,125 per person. The per-person cost of sleep-related issues is

TABLE 1 Economic burden of depression, anxiety, pain, and sleep issues in Canada.

Illness	Direct cost	Indirect cost	Source	Per-person cost*
Depression	Hospital treatment, prescription medication, physician care	Value of lost productivity due to morbidity and mortality, Caregiving costs	The Economic Burden of Illness in Canada, 2010; Mental Health Commission of Canada, 2016 (30, 31)	[4,991, 13,898]**
Pain	Hospital treatment, prescription medication, physician care	Lost productivity	Canadian Pain Task Force Report from, 2019; Canadian STOP-PAIN project, 2010 (32, 33)	[9,197, 20,125]**
Anxiety	Hospital treatment, prescription medication, physician care	Lost productivity	Conference Board of Canada report, 2016 (34)	2,653
Sleep issues	Hospital treatment, prescription medication, physician care	Lost productivity	RAND, 2016 [360]	2,695

*All costs are converted to 20,222 Canadian dollars value.
**Lower bound and upper bound are reported.

TABLE 2 Depreciation rates of treatment effect over time by treatment group.

Treatment group	Treatment effect duration	Depreciation rate*
12 Treatments	6 months	50%
9–11 Treatments	4 months	33%
6–8 Treatments	3 months	25%

*Depreciation rate is calculated using a 12-month time frame. For example, if treatment effect is assumed to diminish at 6 months, the depreciation rate is calculated as 6 months/12 months = 50%.

estimated at CAD 2,695. It is important to note that there are significant discrepancies in the estimates from economic burden of illness studies, which vary depending on the sample, sources of data, and estimation methodologies. To account for this variability, we included estimates at both the low and high ends. In our economic evaluation, we produced ABCHIP cost-saving estimates for three different scenarios: 'minimum' cost savings, using the lower bounds of the burden of illness estimates; 'maximum' cost savings, using the upper bounds; and 'average' cost savings, which are based on the average values of the two scenarios.

2.6 Depreciation factor

While acupuncture can provide immediate relief for pain and mental health conditions, the long-term effects can vary among individuals. Some may experience sustained benefits after treatment, while others may find that the effects gradually diminish over time. For instance, a randomized trial on chronic low back pain found significant relief with acupuncture at 8 weeks, but some effects diminished by 26 or 52 weeks (36). Similarly, a recent UK study indicated that while acupuncture's effects on chronic pain and depression can last several months, they do gradually reduce after treatment ends (10). However, a meta-analysis of 29 trials with 17,922 patients found that acupuncture's benefits diminish slowly and remain relatively stable over 12 months (37).

The existing literature only offers insights into the general pattern of diminishing effects of acupuncture treatment. However, it does not provide an exact timeline for when the effects start to diminish. To err on the side of caution, our cost–benefit analysis adopts the most conservative estimate. For patients receiving 12 treatments, we assumed that the beneficial treatment effects would last for 6 months only, leading to a 50% depreciation rate over 1 year (6/12 = 0.5). For those receiving 9–11 treatments, we anticipated a four-month duration of effects, resulting in a 33% depreciation rate (4/12 = 0.33). For patients receiving 6–8 treatments, we assumed a three-month duration, with a 25% depreciation rate (3/12 = 0.25). These depreciation rates of 50, 33, and 25% over 1 year are detailed in Table 2. Overall, this approach acknowledges that acupuncture benefits may not be permanent and ensures a cautious evaluation, if not under-estimate, of the ABCHIP program's cost-effectiveness.

3 Results

Out of the 606 patients who received treatment in ABCHP, Data from 15 patients were excluded from the analysis due to unanswered questionnaire sections, rendering interpretation impossible. Additionally, data from 91 individuals who received less than six treatments, the minimum required for achieving beneficial results, were not included. This resulted in a valid sample size of 500.

3.1 Clinical outcomes

Our study sample is predominantly female and consists mainly of individuals aged 55 to 74. The largest racial and ethnic group is East Asians, followed by Whites. Income levels vary, with significant proportions of respondents falling into both lower and higher income brackets. Most participants are married or in a common-law relationship. In terms of education, a notable portion of the sample has no post-secondary education, with others having a range of qualifications, including bachelor's degrees, certificates, and graduate degrees. Additionally, a substantial majority of the respondents are immigrants. Primary treatment outcomes were evaluated using a range of instruments, allowing us to measure reductions in pain, depression, and anxiety, as well as improvements in sleep quality.

For our economic evaluation, the clinical outcomes of patients who received different numbers of treatment sessions (12, 9–11, and 6–8) are used.

As presented in Table 3, analysis of data from the 500 patients who received at least 6 acupuncture sessions through ABCHIP showed statistically significant improvements in clinical outcomes. Among them, patients receiving 12 treatments showed substantial

TABLE 3 ABCHIP clinical outcomes.

Outcome	12 Treatments	9–11 Treatments	6–8 Treatments
Pain reduction	83%	68%	60%
Depression reduction	78%	69%	58%
Anxiety reduction	41%	38%	28%
Sleep quality improvement	53%	42%	35%

Source: Lu et al. (29), Effectiveness of acupuncture in treating patients with pain and mental health concerns: the results of the Alberta Complementary Health Integration Project.

TABLE 4 ABCHIP CEA ratios.

Patient group	CEA ratio (CAD/QALY)
Overall sample	12,171
Pain	10,766
Depression	9,331
Anxiety	9,030

CAD = Canadian dollars; QALY = quality-adjusted life year. For each sample, the CEA ratio is calculated by dividing the average cost per patient by the changes in average QALY for that population.

improvement across all categories: an 83% decrease in pain, 78% decline in depression, 41% decrease in anxiety, 53% improvement in sleep quality, and a 43% enhancement in overall quality of life. Similarly, those with 9–11 treatments demonstrated improvement: a 68% decrease in pain, 69% decline in depression, 38% decrease in anxiety, and 42% improvement in sleep quality. Patients with 6–8 treatments also experienced notable improvements: 60% reduction in pain, 58% decrease in depression, 28% decrease in anxiety, and a 35% improvement in sleep quality. Details of the ABCHIP clinical outcome evaluation can be found in a companion paper (29).

3.2 Cost-effectiveness analysis (CEA)

In our CEA analysis, the CEA ratio is calculated as cost per Quality-Adjusted Life Year (QALY). The CEA ratio is a crucial measure used in healthcare economics to evaluate the cost-effectiveness of healthcare interventions. It represents the amount of money that needs to be spent in the intervention program to improve an individual's quality of life by 1 year.

For ABCHIP patients, the survey data revealed a significant improvement in their EQ-5D scores, increasing from 0.63 to 0.86. This increase indicates noteworthy improvement and highlights the success of the ABCHIP program in enhancing the overall health and quality of life of its participants.

As presented in Table 4, the CEA ratios for the ABCHIP program are as follows: CND12,171 per Quality-Adjusted Life Year (QALY) for the overall sample, CND10,766 per QALY for patients with pain, CND9,331 per QALY for patients with depression, and CND9,030 per QALY for patients with anxiety.

The CEA ratio benchmark, which is used to assess the cost-effectiveness of interventions, varies by country and healthcare system. In the UK, the National Health Services (NHS) has set a benchmark CEA ratio of £20,000 to £30,000 per Quality-Adjusted Life Year (QALY), which is approximately CND$32,000 to $48,000 (38). This benchmark helps determine whether an intervention provides favorable value by "buying" QALYs at a reasonable cost, below the benchmark value. If the ratio exceeds the benchmark, the intervention is considered to have unfavorable value, as it "buys" QALYs at a higher cost. In Australia, the CEA ratio for QALY is approximately A$42,000 to A$67,000 per QALY, which is approximately CND$37,800 to $60,300 (39). In the United States, the CEA ratio for QALY ranges from US$50,000 to US$150,000 per QALY, which is approximately CND$64,000 to $192,000 (40).

In all patient groups, the ABCHIP CEA ratios are significantly lower than the benchmarks used in the UK, Australia, and the US. This indicates that the ABCHIP program is a cost-effective intervention and represents a valuable investment. Particularly for patients with pain, depression, and anxiety, the CEA ratios for these specific groups are even lower than the overall sample, suggesting a higher return on investment for these patient populations.

3.3 Cost–benefit analysis (CBA)

In our CBA analysis, we utilized clinical outcomes from the ABCHIP program and economic benefit data from highly credible sources (29–33). By computing the economic burden of illness per person and overall for each category in the study, we provided a comprehensive overview of the burden of illnesses associated with pain, depression, anxiety, and sleep issues (see Table 1 for the economic burden of illness for each category).

The clinical outcomes were then translated into economic benefits, incorporating treatment effect depreciation rates of 50, 33, and 25% for patients who received 12, 9–11, and 6–8 treatments, respectively. ABCHIP cost savings are calculated as the difference between the economic benefits of the treatment program—estimated using the economic burden of illness data (Table 1) and ABCHIP clinical outcomes (Table 3)—and the per-person program cost, which is determined by dividing the total ABCHIP program budget by the number of participants.

As noted earlier, to account for the variability in burden of illness estimates, we produced ABCHIP cost-saving estimates for three different scenarios: "Minimum" cost savings using the lower bound estimates, "Maximum" cost savings using the upper bound estimates, and "Average" cost savings using the average of the two.

As presented in Table 5, by comparing the per-person project cost with the per-person economic benefits, ABCHIP achieved annual cost savings ranging from CND 1,487 to CND 5,255. On average, an individual could save CND 3,371 annually. To put these numbers in context, according to Canadian Institute of Health Information, per-capita health care expenditure in Alberta in 2022 was CND 8,812 (41). The economic evaluation results demonstrate that the ABCHIP program is a cost-effective investment in improving population health.

TABLE 5 ABCHIP cost savings.

ABCHIP (Annual Cost Saving)	Minimum	Maximum	Average
Per-person cost saving	CND 1,487	CND 5,255	CND 3,371

ABCHIP cost savings are the difference between the estimated economic benefits of the treatment program (using data from Tables 1 and 3) and the per-person program cost, calculated by dividing the total ABCHIP budget by the number of participants.

The economic benefits of the program surpass the per-person project cost, indicating a positive return on investment. The findings also highlight the potential indirect benefits, such as improved productivity, that could further enhance the economic benefits of the program. Overall, the ABCHIP program offers a valuable solution for addressing chronic pain, depression, and anxiety in the population.

4 Discussion

This study provided the economic evaluation of acupuncture treatments offered by ABCHIP and demonstrated that ABCHIP was cost-effective, potentially leading to average annual cost savings of CND 3,371 per person. Integrating acupuncture was shown to generate substantial cost savings in the treatment of pain and mental health conditions. The patients' quality of life, as measured by EQ-5D scores, significantly improved. The cost per Quality-Adjusted Life Year (QALY) for pain, anxiety, and depression was calculated to be CND 10,766, CND 9,030, and CND 9,331, respectively. These findings emphasize the affordability and effectiveness of ABCHIP as a treatment option for individuals dealing with pain and mental health challenges.

Our study has several limitations. First, the evidence generated by this project is based on real-world data. ABCHIP was a community service program and interventional study without a control group, and patient recruitment was not conducted randomly (28, 29). The absence of a control group and randomization limits the ability to draw definitive conclusions about the efficacy of acupuncture treatment in ABCHIP compared to other treatment options. Future studies could address this limitation by adopting a randomized controlled trial design.

Second, our evaluation relies on self-reported information from patients regarding short-term treatment outcomes and utilizes economic burden of illness studies to estimate long-term benefits. The accuracy and validity of self-reported data in health intervention studies are subject to various potential reporting biases, such as social desirability bias, recall bias, and confirmation bias (42–45). For example, social desirability bias could lead to participants underreporting their initial mental health and substance abuse conditions due to the social stigma associated with these issues. Confirmation bias could result in participants overreporting their treatment outcomes if a positive treatment effect aligns with their pre-existing beliefs or expectations about the program, or if they perceive reporting a favorable intervention outcome as a way to express gratitude for the treatment they received. Additionally, many participants are older adult and may have difficulties recalling health conditions, leading to random reporting errors. Our research team underwent rigorous training in survey strategies to mitigate these biases. However, potential biases may still exist. While our study demonstrates real-world evidence on the effectiveness and cost-effectiveness of ABCHIP, further research is necessary to link our data with administrative databases for a more accurate assessment of the long-term effects on healthcare utilization and cost for patients with pain and mental health issues.

Third, this study's findings are specific to the population of Alberta, Canada, where acupuncture has been regulated since the 1980s. We drew estimates of the economic burden of various illnesses in Canada from existing literature to inform the economic evaluation. The generalizability of our results to other populations and healthcare settings depends on various factors, including cultural perceptions of acupuncture and the economic burden of illnesses in specific countries or regions, which can be influenced by a wide range of parameters such as the healthcare system, economic conditions, population demographics, and overall population health. Nonetheless, the findings of this study offer valuable insights into the advantages of integrating acupuncture treatments to improve the quality of life and reduce costs for individuals with chronic pain and mental health conditions.

Last but not least, while we strive to account for the overall cost savings of the ABCHIP program in our economic evaluation, our estimates are limited by the constraints of economic burden of illness studies due to data limitations. For example, there is insufficient data to adequately estimate the short-term and long-term harm reduction effects of our program. It is important to note that sustained improvements in chronic pain and mental health management from programs like ABCHIP lead to broad and long-term cost savings for society, which should be considered in resource allocation decisions.

Data availability statement

The datasets presented in this article are not readily available because access to the data will be subject to the review and approval of the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary. Requests to access the datasets should be directed to Andrea Eidsvik, andrea.eidsvik@ucalgary.ca.

Ethics statement

The studies involving humans were approved by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary (Ethics ID: REB 21-2050). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, Supervision, Validation. SS: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. YT: Conceptualization, Methodology, Writing – review & editing, Validation. XX: Investigation, Methodology, Supervision, Writing – review & editing. GoY: Project administration, Resources, Writing – review & editing, Visualization. YC: Data curation, Investigation, Writing – review & editing, Resources. GuY: Formal analysis, Methodology, Writing

– review & editing, Validation. NR: Formal analysis, Methodology, Writing – review & editing. RA: Formal analysis, Methodology, Writing – review & editing. JJ: Data curation, Methodology, Project administration, Writing – review & editing, Visualization. YX: Data curation, Project administration, Software, Writing – review & editing, Investigation, Visualization. LP: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – review & editing, Visualization. BX: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing, Methodology, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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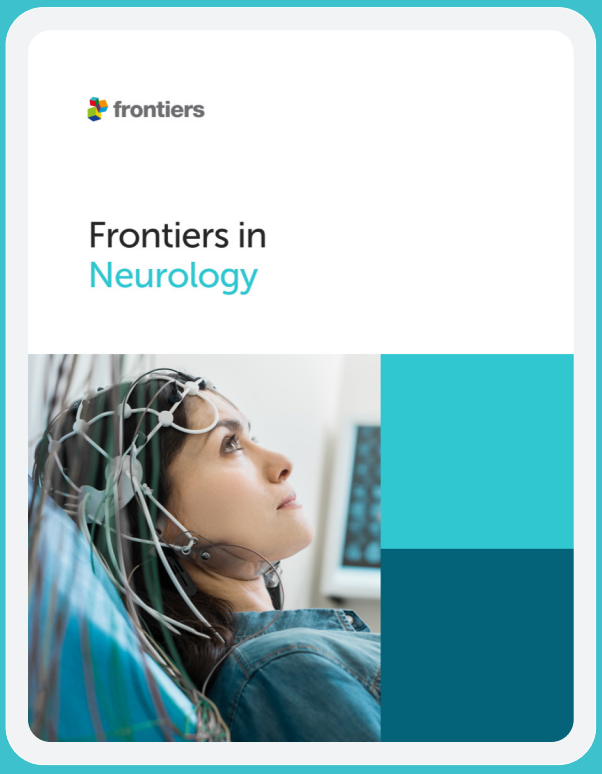

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