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Application and evaluation of acupuncture in the treatment of neurological diseases

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Application and evaluation of acupuncture in the treatment of neurological diseases

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Editorial: Application and evaluation of acupuncture in the treatment of neurological diseases

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KEYWORDS

acupuncture, clinical studies, evidence integration, evidence-based medicine, interdisciplinary technologies, clinical evidence, clinical research

Editorial on the Research Topic
Application and evaluation of acupuncture in the treatment of neurological diseases

Neurological disorders are a significant cause of disability and death worldwide, and they have been posing a serious burden on global health systems, particularly in low- and middle-income countries for the past 35 years (1). Acupuncture, the most widely used traditional Chinese medical practice globally, has been used in 183 countries and regions, and it is a key treatment option for neurological diseases (2).

This Research Topic entitled "*Application and evaluation of acupuncture in the treatment of neurological diseases*" consists of 27 manuscripts focusing on neurological diseases such as Stroke, Pain syndromes, Parkinson's disease (PD), Substance use disorders, Bell's palsy (BP), etc. These contributions offer interesting insights into the effectiveness and safety of acupuncture for the treatment of neurological disorders.

1. Stroke

This specific issue includes six studies focusing on stroke. Stroke is a condition with increasing incidence and prevalence, leading to a significant socio-economic burden and loss of healthy life years worldwide (3). Acupuncture, as a practical and safe traditional Chinese medicine treatment, has been widely used in the rehabilitation of stroke patients (4).

Li, Zhu et al. conducted a multicenter, randomized, parallel controlled trial to evaluate the effectiveness of acupuncture treatment for ischemic stroke rehabilitation. A total of 497 patients with ischemic stroke were enrolled, and the results showed that acupuncture treatment had a better recovery effect than rehabilitation alone.

In the second study by Kim et al., the authors conducted a double-blind, randomized controlled trial (RCT), recruiting 33 patients with subacute stroke. The control group received conventional rehabilitation treatment, while the experimental group received 30 min of electroacupuncture in addition to rehabilitation. The results of the study supported that electroacupuncture could be an effective adjunctive treatment for motor recovery after stroke.

Motor aphasia is one of the most common sequelae after stroke. In a network meta-analysis study by Feng et al., it was found that scalp-tongue acupuncture combined with speech training may be the best acupuncture-related therapy to improve clinical outcomes in patients with motor aphasia after stroke.

Spasticity is also one of the most common complications after stroke, with a prevalence of 30–80% (5). Acupuncture had a better effect than conventional treatment in relieving post-stroke spasticity and could be recommended as an adjunctive treatment for spasticity after stroke. This is confirmed by Xue et al. in their systematic review and meta-analysis of 88 studies.

Disorders of consciousness are prevalent among stroke patients. According to a meta-analysis by Huang Z. et al. acupuncture was found to be more effective in enhancing the level of consciousness, increasing resuscitation rates, and reducing resuscitation times compared to patients who did not receive acupuncture treatment.

Also in this issue, Choi et al. conducted a comprehensive review of 48 published systematic reviews on acupuncture interventions for stroke rehabilitation. The results suggest that acupuncture could potentially be a safer and more effective alternative to rehabilitation in the management of post-stroke shoulder-hand syndrome.

2. Parkinson's disease

PD affects 8.5–10 million people globally, and its prevalence increases with age (6). Qi Huang Needle (QHN) therapy, a combination of acupuncture and manipulation, was used to treat PD in a RCT conducted by Li, Zhou et al. They concluded that QHN therapy was consistently superior to sham acupuncture in reducing both motor and non-motor symptoms and significantly improving muscle stiffness in PD patients.

3. Pain syndromes

Acupuncture is a widely used method for alleviating both acute and chronic pain (7, 8). Kang et al. identify an important issue about tension-type headaches (TTH) by reviewing 31 RCTs. They concluded that acupuncture may be a safe and effective treatment for patients suffering from TTH. In a separate study, Liu et al. investigated the impact of caffeinated beverage intake on the analgesic effect of electroacupuncture in a randomized controlled trial. The study provides evidence for possible reasons for differences in acupuncture effectiveness between Western and Eastern populations.

4. Substance use disorders

Patients who are receiving methadone maintenance treatment (MMT) for opioid use disorder often experience several challenges such as sleep disturbances and headaches (9). Dong et al. had looked at the effects of acupuncture assisted MMT therapy by using a decision tree model. They observed that acupuncture can aid patients in achieving a more proficient reduction of methadone by alleviating the aforementioned side effects.

5. Bell's palsy

BP is a common peripheral facial palsy, accounting for 70% of all cranial mono-neuropathies (10). Acupuncture is commonly used as a complementary therapy for Bell's palsy, however, there is still a debate on the timing of its initiation. In this regard, the papers by Yang et al. and Lan et al. contribute to this aspect. The first one is a retrospective study which showed that acupuncture intervention during the acute stage of BP could shorten recovery time and improve outcomes. In the other paper, the authors presented a clinical case report of a 27-year-old pregnant patient diagnosed with BP, which was treated successfully with five courses of acupuncture treatment resulting in complete recovery.

6. Other neurological diseases

Lee et al. summarized the literature on the efficacy of acupuncture in treating overactive bladder (OAB) symptoms. The results showed that acupuncture had a more favorable effect than sham acupuncture in reducing the symptoms of OAB. Furthermore, acupuncture was found to be as effective as conventional medication in improving OAB symptoms.

Huang Y. et al. performed a comprehensive quantitative and qualitative analysis of publications related to acupuncture for spinal cord injury (SCI). The study found that China and the United States were the hub countries for related publications. Additionally, the authors predicted that there will be more studies on electroacupuncture for promoting nerve repair and regeneration after SCI in the future.

Zhang et al. explored brain activity and neural mechanisms after acupuncture using functional magnetic resonance imaging (fMRI). The study found that acupuncture stimulation can effectively relieve the severity of tinnitus by decreasing functional connectivity of amygdala in subjective tinnitus patients. Huang H. et al. conducted a meta-analysis to study brain activity after acupuncture. The results showed that acupuncturing on ST36 could positively activates the opercular part of the right inferior frontal gyrus (IFG.R), left superior temporal gyrus (STG.L), and right median cingulate/paracingulate gyri (MCG.R) regions. In two other studies (Chen et al.; Li, Lai et al.), researchers examined the best treatment options for acupuncture in the treatment of tic disorders as well as mild cognitive impairment. These studies will serve as a good reference for researchers interested in the acupoint selection and the use of fMRI techniques in acupuncture treatment.

Apart from the aforementioned case report involving BP, we also received four other case reports. These reports included a 50-year-old woman with hemifacial spasm and temporomandibular joint pain (Huang J.-p. et al.); a woman and a man each with olfactory dysfunction after COVID-19 (Morita et al.); a woman with Guillain-Barré syndrome (Li, Xu et al.); and a child in a persistent vegetative state after herpes simplex virus encephalitis (Jin et al.). All these patients achieved satisfactory therapeutic results after receiving acupuncture treatment.

7. Afterword

In conclusion, we hope that the above studies provide compelling evidence for the effectiveness and safety of acupuncture in treating neurological diseases. It is our hope that this evidence will accelerate the incorporation of acupuncture into clinical practice for the treatment of neurological diseases.

Author contributions

CC and LL contributed equally to the writing and editing of this manuscript. All authors contributed to the article and approved the submitted version.

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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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SYSTEMATIC REVIEW
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Traditional Chinese Medicine Interventions in the Rehabilitation of Cognitive and Motor Function in Patients With Stroke: An Overview and Evidence Map

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Evidence mapping of systematic reviews (SRs) systematically and comprehensively identifies, organizes, and summarizes the distribution of scientific evidence in a field. The aim of this evidence map is to provide a synopsis of the best clinical practices and interventions in stroke rehabilitative care and to identify areas with a paucity of evidence to guide future research. PubMed, EMBASE, CDSR, six Korean databases, and two Chinese databases were searched for SRs evaluating the effectiveness of any stroke rehabilitation intervention through October 2021. The quality of the SRs was assessed using AMSTAR 2. A bubble plot was used to graphically display clinical topics, the number of articles, the number of patients included, confidence, and effectiveness. In total, ninety-five SRs were identified; however, after methodological analysis, only 48 had sufficient quality to be included. In total, forty-eight SRs were included in the evidence mapping. The overall search identified SRs from 2015 to 2021. A total of four SRs focused on post-stroke cognitive impairment, whereas the other forty-four SRs focused on post-stroke motor function. In total, nineteen different traditional Chinese medicine (TCM) intervention modalities were included. Acupuncture was the most commonly used treatment. Overall, the quality of the included SRs was low or very low. Most SRs concluded that TCM interventions may have potential benefits in stroke rehabilitation. The results were more promising when acupuncture was used for shoulder–hand syndrome. However, the identified reviews cautioned that firm conclusions cannot be drawn. The evidence map provides a visual overview of the research volume and content involving TCM interventions in stroke rehabilitation. Evidence mapping can facilitate the process of knowledge translation from scientific findings to researchers and policymakers and possibly reduce waste in research.

Keywords: acupuncture, TCM, evidence map, evidence synthesis, overview, stroke rehabilitation, systematic review

INTRODUCTION

Stroke is the second leading cause of death and long-term disability worldwide (1). Despite advances in modern medicine and medications, stroke remains a burden affecting disability-adjusted life years (2). Strokes can cause significant impairments that include different degrees of cognitive and behavioral dysfunction, paralysis, dysphagia, aphasia, and motor dysfunction (3). The mortality rate of stroke has been gradually decreasing, but the disability rate of stroke remains high (4). Appropriate stroke rehabilitation treatment is essential to minimize patient disability, promote the return to social activities, and improve quality of life. However, while modern medicine lacks effective treatment for this recovery period, traditional Chinese medicine (TCM) offers great possibilities (5).

TCM has been used for centuries in the treatment of stroke. Because of fewer side effects, TCM has often been sought to provide intervention therapies for the prevention of and rehabilitation from a stroke in China and Korea. Furthermore, TCM is popular not only in other parts of Asia but also in some Western countries, including USA and Australia. TCM mainly includes herbal medications, acupuncture, moxibustion, cupping, and tuina. More than 100 kinds of TCM interventions have been used to prevent and treat stroke (6). Acupuncture in particular is safe and improves cognitive function and depressive disorder in post-stroke patients (7). TCM has the merits of diminishing disability rates, boosting the quality of life, having low toxicity and side effects, and having low therapy costs for patients in post-stroke recovery (8). However, evidence for the efficacy and safety of these interventions remains inconsistent and uncertain. Meanwhile, the quality of the methodology and evidence in the field remains unknown.

There is a vast amount of scientific literature proposing treatment approaches for stroke rehabilitation. Systematic reviews (SRs) are one of the options used to organize and critically assess published studies and summarize the results of the evidence from healthcare-related primary studies to answer specific research questions. Evidence mapping of SRs systematically and comprehensively identifies, organizes, and summarizes the distribution of scientific evidence in a field, aiming to identify gaps in knowledge and future research needs. This evidence mapping aims to provide a synopsis of the best clinical practices and interventions in stroke rehabilitative care and identify areas with a paucity of evidence to guide future research.

METHODS

Study Design

Evidence mapping is not associated with an official standardized method (9). The approach in this study was adopted from the methodology that Solloway et al. used in the "Evidence Map of Tai Chi" (10).

Electronic Searches and Search Strategy

SRs were searched in 11 databases, including PubMed, EMBASE, and the Cochrane Database of Systematic Reviews (CDSR), and also six Korean databases [Korea Med, the Oriental Medicine Advanced Search Integrated System (OASIS), DBpia, the Korean Medical Database (KM base), the Research Information Service System (RISS) and the Korean Studies Information Services System (KISS)] and two Chinese databases [the China National Knowledge Infrastructure (CNKI) and Wang Fang], from database inception through October 2021. In addition, the reference lists of potentially eligible articles were searched manually to identify additional relevant articles.

The search terms used were based on the text words "systematic review" or "meta-analysis." and "stroke rehabilitation," and database-specific filters for SRs were used to develop the search strategy with no language restrictions (**Supplementary Table 1**).

Inclusion Criteria

Design

Only SRs focusing on TCM interventions in stroke rehabilitation and summarizing primary research studies for all the clinical indications were included. In this study, we considered SRs containing at least one randomized controlled trial (RCT), which addressed the use of TCM in stroke rehabilitation.

Population

We examined trials, including adults (aged over 18 years) with a clinical diagnosis of stroke (all types, severity levels, and stages of stroke), paresis of the upper, lower, or both sets of limbs (motor function), and confirmed cognitive impairment as specified in each trial (cognitive impairments included disruptions in attention and concentration, memory, orientation, and/or executive functions).

Intervention and Comparators

All types of TCM interventions were considered, including but not limited to the following: acupuncture, electroacupuncture (EA), Chinese herbal medicine (CHM), moxibustion, tai chi, qigong, Chinese herbal bath, and tuina. Combination therapies incorporating TCM interventions were also included. Comparators included non-treatment, sham treatment, placebo treatment, and routine treatments (rehabilitation and positive interventions).

Outcomes

SRs reporting on patients' health outcomes were eligible for inclusion. SRs focused on provider outcomes, study design, or intervention features that did not report patient health outcomes were excluded.

SR Selection

All scoping, rapid, critical, and narrative reviews were excluded. Two reviewers (T-YC and JJ) independently screened all the titles and abstracts and selected full-text articles to exclude irrelevant SRs. Disagreements were resolved through discussion and consensus, and an additional reviewer (MSL) was consulted. Where originals and updates of SRs by the same author group were available, only the most recent version was considered, and multiple publications of the same review were counted as one review, although data were extracted from all the available publications. If multiple reviews of similar clinical topics were

identified, the most pertinent and best-performing SR was used for inclusion in evidence maps and was selected based on the results of the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) assessment.

Data Extraction

All the articles were read by two independent reviewers (T-YC and JHJ), data were extracted from the articles based on predefined criteria, and a methodological quality assessment was conducted. Disagreements were resolved by consensus, and when necessary, an additional reviewer (MSL) participated in the discussion. Information on PICO (population, intervention, comparison, and outcomes), the number of RCTs included in each SR, summary effect estimates for main outcomes, overall risk of bias (ROB), publication bias, and conclusions (quoted from the original article) were extracted from the included SRs.

Methodological Quality Assessment

The AMSTAR 2 tool was used to critically appraise the quality of reporting for each included SR. A validated 16-item instrument for critically appraising SRs that assesses the quality and bias using ratings of "yes," "partial yes," or "no" (11). Overall confidence in the results of an SR is rated according to the following four categories: "high" (no or one non-critical weakness), "moderate" (more than one non-critical weakness), "low" (one critical flaw with or without non-critical weaknesses), and "critically low" (more than one critical flaw with or without non-critical weaknesses).

Evidence Mapping Presentation

We used the topics of the identified SRs to categorize the reviews. We presented the evidence mapping in tables describing the characteristics of the included SRs and a graphic display of the mapping based on bubble plots. Each bubble in the chart represents one included SR. The SR grouping into the clinical topics was drafted by one reviewer and discussed among the review team.

The chart displays information in four dimensions:

1) X-axis: stroke rehabilitative symptoms.

Stroke rehabilitative symptoms were classified. The studies were categorized into those assessing cognitive function and those assessing motor function.

2) Y-axis: AMSTAR 2 assessment/strength of findings/

Confidence was decided based on the results of the AMSTAR 2 assessment, and the reviews were classified into four categories as follows: "high," "moderate," "low," or "critically low."

3) Bubble size: number of primary studies included in the SR.

Each SR bubble size is proportional to the number of primary studies included in the SR evaluating the effects of a particular intervention.

4) Circle color: effect estimate.

The clinical effectiveness of the rating of the authors' conclusions and overall ROB are described in the selected SR. Clinical effectiveness was categorized as a green circle if "effective" (if effect estimates were significantly positive and the overall ROB was low), a blue circle if "potentially effective" (if effect estimates were significantly positive but the overall ROB was high), or a yellow circle if "unclear" (if effect estimates were negative or the overall ROB was unclear).

RESULTS

Study Selection

The database search identified 847 potentially relevant studies. The research yielded 432 articles after removing duplicates. After title and abstract screening, 146 articles were obtained for the final full-text review. In total, ninety-five SRs were identified for potential inclusion; however, after methodological analysis, only 48 had sufficient quality to be included (**Figure 1**). Among the forty-eight studies that met the inclusion criteria for use in the evidence map, forty-six bubbles representing the unlimited stage and two bubbles representing the acute stage were created.

Characteristics of the Included SRs

The forty-eight SRs (12–59) included a meta-analysis, and there were forty-five SRs from China and three SRs from Korea published between 2015 and 2021. There were thirty-six SRs published in Chinese, ten in English, and two in Korean. The main characteristics of the forty-eight SRs, including sample size, patient characteristics, interventions, and primary outcomes, are reported in **Tables 1**, **2**. All the SRs contained only RCTs. The number of RCTs included in each SR ranged from 4 (18) to 41 (55). The number of patients included in each SR ranged from 310 (18) to 3,184 (20) adult individuals. The number of databases searched ranged from 2 to 12, and five SRs searched only the Chinese databases (27, 29, 31, 48, 59).

Stroke Rehabilitative Symptoms Included

This article is based on multiple SRs. Four SRs focused on post-stroke cognitive impairment (**Table 1**), whereas the other 44 SRs focused on post-stroke motor function (**Table 2**), with shoulder–hand syndrome ($n = 10$) being the most frequent among them, followed by shoulder pain ($n = 4$), hand spasm ($n = 1$), strephenopodia ($n = 1$), motor dysfunction ($n = 5$), spasticity ($n = 5$), spastic hemiplegia ($n = 9$), hemiplegia ($n = 8$), and thalamic pain ($n = 1$).

Intervention Component Description

In total, nineteen different TCM intervention modalities were included: acupuncture ($n = 11$), EA ($n = 5$), eye acupuncture ($n = 1$), floating acupuncture ($n = 2$), fire-needle acupuncture ($n = 2$), Jin's three-needle acupuncture ($n = 2$), scalp acupuncture ($n = 1$), warm-needle acupuncture ($n = 3$), appoint catgut embedding ($n = 1$), bee venom acupuncture ($n = 1$), needle knife acupuncture ($n = 1$), moxibustion ($n = 2$), CHM ($n = 5$), herbal fumigation ($n = 2$), herbal socking ($n = 1$), taichi ($n = 2$), baduanjin ($n = 1$), daoyin ($n = 1$), and tuina ($n = 4$). Descriptions of the TCM interventions are described in **Supplementary Table 2**.

Quality of Included Systematic Reviews

Most SRs used the Cochrane handbook for risk or quality assessment. ROB was assessed by the Jadad scale in five SRs (29, 54, 55, 57, 59), while two SRs used the Joanna Briggs

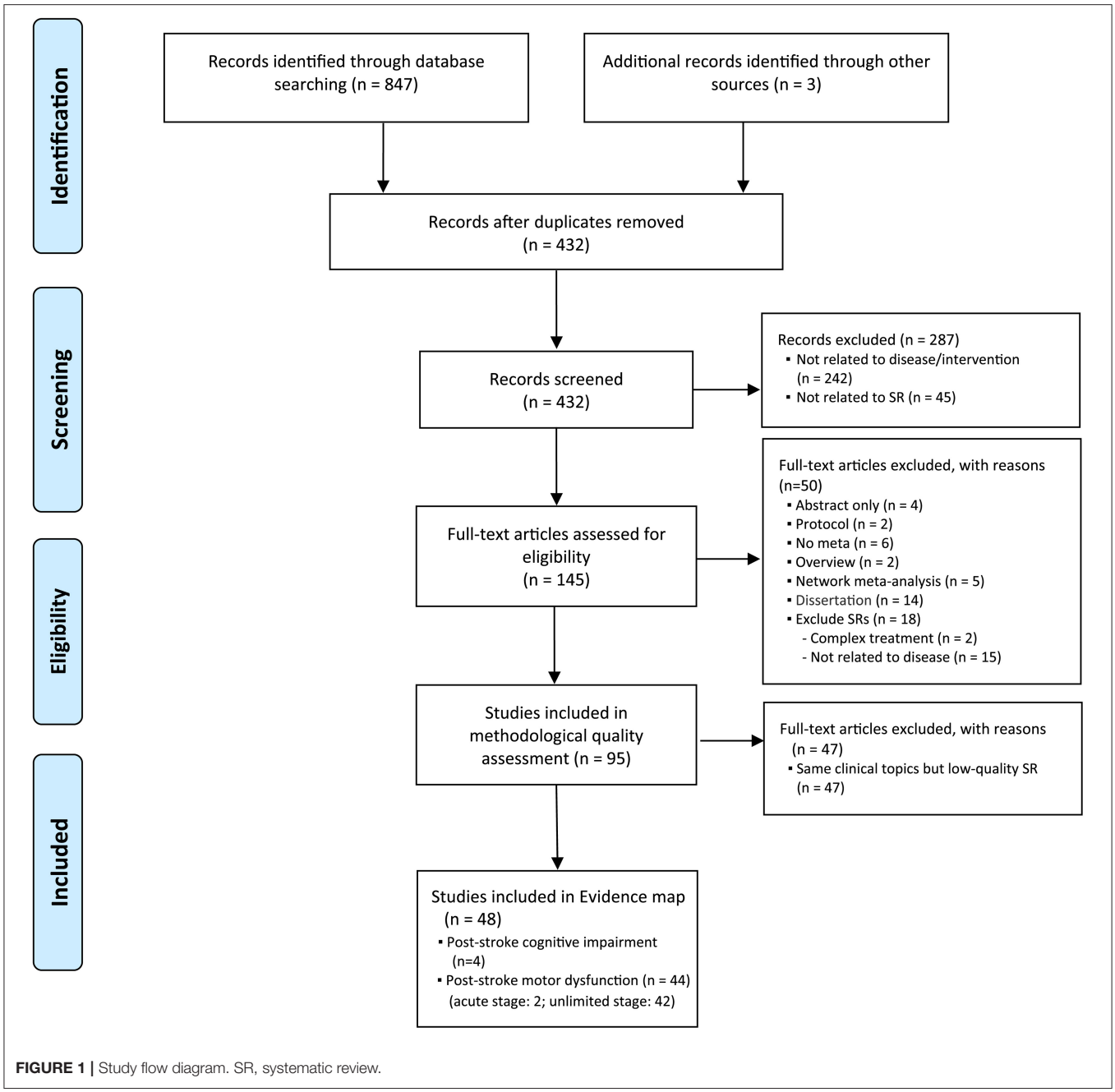

FIGURE 1 | Study flow diagram. SR, systematic review.

Institute's (JBI) critical appraisal tool (25), and two SRs used the Physiotherapy Evidence Database (PEDro) scale (34). Regarding quality assessment for evaluating the overall confidence level of each review, most studies showed moderate to critically low quality (**Supplementary Table 3, Supplementary Figure 1**). The lowest scores were on item 7 (none of the studies provided a list of excluded studies and justified the exclusions), item 2 (none of the studies reported justifications for any significant deviations from the protocol), and item 16 (5 studies did not report any potential sources of conflicts of interest). Overall confidence was rated as "moderate" for 8 SRs, "low" for 24 SRs, and "critically low" for 16 SRs.

Effectiveness

Overall confidence was considered with respect to overlapping diseases. The conclusions were reflected in individual SRs and confirmed through an internal review. We evaluated the effectiveness, literature size, and confidence level for each intervention identified in the SRs.

Effective

The effects of TCM interventions in stroke rehabilitation, indicated by statistically significant pooled treatment effects in an SR ($n = 1$) and based on a substantial number of research

TABLE 1 | Summary of the included systematic reviews of post-stroke cognitive impairment (PSCI).

References, Country	Search date, No. of searched DB studies, No. of primary studies	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Zhou et al. (12), China	December 2019, 7, 37 (2,869)	AT + WM + CRT	WM + CRT	1) MMSE 2) MoCA	1) MD 2.88 [2.09, 3.66], $P < 0.00001$ 2) MD 2.66 [1.95, 3.37], $P < 0.00001$	… effective in improving …	Cochrane ROB High	Potentially effective	Moderate
Zhan et al. (13), China	October 2016, 6, 14 (896)	EA + WM EA + CRT	WM CRT	1) MMSE 2) MoCA 3) P300 latency 4) P300 amplitude 5) FMA 6) ER 7) BI	1) MD 1.78 [0.24, 3.32], $P = 0.02$ 2) MD 1.92 [0.96, 2.88], $P < 0.000\ 1$ 3) MD −11.01 [18.91, −3.11], $P = 0.0006$ 4) MD 1.56 [1.14, 1.98], $P < 0.00001$ 5) MD 10.74 [2.67, 18.82], $P = 0.009$ 6) RR 1.37 [0.98, 1.91], $P = 0.06$ 7) MD 6.38 [−2.41, 15.18], $P = 0.15$	… effective and safe for PSCI, which could improve cognitive function and motor function	Cochrane ROB High	Potentially effective	Low
Xiong et al. (14), China	May 2014, 6, 13 (1,113)	Scalp AT/EA Scalp AT/EA + WM Scalp AT/EA + CRT	WM CRT	1) MMSE 2) P300 latency	1) MD 2.22 [1.38, 3.07], $P < 0.00001$ 2) MD −1.85 [−3.04, −0.66], $P = 0.002$	Insufficient…	Cochrane ROB High	Unclear	Critically low
Shen et al. (15), China	January 2018, 7, 16 (1,296)	HM HM + WM	WM	1) MoCA 2) MMSE 3) BI 4) NIHSS	1) HM + WM vs. WM: MD 2.57 [1.51, 3.63], $P < 0.0001$ 2) HM + WM vs. WM: MD 1.30 [0.45, 2.15], $P = 0.003$ (3 months); HM vs. WM: MD 1.58 [0.66, 2.51], $P = 0.0008$ (3 months) 3) HM + WM vs. WM: MD 12.36 [8.79, 15.92], $P < 0.0001$ 4) HM + WM vs. WM: MD −1.46 [−2.04, −0.86], $P < 0.0001$	… potential advantages in improving …, and it also has certain efficacy in improving…	Cochrane ROB High	Potentially effective	Low

ADL, activities of daily living; AT, acupuncture; BI, barthel index scale; CRT, cognitive rehabilitation; EA, electroacupuncture; ER, effective rate; FMA, fugl-meyer assessment; HM, herbal medicine; NCSE, neurobehavioral cognitive state examination total score; NIHSS, national institutes of health stroke scale; MD, mean difference; MESS, modified edinburgh stroke scale; MMSE, mini mental state examination; MoCA, montreal cognitive assessment scale; ROB, risk of bias; RR, risk ratio; RT, rehabilitation scale; SMD, standardized mean difference; WM, western medicine; WMD, weighted mean difference.

TABLE 2 | Summary of the included systematic reviews of post-stroke motor dysfunction.

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Post-stroke shoulder pain									
Lin et al. (16), China	February 2015, 7, 13 (869)	AT + RT	RT	1) VAS 2) FMA-U 3) ADL	1) MD 1.50 [0.92, 2.09], $P < 0.00001$ 2) MD 6.38 [1.16, 11.60], $P = 0.02$ 3) MD 11.25 [3.00, 19.49], $P = 0.007$	…more effective than….	Cochrane ROB High	Potentially effective	Critically low
Wei et al. (17), China	February 2019, 9, 18 (1,405)	Floating AT Floating AT + RT + UC	RT AT UC	1) SHSS 2) VAS 3) FMA	1) MD 1.75 [1.13, 2.38], $P < 0.00001$ 2) MD 1.55 [1.24, 1.87], $P < 0.00001$ 3) MD 4.24 [1.61, 6.67], $P = 0.002$	… effectively improve the upper limb function…	Cochrane ROB High	Potentially effective	Low
Lim and Lee (18), Korea	August 2014, 9, 4 (310)	BVA BVA+ Other treatment (AT, WM)	Saline injection AT UC	1) VAS 2) FMA	1) SMD 1.46 [0.30, 2.62], $P = 0.01$ 2) SMD 1.60 [−0.53, 3.73], $P = 0.14$	… effective in relieving shoulder pain	Cochrane ROB High	Unclear	Critically low
Oh and Lee (19), Korea	September 2019, 7, 14 (861)	TN + Other treatment (RT, WM, EA, HM)	RT WM EA HM	1) VAS 2) ER	1) Chuna +HM vs. HM: MD −2.02 [−2.73, −1.32], $P < 0.00001$; Chuna + RT vs. RT: MD −1.49 [−1.95, −1.02], $P < 0.00001$ 2) Chuna + RT vs. RT: RR 1.14 [1.04, 1.26], $P = 0.007$; Chuna +EA vs. EA: RR 1.07 [0.81, 1.42], $P = 0.64$	…statistically significant effect in pain reduction	Cochrane ROB High	Potentially effective	Low
Post-stroke shoulder-hand syndrome									
Liu et al. (20), China	January 2019, 9, 38 (3,184)	AT/EA + RT	RT	1) FMA 2) VAS	1) Overall: 8.01 [6.69, 9.33], $P < 0.00001$; EA + RT vs. RT: MD 9.08 [6.81, 11.35], $P < 0.00001$; AT + RT vs. RT: MD 7.80 [6.30, 9.30], $P < 0.00001$ 2) Overall: MD −1.59 [−1.86, −1.32], $P < 0.00001$; EA + RT vs. RT: MD −1.50 [−1.84, −1.17], $P < 0.00001$; AT + RT vs. RT: MD −1.62 [−1.97, −1.28], $P < 0.00001$	… effective for motor function, pain relief and activities of daily living in stroke patients …	Cochrane ROB High	Effective	Low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Wang et al. (21), China	October 2018, 7, 23 (1,580)	EA+ RT	RT	1) ER 2) FMA 3) MBI 4) VAS	1) RR 1.12 [1.08, 1.17], $P < 0.0001$ 2) MD 7.36 [4.71, 10.02], $P < 0.0001$ 3) MD 16.09 [−7.52, 39.70], $P < 0.0001$ 4) MD −1.54 [−1.86, −1.21], $P < 0.0001$	…has a significant effect…	Cochrane ROB High	Potentially effective	Low
Li et al. (22), China	March 2016, 7, 15 (981)	Jin's three-AT Jin's three-AT + Other treatment (RT, AT, Warm AT, WM)	RT AT WM	1) ER 2) FMA 3) VAS	1) J3N vs. Other treatment: RR 1.10 [0.98, 1.25], $P = 0.11$; J3N + Other treatment vs. Other treatment: RR 1.24 [1.12, 1.38], $P < 0.0001$ 2) MD −1.78 [−2.29, −1.28], $P < 0.00001$ 3) MD 9.20 [8.50, 9.90], $P < 0.00001$	…effective to treat shoulder hand syndrome after stroke...	Cochrane ROB High	Potentially effective	Critically low
An (23) China	July 2016, 12, 6 (400)	Warm AT + Other treatment (AT, RT, UC)	AT + Other treatment (UC, RT)	1) VAS 2) FMA 3) STEF	1) MD −2.34 [−4.65, −0.02], $P = 0.05$ 2) MD 6.87 [3.39, 10.35], $P < 0.01$ 3) MD −2.67 [−7.10, 1.76], $P > 0.05$	… can improve pain and edema & swelling, …. better than …	Cochrane ROB High	Unclear	Critically low
Wu et al. (24), China	January 2018, 8, 14 (1, 43)	Floating AT	EA RT	1) ER 2) FMA 3) VAS 4) SHSS	1) OR 5.42 [3.45, 8.52], $P < 0.00001$ 2) MD 2.93 [−1.97, 7.83], $P = 0.24$ 3) MD −1.46 [−1.87, −1.06], $P = 0.00001$ 4) MD −0.45 [−0.67, −0.22], $P = 0.0001$	…better effect for the treatment of shoulder- hand syndrome after stroke…	Cochrane ROB High	Potentially effective	Low
Hou et al. (25), China	September 2019, 7, 10 (640)	Acupoint catgut embedding + UC	UC	1) ER 2) VAS 3) FMA 4) BI	1) OR 3.43, [1.97, 6.00], $P < 0.0001$ 2) MD −1.36 [−1.76, −0.96], $P < 0.0001$ 3) MD 8.19 [5.00, 11.39], $P < 0.00001$ 4) MD 7.94 [4.53, 11.34], $P < 0.00001$	…could effective improve…	JBI High	Potentially effective	Low
Lin et al. (26), China	January 2017, 6, 15 (1,421)	Tuina + Other treatment (AT, RT, UC)	RT UC	1) FMA-U 2) VAS	1) MD 10.12 [9.62, 10.62], $P < 0.00001$ 2) MD −1.68 [−1.91, −1.45], $P < 0.00001$	…can improve…	Cochrane ROB High	Potentially effective	Critically low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Zheng et al. (27) China	July 2018, 4 (only China), 12 (1,180)	Herbal socking + Other treatment (RT, AT, Tuina)	RT	1) ER 2) NRS 3) FMA 4) BI	1) RR 3.72 [2.61, 5.30], $P < 0.00001$ 2) MD −1.55 [−1.80, −1.30], $P < 0.00001$ 3) MD 7.85 [5.65, 9.51], $P < 0.00001$ 4) MD 33.87 [16.67, 51.08], $P < 0.0001$	…certain effect on….	Cochrane ROB High	Potentially effective	Low
Wang et al. (28), China	April 2019, 8, 12 (887)	Herbal fumigation + Other treatment (AT, RT)	RT AT RT + AT	1) ER 2) FMA 3) VAS	1) OR 3.11 [1.48, 6.52], $P < 0.003$ 2) MD 4.16 [2.90, 5.42], $P < 0.00001$ (2 wks); MD 6.01 [4.95, 7.08], $P < 0.00001$ (4 wks) 3) MD −0.76 [−0.82, −0.69], $P < 0.00001$ (Age > 60); MD −2.06, [−2.22, 1.90], $P < 0.00001$ (Age < 60)	… can relieve limb pain, improve upper limb motor function and clinical efficacy	Cochrane ROB High	Potentially effective	Low
Guo et al. (29) China	December 2014, 4 (only China), 20 (1,399)	CHM CHM + Other treatment (AT, RT, WM, UC)	RT AT WM UC	1) ER 2) FMA 3) VAS	1) OR 2.55 [1.68, 3.85], $P < 0.00001$ 2) MD 5.95 [3.88, 8.03], $P < 0.00001$ 3) MD −2.43 [−3.51, −1.36], $P < 0.00001$	…improve the motor function of supper limb, reduce the pain of patients.	Jadad High	Potentially effective	Critically low
Post-stroke hand spasm									
Qi et al. (30), China	April 2018, 6, 10 (875)	AT AT + RT	RT	1) MAS 2) MBI 3) FMA 4) ADL	1) MD −0.97 [−1.16, 0.77], $P < 0.0001$ 2) MD 7.07 [3.96, 10.17], $P < 0.00001$ 3) MD 2.55 [1.56, 3.54], $P < 0.00001$ 4) MD 9.57 [4.63, 14.50], $P = 0.0001$	…certain therapeutic effect ….	Cochrane ROB High	Potentially effective	Low
Post-stroke strephenopodia									
Zhang et al. (31), China	February 2015, 5 (only China), 12 (787)	AT + RT	RT	1) ER 2) FMA 3) Ashworth 4) CSI	1) RR 1.19 [1.09, 1.31], $P = 0.0001$ 2) MD 5.07 [4.18, 5.95], $P < 0.00001$ 3) MD −0.68 [−0.91, −0.45], $P < 0.00001$ 4) MD −0.58 [−1.18, −0.18], $P = 0.007$	…was effective	Cochrane ROB High	Potentially effective	Critically low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Post-stroke motor dysfunction									
Zhan et al. (32), China	November 2015, 5, 12 (889)	EA + Other treatment	RT Exercise AT	1) FMA-U 2) FMA-L 3) FMA 4) BI 5) NIHSS	1) MD −3.87 [−6.32, −1.42], $P = 0.002$ 2) MD 2.80 [−3.29, −8.88], $P = 0.37$ 3) MD 9.59 [8.93, 10.24], $P < 0.00001$ 4) MD 8.91 [2.96, 14.86], $P < 0.00001$ 5) MD 1.10 [0.94, 1.29], $P = 0.22$	…suggests that EA is effective and safe for recovery of patients with post stroke motor dysfunction	Cochrane ROB High	Potentially effective	Critically low
Lyu et al. (33), China	October 2017, 8, 21 (1,293)	Tai Chi + RT	RT	1) ADL 2) FMA 3) FMA-U 4) FMA-L 5) BBS 6) Holden scale 7) TUGT	1) MD 9.92 [6.82, 13.02], $P < 0.00001$ 2) MD 4.49 [1.92, 7.06], $P = 0.0006$ 3) MD 8.27 [4.69, 11.84], $P < 0.0001$ 4) MD 2.75 [0.95, 4.56], $P = 0.003$ 5) MD 5.23 [3.42, 7.05], $P < 0.00001$ 6) MD 0.61 [0.38, 0.85], $P < 0.00001$ 7) MD 2.59 [1.76, 3.43], $P < 0.00001$	… beneficial effect on ADL, balance, limb motor function, and walking ability among stroke survivors	Cochrane ROB High	Potentially effective	Low
Zou et al. (34), China	December 2017, 8, 8 (822)	Baduanjin + Other treatment (RT, Balance training, Educational lessons)	RT Balance training Educational lessons	BBS	MD 2.39 [2.14, 2.65], $P < 0.001$	… as an adjunctive and safe method may be conducive … achieve the best possible short-term outcome…	PEDro High	Potentially effective	Moderate
Zheng et al. (35), China	August 2014, 9, 16 (1,280)	AT	Usual care	1) ER 2) FMA 3) BI 4) NIHSS	1) OR 3.20 [2.01, 5.10], $P < 0.01$ 2) WMD 9.86 [6.34, 13.37], $P < 0.00001$ 3) WMD 7.02 [3.17, 10.88], $P = 0.0004$ 4) WMD −1.48 [−2.09, −0.88], $P < 0.00001$	…was effective	Cochrane ROB High	Potentially effective	Low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Zhan et al. (36), China	December 2016, 6, 19 (1,434) Acute stroke survivors within 14 days	EA + RT/WM	RT/WM	1) FMA 2) FMA-L 3) ER 4) ADL	1) EA vs. non-EA: WMD 10.79 [6.39, 15.20], $P < 0.001$; EA plus RT plus WM vs. RT plus WM: MD 8.03 [5.17, 10.90], $P < 0.001$ 2) EA vs. non-EA: WMD 5.16 [3.78, 6.54], $P < 0.001$ 3) EA vs. non-EA: RR 1.13 [1.00, 1.27], $P = 0.050$ 4) EA vs. non-EA: MD 1.37 [0.79, 1.96], $P < 0.001$; EA plus RT plus WM vs. RT plus WM: 1.29 [0.55, 2.02], $P < 0.001$	...provides new evidence for the effectiveness and safety...	Cochrane ROB High	Potentially effective	Moderate
Post-stroke spasticity									
Ye et al. (37), China	December 2015, 6, 30 (2,453)	AT + RT	RT	1) ER 2) MAS 3) CSI	1) OR 2.69 [2.08, 3.47], $P < 0.001$ 2) OR 2.47 [2.02, 3.02], $P < 0.001$ 3) MD −1.01 [−1.47, −0.54], $P < 0.001$	… could be effective in decreasing spasticity after stroke, …	Cochrane ROB High	Potentially effective	Critically low
Qiu et al. (38), China	August 2020, 8, 16 (1,118)	Fire AT	AT	1) ER 2) Recover rate 3) FMA 4) MAS 5) BI 6) NDS	1) RR 1.51 [1.36, 1.66], $P < 0.00001$ 2) RR 2.59 [1.75, 3.84], $P < 0.00001$ 3) SMD 2.27 [1.40, 3.13], $P < 0.00001$ 4) SMD 0.47 [0.18, 0.77], $P = 0.002$ 5) SMD 1.46 [1.03, 1.90], $P < 0.00001$ 6) SMD 0.90 [0.44, 1.35], $P = 0.0001$	… provide a better clinical effect than conventional AT, …	Cochrane ROB High	Potentially effective	Moderate
Yang et al. (39), China	February 2016, 10, 12 (878)	Warm AT Warm AT + RT	AT/EA AT/EA + RT	1) FMA 2) BI 3) ADL	1) EA: MD −0.53 [−0.75, −0.31], $P < 0.00001$; AT: SMD −0.66 [−1.19, −0.13], $P = 0.01$ 2) EA: MD 7.70 [4.78, 10.63], $P < 0.00001$; AT: MD 7.78 [4.36, 11.21], $P < 0.00001$ 3) EA: MD 12.64 [11.71, 13.57], $P < 0.00001$; AT: MD 3.79 [−3.06, 10.65], $P = 0.28$	… promising intervention to reduce limb spasm as well as improve motor function and daily living activities …	Cochrane ROB High	Potentially effective	Critically low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Cai et al. (40), China	February 2018, 12, 35 (2,457)	HM	RT	1) MAS-U 2) MAS-L 3) FMA 4) FMA-U 5) FMA-L 6) BI	1) Oral HM: SMD −1.79 [−3.00, −0.57], $P = 0.004$; Topical HM: SMD −1.06 [−1.40, −0.72], $P < 0.00001$ 2) Oral HM: SMD −1.01 [−1.43, −0.59], $P < 0.00001$; Topical HM: SMD −1.16 [−1.83, −0.49], $P = 0.0007$ 3) Oral HM: SMD 12.14 [1.57, 22.71], $P = 0.02$; Topical HM: MD 5.56 [2.38, 8.74], $P = 0.0006$ 4) Oral HM: SMD 7.64 [−1.29, 16.57], $P = 0.09$; Topical HM: MD 5.88 [4.09, 7.68], $P < 0.00001$ 5) Oral HM: SMD 4.03 [1.90, 16.57], $P = 0.0002$ 6) Oral HM: MD 13.15 [4.37, 21.93], $P = 0.003$; Topical HM: MD 12.01 [2.81,21.22], $P = 0.01$	… suggests that HM appears to be a well-tolerated therapy for patients with PSS	High	Potentially effective	Low
Yan et al. (41), China	April 2014, 8, 20 (1,720)	Tuina Tuina + Other treatment (AT, WM, RT, BT)	UC WM RT Tuina	1) MAS 2) FMA 3) MBI	1) MD −1.42 [−3.19, −0.36], n.r. 2) MD 4.72 [2.96, 6.48], n.r. 3) MD 10.39 [8.92, 11.86], n.r.	… improving motor function and daily life has significant curative effect, …	Cochrane ROB High	Potentially effective	Critically low
Post-stroke spastic hemiplegia									
Fan et al. (42), China	July 2019, 9, 38 (2,628)	AT/EA AT/EA + RT	RT	1) FMA 2) ASS 3) BI	1) MD 8.43 [6.57, 10.28], $P < 0.00001$ 2) MD −0.46 [−0.65, −0.27], $P < 0.00001$ 3) MD 8.32 [5.30, 11.35], $P < 0.00001$	… be a safe and effective adjuvant therapy …	Cochrane ROB High	Potentially effective	Moderate

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Li and Wang (43), China	March 2020, 7, 11 (879)	EA+ RT	RT AT	1) ER 2) FMA 3) MAS 4) MBI 5) NDS 6) CSI	1) RR 1.27 [1.16, 1.40], $P < 0.00001$ 2) MD 9.09 [7.47, 10.71], $P < 0.00001$ 3) MD −0.36 [−0.57, −0.16], $P = 0.0005$ 4) MD 6.85 [5.16, 8.53], $P < 0.00001$ 5) MD −2.61[−3.01, −2.20], $P < 0.00001$ 6) MD −1.11 [−1.60, −0.62], $P < 0.00001$	… certain effect on spastic paralysis after stroke	Cochrane ROB High	Effective	Low
You et al. (44), China	February 2018, 6, 14 (918)	Fire AT Fire AT + Other treatment (UC, RT)	AT/EA AT/EA + Other treatment (UC, RT, moxa)	1) ER 2) FMA 3) BI 4) MAS 5) CSI 6) NDS	1) OR 2.87 [1.94, 4.25], $P < 0.00001$ 2) SMD 1.00 [0.51, 1.50], $P < 0.0001$ 3) SMD 1.42 [0.71, 2.12], $P < 0.0001$ 4) SMD −0.67 [−1.06, −0.27], $P = 0010$ 5) SMD −0.99 [−1.94, −0.03], $P = 0.04$ 6) SMD −0.83 [−1.49, −0.17], $P = 0.01$	… effective and safe treatment for spastic paralysis after stroke	Cochrane ROB High	Potentially effective	Low
Xie et al. (45), China	November 2019, 4, 8 (690)	Needle-Knife Needle-knife + Other treatment (RT, HM)	RT RT + Other treatment (WM, AT)	1) ER 2) FMA 3) CSI	1) RR 1.20 [1.10, 1.32], $P < 0.0001$ 2) MD 7.95 [4.85, 11.05], $P < 0.00001$ 3) MD −1.79 [−2.67, −0.92], $P < 0.0001$	… can improve spasticity and improve clinical efficacy	Cochrane ROB High	Potentially effective	Low
Yu and Wu (46), China	February 2018, 6, 13 (1148)	Warm AT	EA AT	1) ER 2) BI 3) FMA 4) MAS 5) MAS-U 6) MAS-L	1) RR 1.25 [1.15, 1.37], $P < 0.00001$ 2) MD 12.75 [12.14, 13.36], $P < 0.00001$ 3) MD 9.42 [8.63, 10.21], $P < 0.00001$ 4) MD −0.57[−0.74, −0.40], $P < 0.00001$ 5) MD −0.47 [−0.66, −0.28], $P < 0.00001$ 6) MD −3.21 [−3.51, −2.91], $P < 0.00001$	… can improve the curative effect of spastic hemiplegia patients after stroke and accelerate the RT	Cochrane ROB High	Potentially effective	Critically low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Wen et al. (47), China	May 2018, 7, 8 (689)	Jin's three-AT Jin's three-AT + RT	RT	1) NDS 2) FMA 3) ADL 4) CSI 5) FCA	1) MD −3.36 [−3.93, −2.79], $P < 0.00001$ 2) MD 15.09 [12.19, 18], $P < 0.00001$ 3) MD 13.61 [10.72, 16.51], $P < 0.0001$ 4) MD −1.44 [−2.05, −0.83], $P < 0.00001$ 5) MD 10.22 [6.94, 13.50], $P < 0.00001$	… can improve the treatment efficiency …	Cochrane ROB High	Potentially effective	Low
Chen and Tan (48) China	November 2015, 3 (only China), 10 (732)	CHM (Shaoyao gancao decoction) CHM (Shaoyao gancao decoction) + Other treatment (RT, WM, herbal umigation)	RT WM	1) FMA 2) ER 3) BI	1) MD 9.22 [6.31, 12.14], $P < 0.00001$ 2) MD 7.11 [4.34, 9.89], $P < 0.00001$ 3) RR 1.15 [1.05, 1.27], $P = 0.003$	… has a certain curative effect on the treatment of …	Cochrane ROB High	Potentially effective	Critically low
Ma et al. (49), China	June 2015, 8, 11 (765)	Moxa Moxa + Other treatment (AT, UC, RT)	AT RT AT + RT	1) MAS 2) FMA 3) BI 4) ER	1) SMD −2.06 [−3.58, –.54], $P = 0.008$ 2) MD 11.29 [7.23, 15.36], $P < 0.00001$ 3) SMD 1.05 [0.25, 1.86], $P = 0.010$ 4) RR 1.23 [1.07, 1.41], $P = 0.004$	… can relieve spasm and improve the motion ability …	Cochrane ROB High	Potentially effective	Critically low
Fan et al. (50), China	July 2014, 7, 16 (1,098)	Tuina Tuina + Other treatment (Bobath therapy, UC, Moxa, RT)	AT RT	1) FMA 2) MAS 3) BI 4) NDS 5) CSI	1) MD 4.59 [1.81, 7.36], $P = 0.001$ 2) MD −0.37 [−0.64, −0.10], $P = 0.006$ 3) MD 6.15 [−1.33, 13.62], $P = 0.11$ 4) MD −2.33 [−7.24, 2.58], $P = 0.35$ 5) MD 0.62[−1.10, −0.14], $P = 0.01$	…can improve the conditions of post stroke spastic hemiplegia	Cochrane ROB High	Potentially effective	Critically low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Post-stroke hemiplegia									
Chen et al. (51), China	December 2018, 5, 9 (762)	AT + Other treatment (Tuina, HM, Cupping, WM, Moxa, venesection)	WM HM	ER	OR 3.71 [2.09, 6.58], $P < 0.00001$	… a positive effect on the improvement of ER …	Cochrane ROB High	Potentially effective	Moderate
Liu and Wang (52) China	December 2015, 6 (385)	Eyes AT	WM	ER	OR 5.05 [3.13, 8.18], $P < 0.00001$	… more effective than …	Cochrane ROB High	Unclear	Critically low
Zhang et al. (53), China	March 2019, 6, 12 (1,259)	Herbal fumigation + Other treatment (WM, RT)	WM RT	1) ER 2) FMA 3) BI 4) MBI	1) RR 1.26 [1.17, 1.34], $P < 0.00001$ 2) MD 9.24 [6.27, 12.22], $P < 0.00001$ 3) MD 9.38 [6.45, 12.30]], $P < 0.00001$ 4) MD 9.27 [5.80, 12.73], $P < 0.00001$	… can improve the clinical effect …, and is better than WM alone or RT	Cochrane ROB High	Potentially effective	Low
Gou et al. (54), China	January 2018, 8, 8 (765)	CHM (Buyang huanwu decoction) + AT/EA	HM (Buyang huanwu decoction)	1) ER 2) BI	1) OR 3.89 [2.58, 5.86], $P < 0.00001$ 2) SMD 2.35 [2.04, 2.66], $P < 0.00001$	… positive effect on the improvement of activity of daily life, …	Jadad High	Effective	Low
Ji and Guan (55), China	March 2019, 8, 41 (3,145)	Moxa + Other treatment (RT, AT, WM, UC)	WM AT RT UC	1) ER 2) NIHSS 3) FMA 4) BI	1) RR 1.26 [1.14, 1.39], $P < 0.00001$ 2) MD −2.19 [−2.62, −1.76], $P < 0.00001$ 3) MD 16.03 [11.12, 20.94], $P = 0.33$ 4) SMD 1.11 [0.92, 1.30], $P = 0.72$	… has a positive effect on the improvement of motor function, … some of the results are heterogeneous	Jadad High	Potentially effective	Moderate
Lee et al. (56), Korea	October 2019, 11, 11 (863)	Daoyin Daoyin + RT	RT Brunnstrom's movement	1) FMA 2) MBI 3) NIHSS	1) Daoyin vs. RT: SMD 2.80[2.31, 3.30], $P < 0.00001$; Daoyin + RT vs. RT: SMD 0.81[0.11, 1.51], $P = 0.02$ 2) Daoyin vs. RT: SMD 1.87 [0.57, 3.17], $P = 0.005$; Daoyin + RT vs. RT: SMD 0.89[0.61, 1.17], $P < 0.0001$ 3) Daoyin + RT vs. RT: SMD −0.96 [−1.22, −0.07], $P < 0.0001$	…effects in functional recovery and in enhancing the independence of daily living activities for stroke patients	Cochrane ROB High	Potentially effective	Low

(Continued)

TABLE 2 | Continued

References, Country	Search date, No. of searched DB studies, No. of primary studies (total No. of patients)	Intervention	Comparator	Outcome	Effect estimates for main outcomes (meta-analysis)	Conclusion (quote from the original paper)	Overall risk of bias	Overall confidence	AMSTAR2 Rating overall confidence
Wang et al. (57), China	n.r., 8, 8 (408)	Tai Chi Tai Chi + RT	RT	1) BBS 2) FMA 3) FAC	1) SMD 2.49 [0.90, 4.07], $P = 0.002$ 2) SMD 1.71 [1.21, 2.20], $P = 0.00001$ 3) SMD 0.20 [−1.20, 0.81], $P = 0.70$	… positive effect on the improvement of …	Jadad High	Potentially effective	Low
Lin and Liu (58), China	October 2014, 9, 6 (410) Acute stage	AT/EA	RT UC	MA	MD 6.71 [5.51, 7.90], $P < 0.00001$	… positive effect on the improvement of FMA, …	Cochrane ROB High	Potentially effective	Moderate
Post-stroke thalamic pain									
Bu and Ren (59), China	April 2016, 3 (only China), 10 (627)	AT/HM AT/HM + WM	WM	1) ER 2) Degradation rate	1) OR 3.32 [2.25, 4.90], $P < 0.00001$ 2) OR 0.24 [0.08, 0.69], $P = 0.009$	… effective for post stroke thalamic pain …	Jadad High	Potentially effective	Critically low

ACE, Acupoint catgut embedding; ADL, Activities of Daily Living; AT, acupuncture; ASS, Ashworth scale for spasticity; BBS, Berg Balance Scale; BDJ, Baduanjin; BI, Barthel Index scale; BMIT, Boston Motor Inventory Test; BT, Bobath therapy; BVA, Bee venom acupuncture; CHM, Chinese Herbal medicine; CSI, clinical spasm index; DB, databases; DGI, Dynamic Gait Index; DN, dry needing; DY, Daoyin; EA, Electroacupuncture; EAT, Eyes acupuncture; ER, Effective Rate; FAC, functional ambulation category scale; FAT, Floating acupuncture; FCA, functional comprehensive assessment; FIM, Functional Independence Measure; FNA, Fire-needle acupuncture; FMA, Fugl-Meyer Assessment; FMA-L, Fugl-Meyer Assessment of Lower Limb; FMA-U, Fugl-Meyer Assessment of Upper Limb; HF, Herbal fumigation, HM, Herbal medicine; HS, Herbal socking; JBI, Joanna Briggs Institute's critical appraisal tool; JTA, Jin's three-needle acupuncture; NDS, neurological functional defect scores; NKA, Needle knife acupuncture; NI, neurological impairment; NIHSS, National Institutes of Health Stroke Scale; NR, Not reported; NRS, numerical rating scale; MAS, The modified ashworth scale; MAS-L, The modified ashworth scale of Lower Limb; MAS-U, The modified ashworth scale of Upper Limb; MBI, Modified Barthel Index scale; MESS, modified Edinburgh Stroke Scale; MD, mean difference; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment Scale; Moxa, Moxibustion; OR, odds ratio; PEDro, Physiotherapy Evidence Database scale; PSS, post-stroke spasticity; ROB, risk of bias; RR, risk ratio; RT, rehabilitation scale; SAT, Scalp acupuncture; SF-36, 36-Item Short Form Health Survey; SHSS, shoulder-hand syndrome scale; SS-QOL, Stroke Specific Quality of Life Scale; SMD, standardized mean difference; SSS, Scandinavian Stroke Scale; SPBB, Short Physical performance Battery for Balance; STEF, simple test for evaluating hand function; TC, Taichi; TCM, Traditional Chinese Medicine; TCE, traditional Chinese exercises; TUGT, timed-up-and-go test; UC, usual care; QoL, Quality of Life; VAS, Visual analog scale; WM, western medicine.

studies, included findings with acupuncture for shoulder–hand syndrome (20).

Potentially Promising Effects

Promising effects of TCM interventions in stroke rehabilitation, indicated by statistically significant pooled treatment effects in the SRs ($n = 43$) and based on a substantial number of research studies, included acupuncture for cognitive impairment (12), EA for motor dysfunction (36), CHM for spasticity (40), and moxibustion for hemiplegia (55). Most SRs reached the conclusion that there may be potential benefits of TCM interventions in stroke rehabilitation.

Unclear Effect

The map includes a small number of SRs ($n = 4$) that provided evidence of the potential lack of effectiveness of TCM interventions in stroke rehabilitation for clinical indications across more than one included study: scalp acupuncture for cognitive impairment (14), bee venom acupuncture for shoulder pain (18), warm-needle acupuncture for shoulder–hand syndrome (23), and eye-acupuncture for hemiplegia (52). These promising results are, however, compromised by the low-quality overall of the clinical trials. The identified reviews cautioned that firm conclusions cannot be drawn.

Evidence Map

Figure 2 presents the results of the evidence mapping process. The evidence map displays each of the 48 included SRs as 48 bubbles. As noted in the Materials and Methods Section, the bubble label represents the TCM intervention in that review. The bubble size represents the effect of the number of included primary studies in the context of stroke rehabilitation. Primary studies may have been included in multiple SRs. Each bubble was plotted based on the effect of the TCM intervention in stroke rehabilitation (color) in the space defined by the symptoms of stroke rehabilitation (x-axis) and the strength of the findings for the TCM intervention in stroke rehabilitation (y-axis). The evidence tables provide details of the included SRs (**Tables 1**, **2**).

The SR authors concluded across the identified studies that TCM interventions in stroke rehabilitation improved outcomes of interest; however, the number of existing studies in the identified topic areas was small in all of the identified topic areas. The evidence mapping showed that only a limited number of TCM interventions have been assessed in stroke rehabilitation and that the clinical evidence for these interventions is inconclusive, indicating a need for more original research in this area (**Figure 2**).

DISCUSSION

The 48 published SRs included in our evidence map provide a comprehensive overview of the evidence for TCM interventions in stroke rehabilitation published between 2015 and 2021. The evidence compiled by this overview indicated that TCM interventions (acupuncture, EA, CHM, moxibustion, etc.), in combination with conventional interventions, could improve cognitive and motor function. The results of this evidence map showed that in-line with available evidence, there is a sparsity of SRs evaluating TCM interventions in the context of stroke rehabilitation (cognitive and motor function). Furthermore, acupuncture can be more effective and safer than rehabilitation training in the treatment of post-stroke shoulder–hand syndrome (20). Some identified SRs included a large number of RCTs, but they addressed very broad topics, such as post-stroke motor dysfunction (32–36). On the other hand, evidence on the role of bee venom acupuncture in a number of specific conditions (post-stroke shoulder pain) is very limited due to the small number of published studies (18). The main beneficial treatment reported by the authors for patients with unlimited stage stroke was acupuncture with shoulder–hand syndrome. Evidence about the benefits of treatments for acute-stage stroke rehabilitation is lacking.

This evidence map describes the research foci that were reported in the existing SRs and displays the gaps in evidence so that areas that should be prioritized in future research can be identified. However, this evidence map is unable to answer more refined questions, such as what the best TCM interventions for specific applications and the differences between health services are. To advance our evidence-based knowledge of TCM, we should collect more data on the effectiveness of TCM for rehabilitating stroke symptoms and patient populations through meta-analyses across primary studies. In addition, the large number of treatments that were classified as having potential effectiveness warrants additional primary studies. More studies have been published in some of the areas of interest included in the unclear evidence category, and the currently available SRs must be updated. As there might be other efficient ways of drawing evidence maps, further research should also include developing evidence maps of other research designs.

The evidence map has several limitations. First, most publications are from mainland China and are written in Chinese, which eliminated their inclusion in this mapping of available evidence published in any other language. The generalization of these results to other countries might be limited. Second, the analysis was based on published SRs, and primary studies contributed to more than one included SR. Furthermore, individual review conclusions may have been limited by the quality of the primary studies and susceptible to publication and outcome reporting bias. There may be clinical trials that were included in more than one SR that might have an impact on the synthesized findings. Third, we attempted to retrieve possible eligible studies through comprehensive searches of numerous databases regardless of publication language, but there may have been missed trials related to this topic. Finally, the methodological quality of most included SRs scored "low" and "critically low." More high-quality RCTs and SRs are needed to support clinical decision-making about the use of TCM interventions in stroke rehabilitation regimens. These findings highlight the need to conduct future research focusing on new treatments and addressing knowledge gaps in this field, and increased efforts are required to improve the methodological quality and reporting process of SRs on treatments to be used in stroke rehabilitation.

Stroke prevention and treatment remain a challenge worldwide. In China and Korea, many stroke patients are treated using traditional medicine, and there have been reports on

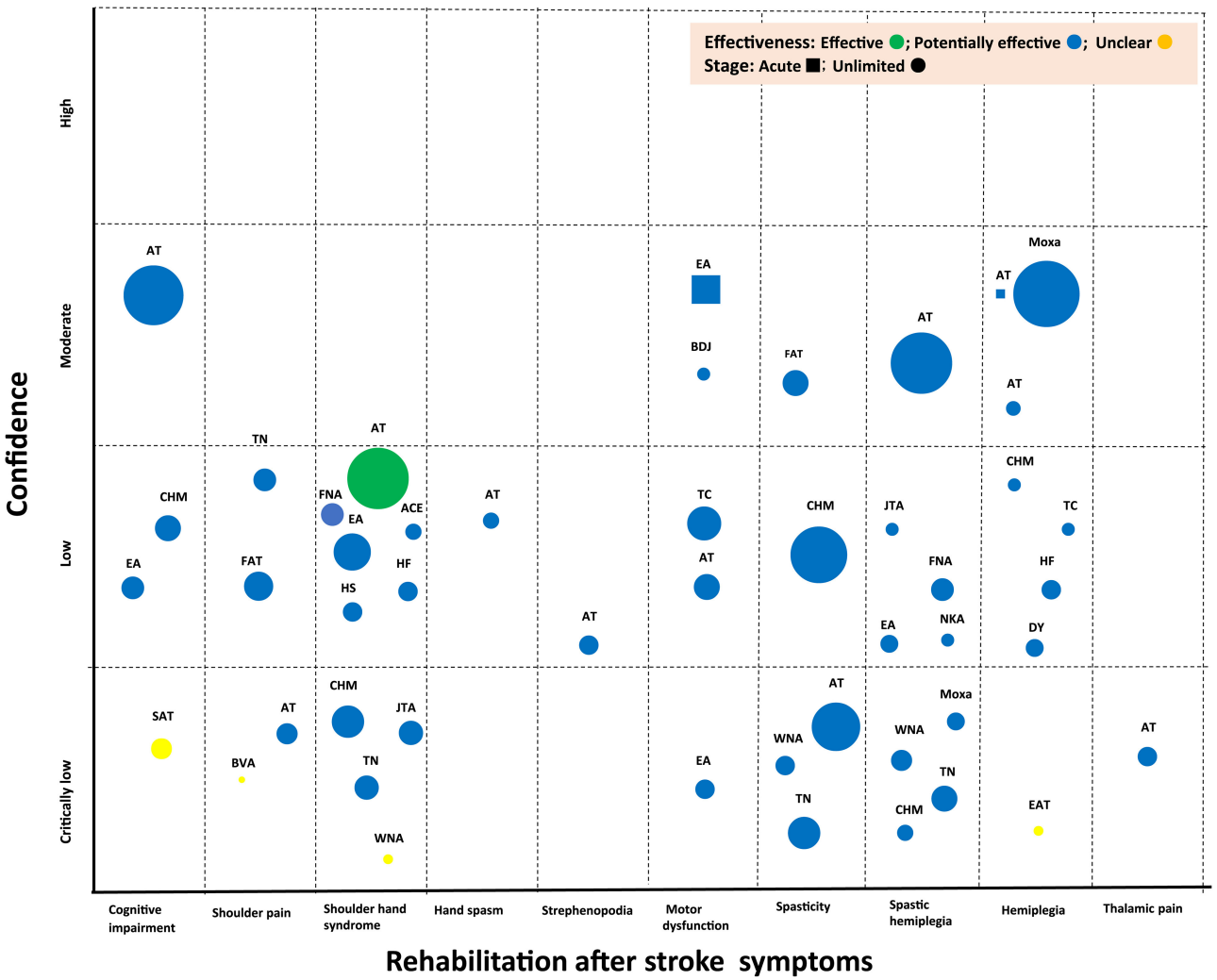

FIGURE 2 | Evidence map of TCM for stroke rehabilitation. ACE, acupoint catgut embedding; AT, acupuncture; BDJ, Baduanjin; BVA, bee venom acupuncture; CHM, Chinese herbal medicine; DY, daoyin; EA: electroacupuncture; EAT, eyes acupuncture; FAT, floating acupuncture; FNA, fire-needle acupuncture; HF, herbal fumigation; HS, herbal socking; JTA, Jin's three-needle acupuncture; NKA, needle knife acupuncture; SAT, scalp acupuncture; TC, Taichi; TN, tuina; WNA, warm-needle acupuncture.

their functional recovery (60, 61). Most alternative therapies are of unproven benefit in rehabilitation. Well-conducted trials are needed to better define the role of alternative therapies in the process of post-stroke recovery. In addition to future studies, better health education and rehabilitation services are also required.

CONCLUSION

This evidence map summarized, organized, and provided a visual overview of the currently available research volume and content related to TCM interventions during stroke rehabilitation involving cognitive function and motor function. This visualization facilitates an easy and engaging overview and suggests evidence mapping as a useful tool for a large array of stakeholders and for informing policy and clinical decision-makers. Our results provide policy and clinical decision-makers guidance regarding the interpretation of the current state of evidence regarding the effectiveness of TCM interventions in stroke rehabilitation.

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

T-YC and MSL conceptualized the study and wrote the original draft. T-YC, JHJ, and MSL contributed to methodology. T-YC and J-MY contributed to the software and resources. HWL and MCJ validated the study and investigated the study. T-YC and JHJ contributed to formal analysis. JHJ and HWL contributed

to data curation. JHJ, HWL, J-MY, and MCJ contributed to writing, reviewing, and editing the manuscript. T-YC visualized the study. MCJ and MSL contributed to supervision and funding acquisition. HWL contributed to project administration. All the authors read and approved the final manuscript.

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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.2022.885095/full#supplementary-material

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STUDY PROTOCOL
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Effects of *Qihuang* Needling on Motor Function for Patients With Parkinson's Disease: Study Protocol for a Multicenter, Randomized Controlled Trial

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Background: Although significant progress has been made in the pharmacologic management of Parkinson's Disease (PD), effective management of movement disorders is still a hurdle for therapeutics targeting PD. Acupuncture is one therapeutic option that could potentially improve the motor function of PD and is widely used as adjuvant therapy. Among the various acupuncture approaches, *Qihuang Needling* (QHN) therapy has been found to improve motor-function control for patients with PD. However, evidence regarding its efficacy remains scarce. Therefore, to address this need, this study will determine the effects of QHN therapy on motor function in patients with PD and compare it to placebo effects.

Methods: This trial is a multicenter, prospective randomized controlled clinical trial. We randomly allocated 144 participants to two groups of 72 patients. Patients in the treatment group were treated with QHN therapy. The control group had undergone insertion of acupuncture needles at sham acupoints not corresponded to acupuncture points. Participants in the verum treatment group and sham-acupuncture control group received 9 sessions over 6 weeks followed by 8 weeks of follow-up. The primary outcome was the change of motor function from baseline to weeks 6 and 14 measured by the PD Rating Scale-Part III Motor Examination (UPDRS-III). Secondary outcome measures included the change of PD daily quality of life-39 (PDQ-39) and Non-Motor Symptoms Scale for PD (NMSS) from baseline to weeks 6 and 14.

Discussion: The results of this trial will generate data to improve our general understanding of the efficacy of QHN therapy on motor function in patients with PD and thoroughly compare these responses to the placebo effect.

Trial Registration: The trial was registered at the Chinese Clinical Trials Registry (ChiCTR- 2000030871) on 16 March 2020.

Keywords: study protocol, randomized controlled trial (MeSH), acupuncture, Parkinson's disease, Qihuang Needling therapy

BACKGROUND

Parkinson's disease (PD) is a progressive neurodegenerative condition in which patients present clinical motor symptoms, such as bradykinesia, rigidity, resting tremor of distal extremities, and postural instability (1). Additionally, patients with PD may develop a series of non-motor symptoms, such as depression, cognitive impairment, sleep disorder, and autonomic disturbance (2). Unfortunately, PD has become the second-most common neurodegenerative disorder that affects estimated 6 million people worldwide (3).

The core pathological changes of PD lie in intracellular inclusions containing aggregates of α-synuclein and striatal dopamine deficiency induced by the loss of neurons in the substantia nigra. With the discovery of the role of dopamine deficiency in PD, pharmacologic dopamine substitution treatment became the foundation of current drug therapies for PD (4). In addition to oral medications, surgical intervention, such as deep brain stimulation, has been beneficial to patients with troublesome motor fluctuations and dyskinesia due to the advanced stages of PD. However, there remain challenges in developing effective treatment options for PD with these advancements. Due to none of these treatments effectively modifies disease progression and/or delay disability, patients with PD can often suffer from progressive degeneration of motor function. As the benefits of medications wane over time with disease progression, effective management of tremor, gait, balance, posture, and dexterity are major challenges for therapeutics designed for PD movement disorders (5). Beyond these unmanaged motor symptoms, many non-motor symptoms add considerably to the overall burden of the disease (6).

Acupuncture has existed for over 4,000 years as one of the main treatments of traditional Chinese medicine. As an adjuvant therapy, acupuncture is widely used in the treatment of PD, particularly in East Asia (7). Numerous clinical trials have shown that acupuncture could improve motor symptoms and the quality of sleep, reduce the dose and frequency of anti-PD drugs, and alleviate their side effects (8–11). However, none of these studies could verify whether the benefits are due to the efficacy of the treatment or as a result of the placebo effect (12, 13).

The different operating modes of acupuncture can be divided into manual acupuncture (MA) and electroacupuncture (EA). Based on the preliminary clinical observation, *Qihuang Needling* (QHN, a kind of MA technique based on traditional meridian theory) therapy has shown promising benefits targeted against better control for PD. However, the evidence for its efficacy remains scarce. Therefore, to address this gap, we aim to investigate the efficacy of QHN therapy when compared with sham acupuncture in patients with PD.

Abbreviations: PD, Parkinson's Disease; QHN, Qihuang Needling; RCT, Randomized controlled trial; AEs, Adverse events; CRF, Case report form; HY, Hoehn-Yahr; DMC, Data Monitoring Committee; UPDRS-III, Parkinson's Disease Rating Scale-Part III; PDQ-39, Parkinson disease daily quality of life-39; NMSS, Non-Motor Symptoms Scale for Parkinson's disease; SD, standard deviation; AEs, adverse events.

Trial Design

For this study, we designed a multicenter, assessor and statistician blinded, randomized controlled trial (RCT) to compare QHN therapy with sham acupuncture in patients with PD. Trials were conducted in three medical centers: the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, the Third Affiliated Hospital of Sun Yet-Sen University, and the Guangdong 999 Brain Hospital.

A total of 144 patients with PD were recruited and randomly assigned to either the QHN therapy group (treatment group) or sham-acupuncture group (control group) at a 1:1 ratio (**Figure 1**). Our study was conducted according to the Declaration of Helsinki, and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is given in **Supplementary File 1**.

Inclusion Criteria

The inclusion criteria in this study are as follows: (1) patients with PD, (2) patients of the age of 40–80 years old, (3) patients with a duration of PD of more than 1 year; (4) modified Hoehn-Yahr (HY) grades from 1 to 4; (5) patients who needed to take a stable dose of anti-PD drugs for more than 2 months, if treated with anti-PD drugs, or patients who had not received anti-PD medication for more than 2 months; (6) had clear consciousness and stable vital signs; and (7) patients who fully understood the study protocol and signed the consent form.

Exclusion Criteria

Patients with any of the following criteria were excluded: (1) patients with severe hepatorenal disease, blood disease, tumor, endocrine disease, and/or infection. (2) Those who participated in other clinical trials during the same period; (3) patients with schizophrenia or other mental disorders that affected the compliance of patient; (4) those who were deaf or had communication difficulties caused by dementia; and (5) those who had a history of alcohol or drug abuse.

Recruitment

Participants were recruited by advertisements on bulletin boards located at the Department of acupuncture and the Department of Neurology at the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong 999 Brain Hospital, and the Third Affiliated Hospital of Sun yet-sun University. An independent assessor working in these departments was responsible for screening and registering the participants that met this study's inclusion criteria. The details of the participants were conserved by the Data Monitoring Committee (DMC) to ensure patient confidentiality.

Randomization and Allocation Concealment

Central randomization was performed by the College of Acupuncture and Rehabilitation, Guangzhou University of Traditional Chinese Medicine. The random assignment operation was programmed and executed by using the SAS9.2 software. An independent researcher received the random

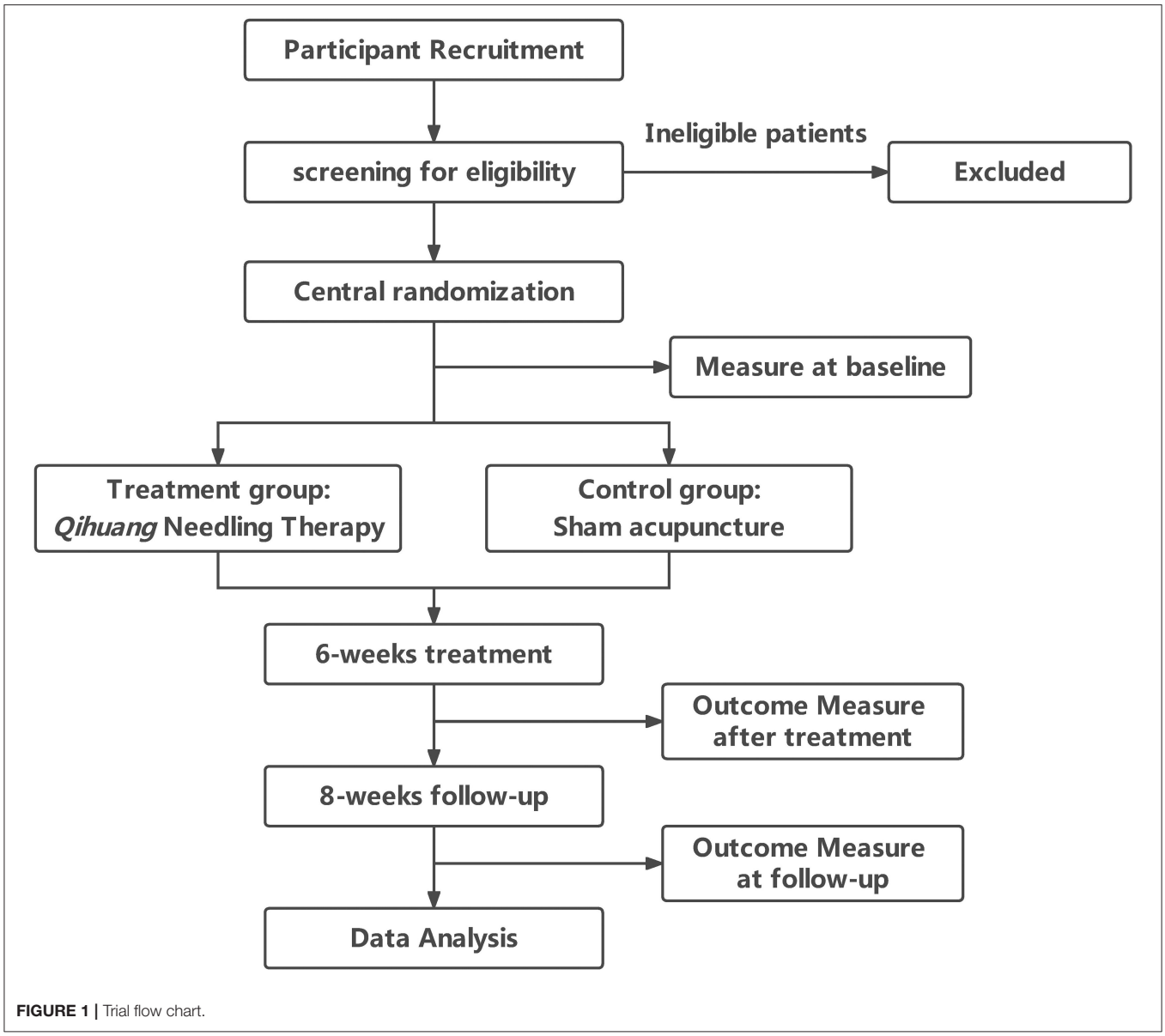

FIGURE 1 | Trial flow chart.

numbers and group assignment after inputting the patients' information through an online application.

Ethical Requirements and Registration

This study protocol was approved by the Ethics Committee of the Guangzhou University of TCM (Guangzhou, China) in July 2019 and was designated with permission number K2019-007. The trial was registered in the Chinese Clinical Trial Registry with approval number ChiCTR2000030871.

Blinding

All evaluations were blinded. The person in charge of the efficacy evaluation was hired separately and was not aware of the grouping situation of the patients. The person in charge of the data analysis was also hired separately and did not participate in the subjects' specific clinical implementation work and/or design scheme.

Interventions

To ensure the participants' safety and compliance and fulfill ethics necessities, we followed the recommendation of the Chinese Guidelines for the management of patients with PD (14). All participants in two groups received Madopar, whose dosage was recorded in detail. The original drug solutions and dosage were changed if the patients had already taken the anti-Parkinson's medicine before recruitment. In some cases, if the medications needed to be altered, the details were recorded carefully, such as the drug's name, administration time, and dosage. The whole treatment was carried out by licensed acupuncturists who had more than 5 years of clinical experience.

TABLE 1 | Location of acupoints in the treatment group.

Session	Acupoints	Location
1, 4, 7	EX-B2	0.5 *cun* lateral to the depression below the spinous process of the 4th cervical vertebra
	LI 10	on the dorsal-radial side of the forearm, 2 *cun* inferior the transverse crease of the elbow, on the line joining LI5 and LI11
	EX-UE	on the midpoint of the line between the top of anterior axillary folds and LI15 acupoint
	GB 29	at the lateral gluteal, the midpoint of the line between anterior superior iliac spine and the most convex point of the greater trochanter
	GB 33	on the lateral side of the knee, the depression above the external epicondyle of the femur
2, 5, 8	SJ14	in the depression posteroinferior to the acromion when arm is abducted
	LU5	on the transverse cubital crease, the radial side of the tendon of the biceps brachii
	SJ4	in the dorsal of the transverse crease of the wrist, the depression of the ulnar border of the total extensor tendon
	BL24	1.5 *cun* lateral to the depression below the spinous process of the 3th lumbar vertebra
	BL40	the midpoint of the transverse crease of the popliteal fossa
	BL58	on the lateral of the calf, 7 *cun* above the BL60 acupoint
3, 6, 9	LI14	7 *cun* above the transverse crease of the elbow, on the line joining LI11 and LI15
	PC3	on the transverse cubital crease, the depression of the ulnar border of the tendon of biceps brachii
	LI5	at the dorsal transverse crease of the wrist, at the depression between the tendons of the short extensor and long extensor of the thumb when the thumb is upward
	ST31	In anterior of the thigh, flush with the transverse crease of the hips, on the line joining the anterior superior iliac spine and the lateral side on the bottom of the patella
	LR8	on the medial side of transverse crease of the knee, the posterior edge of the medial condyle of the femur when bending the knee

**Additional points could be chosen according to syndrome differentiation.*
(1)constipation: ST25: (2) insomnia: BL14.

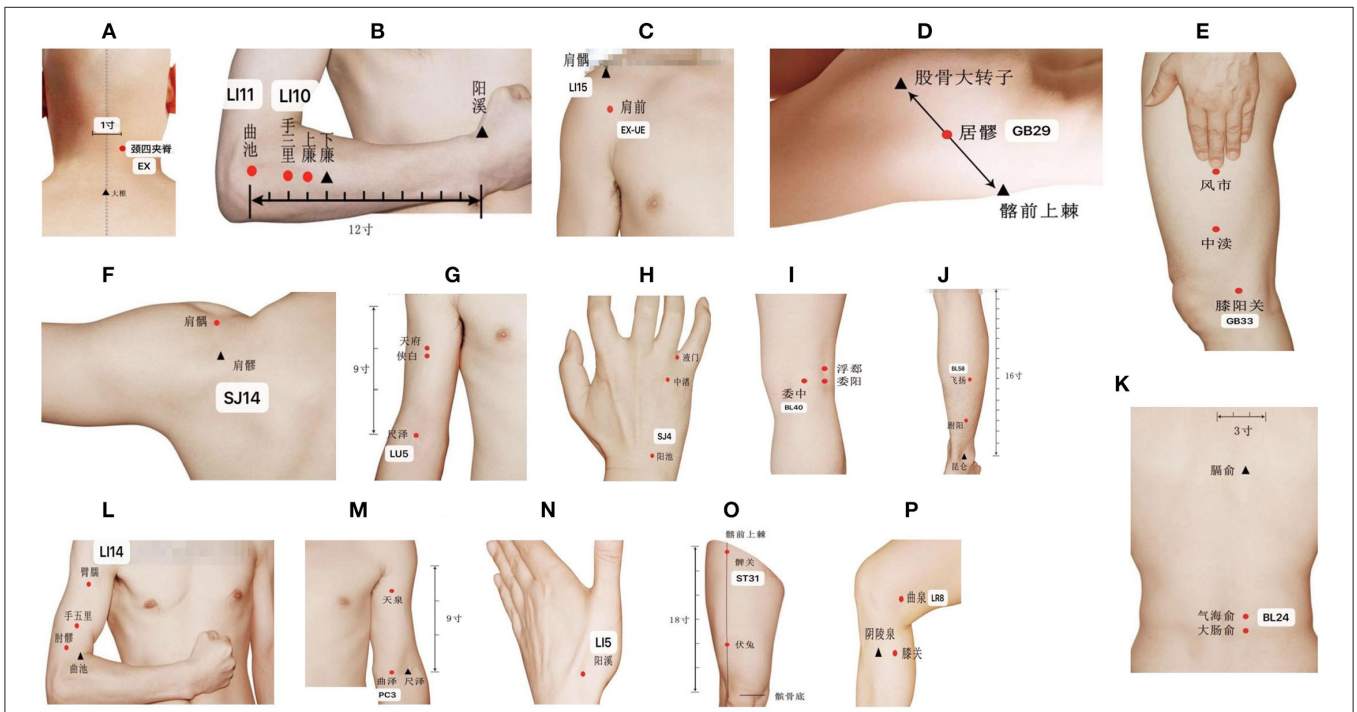

FIGURE 2 | Location of acupoints. **(A)** EX-B2; **(B)** LI10; **(C)** EX-UE & LI15; **(D)** GB29; **(E)** GB33; **(F)** SJ14; **(G)** LU5; **(H)** SJ4; **(I)** BL40; **(J)** BL58; **(K)** BL24; **(L)** LI14; **(M)** PC3; **(N)** LI5; **(O)** ST31; **(P)** LR8.

Treatment Group

The design of the treatment group was based on the theory of Traditional Chinese Medicine. In addition to the standard routine care, the treatment group received QHN therapy. The location and needling methods for acupoints are demonstrated in **Table 1**, **Figure 2**, which were located in four limbs, the neck, and the back. A tailored sterile, stainless-steel needle (length: 50 mm; diameter: 0.5 mm; QH; Chongqing, **Figure 3**) was inserted into

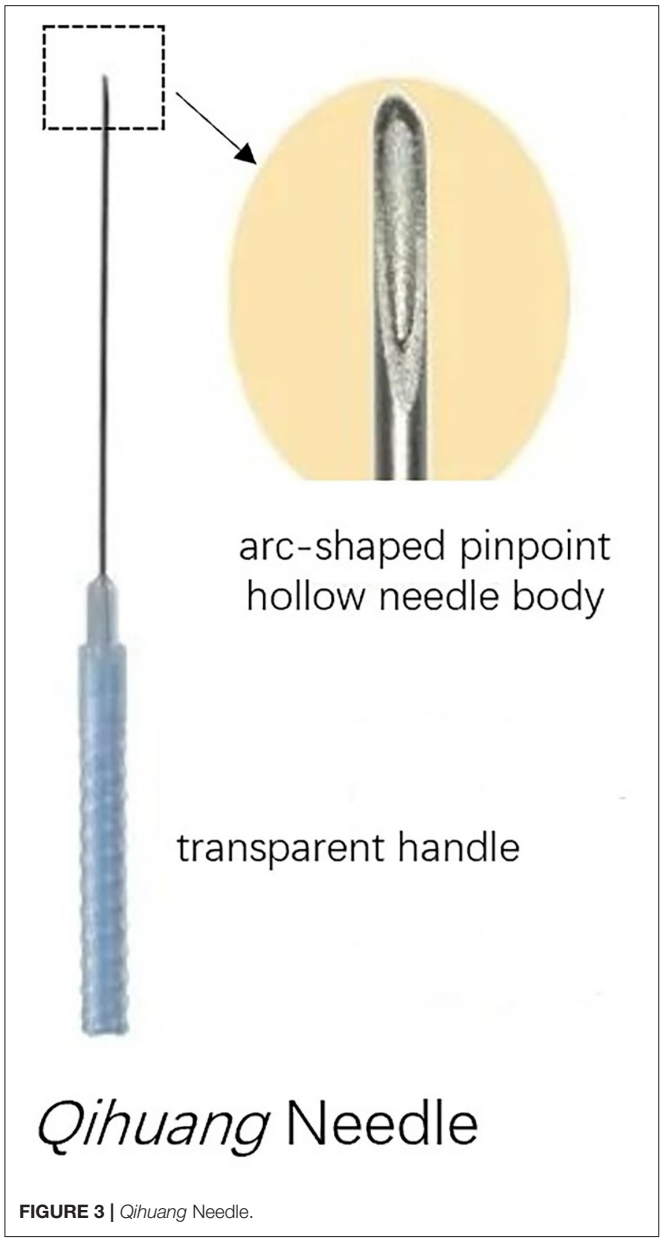

FIGURE 3 | *Qihuang* Needle.

the described acupoints at a depth of 25–40 mm. After the patients felt the *Deqi* sensation, the needles were removed and re-applied at a 30° angle. All needles were withdrawn with clean cotton balls pressed to the skin to prevent bleeding. Participants received a total of nine sessions of treatments within 6 weeks. Treatment was given 2 times per week for the first 3 weeks and 1 time per week for the following 3 weeks.

Control Group

The control group of this study was provided sham-acupuncture therapy. Sham acupoints are defined as 20-mm lateral of the verum acupoints. To do so, a needle was inserted into the sham acupoints at a depth of 3 mm without any subsequent manipulation. At these points, the patient did not feel the *Deqi* sensation. Similar to the treatment group, sham treatment was given 2 times per week for the first 3 weeks and 1 time per week for the following 3 weeks.

Outcome Measurements

All outcome measurements were taken at baseline (before treatment), 6 weeks after treatment, and 14 weeks after treatment.

Primary Outcome Measurement

Parkinson's Disease Rating Scale-Part III Motor Examination (UPDRS-III)

Parkinson's Disease Rating Scale-Part III Motor Examination-III is an assessor-rated scale that is used to evaluate the motor function of patients with PD. It contains 18 items, and each item is scored "0–4" depending on the severity of the motor disability, in which "0" represents normal and "4" indicates severe impairment. Higher scores indicate severe motor function and disability. This scale effectively assesses the severity of PD and has demonstrated high efficiency, validity, and reliability (15).

Secondary Outcome Measurement

Parkinson's Disease Daily Quality of Life-39 (PDQ-39

Parkinson's disease daily quality of life-39 is a questionnaire used to assess the health-related quality of life (HRQoL) of patients with PD (16). This questionnaire contains 39 questions and evaluates eight dimensions: mobility, activities of daily living, emotional wellbeing, stigmatization, social support, cognition, communication, and bodily discomfort. Each question has five choices, in which higher scores indicate higher incidence rates of the physiological or psychological status of the patients, suggesting a low HRQoL.

Non-Motor Symptoms Scale for Parkinson's Disease (NMSS)

Non-Motor Symptoms Scale for Parkinson's disease is a 30-item scale for assessing the non-motor symptoms of PD. It is used to evaluate cardiovascular symptoms, sleep, cognition, memory, dysesthesia, gastrointestinal symptoms, and urinary symptoms. Each item is rated using a "1–3" and "1–4" scale, where the former represents the severity of the non-motor symptom, whereas the latter indicates its frequency. Higher scores indicate a more severe non-motor disorder. Validation of this tool has been shown by excellent correlations between the H-Y scale and UPDRS scores.

Sample-Size Calculation

This trial used a clinical-superiority design to verify that QHN therapy's effect was superior to that of sham acupuncture. The primary outcome measure was the UPDRS-III score difference before and after the treatment. According to previous research (17), assuming the standard deviation (SD) to be 8.0 and the mean of the treatment effect of the two groups to be 4.36 and 0.25, respectively, the statistical power was 80%, and the significance level was 0.05. Using PASS software requires each group to contain no <61 patients. With an estimated 15% dropout rate, we planned to recruit 72 patients for each group, for a total of 144 patients.

Statistical Analysis

We used mean and SD for normally distributed variables, or median (interquartile) for the variables not normally distributed, to summarize the participants' demographic, health conditions, and clinical outcomes at three different time points. Two statisticians, blinded to the group setting, analyzed the data independently *via* SPSS software (version 26.0). Missing data were imputed according to the last-observation-carried-forward (LOCF) principle. Furthermore, the data were analyzed by the intent-to-treat principle.

The normality of the variables was assessed using the normal probability plot. The continuous variables normally distributed were assessed by the student's t-test. Otherwise, the Mann-Whitney test or Wilcoxon test was applied. The Fisher's exact or the chi-square test was adopted for categorical data, and statistical significance was set at $p < 0.05$.

Safety and Adverse Events (AEs)

Acupuncture is generally regarded as a safe therapy. Although AEs of acupuncture are rare, participants still may encounter hematoncus, dizziness, or fainting. If the above events occur, the acupuncture treatment will be stopped immediately, and the subject will be instructed to lie flat on the bed and drink warm water. AEs are caused by oral drugs that mainly include nausea, vomiting, dyspepsia, abdominal distension, orthostatic hypotension, hypohepatia, and renal function impairment. If these adverse reactions occur, participants will halt the use of medication, the respective alternative medicine, and symptomatic treatment as necessary. These AEs will be subcategorized by severity: mild, moderate, and severe AEs. For this study, mild AEs were defined as transient and tolerable AEs. Moderate AEs were defined as those that caused discomfort and potentially interfered with the subject's daily life. Severe AEs were defined as those that seriously affected the participants' physical health and even led to the risk of life. The details of AEs, such as time, duration, performance, measures to be taken, and the outcome, were recorded. The trial was stopped if there was an unacceptable risk of serious AEs in one or both treatment arms.

Data Management and Monitoring

A case report form (CRF) was designed and utilized for data collection. The DMC recorded data information regarding subject demographics and assessment of patients. As necessary, the reason for patient dropout was documented in the CRF. At the end of the study, the investigator submitted all CRFs to the data management committee for review.

If more than 25% of the patients stopped treatment due to moderate or severe AEs, trial continuation would be required to be reassessed. The DMC was independently chaired by the Statistics Teaching and Research Office of Guangzhou University of Chinese Medicine and claimed to have no conflict of interest. The South China Research Center for Acupuncture and Moxibustion acted as an independent committee to monitor the progress and provide advice. The Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine took part in endpoint adjudication.

For the duration of this study, the Project Management Group met every week to review trial conduct. Likewise, the Trial Steering Group met every month, and the independent Data Monitoring and Ethics Committee met every 6 months to review conduct throughout the trial period.

DISCUSSION

Previous investigations have investigated the efficacy of acupuncture for PD, with data supporting using these methods to benefit patients with PD (18, 19). Our findings from this study will further support our general understanding of therapeutic options and elucidate the benefits of QHN therapy in terms of improving motor symptoms, such as postural instability and functional mobility. If identified that it effectively alleviates motor symptoms and improves HRQoL, it could serve as a low-cost adjuvant therapy for patients with PD with motor symptoms.

This research will also evaluate the efficacy of QHN therapy for non-motor symptoms of PD, such as chronic constipation and insomnia. In addition, we aimed to explore alterations in regional brain activity before and after therapy through Functional brain imaging techniques.

Qihuang Needling therapy adopts a tailored disposable sterile needle characterized by its arc-shaped pinpoint, hollow-stiff needle body, and transparent handle. Compared with ordinary traditional manual acupuncture (TMA), the advantages of QHN therapy are that it provides a stronger *Deqi* sensation at the acupoint, reduces puncture pain, and has shorter operation times. Furthermore, it is regarded as safer than TMA because an acupuncturist could identify bleeding directly through a transparent handle to avoid damage to blood vessels. In support of these benefits, previous trials have shown that the efficacy of QHN therapy for musculoskeletal diseases is superior to TMA (20–23).

Several studies have demonstrated that acupuncture is widely used for Chinese patients with PD (7). Additionally, our previous clinical observation indicates that QHN therapy may have sustained effects, which may be superior to other acupuncture approaches. However, evidence for the therapeutic effects of acupuncture is limited. A review study summarizing 35 investigations in mainland China, Japan, Korea, Taiwan, and the United States of America demonstrated that most of these trials had small sample sizes, and some were individual case reports (10). Additionally, many studies are limited by methodological approaches, such as the lack of a placebo control group and/or deficiencies in their randomized design. To further elucidate QHM efficacy and address these previous research limitations, this research uses a multicenter, randomized, placebo-controlled trial with 400+ subjects to provide advantages in methodological design.

Limitations

Our study has several recognized limitations. Firstly, it is an open-label research investigation due to the inability of blind acupuncturists. Despite blinding assessments being

performed, we did not control for patients' and acupuncturists' expectations of efficacy, which may alter the results of the blinding assessment and the effects of QHN therapy. Secondly, the longer-term follow-up has not been well assessed because PD is a chronic and progressive condition. Thirdly, limited by the expenditure, gait examination will not be performed in patients with PD. Therefore, future clinical trials may need to include taking gait examination as the primary outcome, and a comparison to standard care and a waiting list.

TRIAL STATUS

This protocol is version 2.0. 2019-03-17. The participants will be recruited from 1 March 2022 to 1 June 2023.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Guangzhou University of Traditional Chinese Medicine (Guangzhou, China) in July 2019 (K2019-007). Written informed consent will be obtained from eligible participants before any assessment or intervention.

AUTHOR CONTRIBUTIONS

L-SY and Y-ML drafted the manuscript. D-FZ edited the manuscript. L-SY, D-FZ, and B-MZ performed the intervention. Y-ML and S-ZZ collected the data and helped to statistical analysis. Z-HC, KZ, and L-ML carried out the design of the study. All authors issued final approval for the version to be submitted.

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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.2022.902170/full#supplementary-material

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CASE REPORT
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Acupuncture Treatment of Guillain–Barré Syndrome After Using Immune Checkpoint Inhibitors: A Case Report

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Guillain–Barré syndrome(GBS) is an autoimmune-mediated peripheral neuropathy. Immune checkpoint inhibitors (ICIs) are the standard treatment for cancer and may lead to immune-related adverse events (irAEs) such as GBS. Corticosteroids, plasma exchange (PE), and intravenous immunoglobulin (IVIG) are currently accepted treatments for ICI-induced GBS. However, there are still adverse reactions, and the effect of relieving symptoms is not as good as expected. Safe and effective complementary replacement therapy to alleviate GBS symptoms and ameliorate the quality of life is urgently required. In this case, a 63-year-old man received ICI therapy and antitumor chemotherapy for lung malignancy. After two courses of treatment, the patient gradually developed limb weakness, numbness, and pain at the ends of the limbs, with cerebrospinal fluid (CSF) albuminocytological dissociation, and electromyography (EMG) suggested demyelinating changes and was diagnosed as GBS. Although the patient received high doses of intravenous gamma globulin and limb weakness symptoms were alleviated, there was still significant numbness and pain in the extremities. After four times of acupuncture treatments, the patient complained that the symptoms of limb numbness and fatigue were significantly alleviated without any discomfort. This case report may provide a new alternative and complementary therapy for immune checkpoint inhibitor-induced GBS, but more definitive and robust evidence is needed to support its efficacy.

Keywords: acupuncture, Guillain–Barré syndrome, immune checkpoint inhibitors, immune-related adverse events, case report, limb weakness, numbness

INTRODUCTION

Guillain–Barré syndrome (GBS) is an autoimmune-mediated peripheral neuropathy (1). The classic clinical presentation of GBS is symmetrical progressive limb weakness with diminished or absent tendon reflexes (2), and limb paresthesias are also present in most patients. Electromyography (ECG) can detect polyradiculoneuropathy, and cerebrospinal fluid analysis can demonstrate albumin cytology dissociation (3). The incidence of GBS ranges widely (4, 5), with an estimated 100,000 patients diagnosed worldwide each year (1). Otherwise, the incidence rate of

GBS increased with age, and the probability of males onset was higher than that of females (3). Symptom severity in GBS typically peaks within 1 month (3), followed by a recovery period of months or years. However, about 5% of patients eventually die due to complications such as respiratory failure, infection, hypotension, and severe cardiac arrhythmias, and about 20% are unable to walk independently (3).

Immune checkpoint inhibitors (ICIs) are widely used in cancer, bringing new hope to patients with advanced cancer. However, ICIs activate the autoimmune system, leading to the attack on normal tissues or organs, resulting in various adverse effects (6). Such adverse reactions caused by ICIs are called immune-related adverse events (irAEs), especially neurological immune-related adverse events, which are rare but potentially life-threatening and require prompt diagnosis and intervention (7). The reported incidence of GBS associated with ICIs is 0.3% (8), and its clinical presentation is not different from classic GBS (9). Plasma exchange (PE) and intravenous immunoglobulin (IVIG) are recognized as methods that can promote rehabilitation and improve disease outcomes in GBS (3). In addition, corticosteroids are the mainstay of treatment for GBS associated with ICIs (10). However, they also cause certain adverse reactions, such as fatigue, pain, anxiety, and so on (11, 12). The effect of alleviating symptoms is not satisfactory, resulting in the impact of the curative effect or quality of life of patients with cancer. Therefore, safe and effective complementary replacement therapy to alleviate the symptoms and enhance the quality of life is urgently required.

Acupuncture is a traditional Chinese medicine therapy. Modern research shows that acupuncture has an excellent curative effect on pain, anxiety, limb dysfunction, and paresthesia and can effectively improve neurological function (13, 14). It has been widely used as a supplementary treatment for cancer pain and neurovascular diseases (15). In this study, we tried acupuncture for a patient with GBS following an ICIs. We surprisingly found that acupuncture completely relieved the patient's symptoms of limb weakness and paresthesia, and the living quality of the patient was enhanced. Here, we report the case in detail.

CASE REPORT

Clinical History

A 63-year-old man was admitted to the intensive care unit (ICU) due to coughing up bloody sputum for more than 2 months without apparent cause. Symptomatic treatment was given for anti-infection, hemostasis, phlegm reduction, and nutritional support. After the condition was stable, the patient underwent an ultrasound-guided percutaneous lung biopsy, and the pathology report suggested mucinous adenocarcinoma. The patient's final diagnosis was lung malignancy (mucinous adenocarcinoma cT3N0M1a stage IV). Subsequently, the patient came to our hospital for a 3-week course of antitumor chemotherapy and immune checkpoint inhibitor therapy. The specific regimen was as follows: docetaxel 120 mg and tislelizumab 200 mg. After two courses of treatment, the patient came to our hospital for further treatment. On admission, the patient complained of occasional cough, coughing up a small amount of white sputum and wheezing easily after activities. Symptoms of limb weakness, numbness, and pain in the extremities began to appear 1 week ago, and the patient emphasized that the numbness felt like wearing gloves and socks.

TABLE 1 | Analysis of cerebrospinal fluid.

Item	Result		Unit	Reference interval
Color	Colorless			
Transparency	Clear			
Clot	No clots			
Pandy test	+	*		
RBC	300		E+6/L	
WBC	0		E+6/L	
K	2.91		mmol/L	
Na	145.9		mmol/L	
Cl	125.5		mmol/L	120–132
Glu	3.9		mmol/L	2.50–4.50
M-TP	911	↑	mg/L	150–450
LDH	24		U/L	
ADA	0		U/L	0–8

*RBC, red blood cell; WBC, white blood cell; Glu, glucose level; M-TP, micro-amount of proteins; LDH, lactate dehydrogenase; ADA, adenosine deaminase. *, means different from normal - ; ↑, means higher than normal range.*

Clinical and Laboratory Examinations

The size of the bilateral pupils is equal, light reflexes of both pupils were sensitive, and the corneal reflexes were present. The muscle tone of the limbs decreased, the muscle strength of the proximal end of both upper limbs was grade 4, the distal end was grade 2, and the lower limbs were grade 3. The tendon reflexes disappeared symmetrically, and the signs of pyramidal tract and meningeal irritation were negative. Analysis of cerebrospinal fluid showed that the Pandy test was positive, white blood cell (WBC) count was 0, and micro-amount of proteins (M-TP) was 911 mg/L (normal reference value range was 150–450 mg/L), suggesting significant CSF albuminocytological dissociation (**Table 1**).

EMG and Neuroimaging

Electromyography showed that bilateral tibial nerves, bilateral common peroneal nerves, bilateral superficial peroneal nerves, bilateral sural nerves, bilateral median nerves, bilateral ulnar nerves, L4-S1, and C5-T1 nerve roots were all damaged. Nerve conduction velocity is slowed, and F-wave latency is prolonged, suggesting nerve demyelination. Brain MRI examination showed mild white matter degeneration, and the rest showed no evident abnormality. Spinal MRI examination showed mild bulging of C5/6, C6/7 intervertebral disks and bulging of L2/3-L5/S1 intervertebral disks. There was no evident stenosis of the spinal canal, and the spinal cord and nerve roots were not compressed. According to the history, symptoms, signs, and auxiliary examinations, we considered the diagnosis of Guillain–Barre syndrome induced by ICIs.

Acupuncture Treatment

In the beginning, the patient received a five-day pulse of intravenous gamma globulin, combined with mecobalamin and pregabalin to nourish the nerves. After the end of intravenous immune globulin pulse therapy, the patient complained that the symptoms of limb weakness improved, but there was still noticeable numbness and pain in the extremities. Physical examination showed that the distal muscle strength of both upper limbs increased to grade 3, but there was no significant change in the muscle strength of other limbs. Therefore, an acupuncture doctor with 7 years of experience in acupuncture was arranged to perform acupuncture treatment for him to relieve the weakness and numbness of the limbs and pain. After the skin was disinfected, bilateral Tianshu (ST25), Zhongwan (CV12), Xiawan (CV10), Qihai (CV6), Guanyuan (CV4), bilateral Quchi (LI11), bilateral Hegu (LI4), bilateral Zusanli (ST36), and bilateral Sanyinjiao (SP6) were pierced with stainless steel needles (0.25 mm × 40 mm, TianXie, China). The acupuncturist did not do any manipulations on the acupuncture needles and kept them for 25 min (**Figure 1**).

After accomplishing the first acupuncture treatment, the patient complained that the symptoms of limb weakness were significantly improved, and the physical examination showed that the muscle strength of the limbs was all grade 4. After completing the second acupuncture treatment, the patient said that there was no limb weakness, and the muscle strength of the limbs could reach grade 5, but numbness and pain at the ends of the limbs were still left. The patient reported that the numbness and pain in the extremities were significantly relieved after finishing the third acupuncture. After four acupuncture treatments, the patient expressed that there was no numbness and pain in the extremities, and there was no adverse acupuncture reaction, which made him extremely satisfied. During the follow-up, the patient stated that the disease had not recurred for 1 year after discharge (**Figure 2**).

DISCUSSION

As the most common and most severe autoimmune-mediated acute paralytic neuropathy in neurology (3), GBS is divided into several subtypes, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher syndrome (MFS), acute panautonomic neuropathy (APN), and acute sensory neuropathy (ASN), the most common subphenotypes being AIDP and AMAN (16). This case can be diagnosed as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) based on the patient's medical history, symptoms, signs, and auxiliary examinations. In addition, since the course of GBS is self-limiting and we did not review CSF analysis before discharge, we need to distinguish it from acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) (17) to prevent doubts about the efficacy of acupuncture in alleviating symptoms. Studies have shown that A-CIDP can only be diagnosed when a patient has GBS and has relapsed or relapsed more than three times 8 weeks after the onset of GBS (2, 17). However, we followed up with this patient, and the patient reported that there had been no recurrence of GBS within 1 year from discharge to the present. Therefore, we can rule out the diagnosis of A-CIDP.

It is worth noting that antitumor chemotherapy drugs can also induce peripheral neuropathy, such as taxanes, platinums, vinblastines, and so on (18), which we call chemotherapy-induced peripheral neuropathy (CIPN) (19). CIPN is a neuropathy mainly involving sensory nerves (20). It is characterized by symmetrical numbness, paresthesia, pain, and hyperesthesia at the distal end of the limb, with a typical "glove"–"sock" distribution (21), which is almost the same as the sensory symptoms presented by GBS. In this case, the patient also used docetaxel for antitumor chemotherapy while using ICIs. Docetaxel belongs to the taxane class of antitumor drugs and has the risk of inducing CIPN. Therefore, we do not rule out the possibility of additional adverse reactions of docetaxel for the symptoms of numbness and pain in the patient's extremities.

The exact etiology of classic GBS is unknown, researchers consider that the infection of the peripheral nerves or nerve roots leads to extensive inflammatory demyelinating lesions in the peripheral nervous system (22). Most patients had a history of infections, mainly upper respiratory tract infections and gastrointestinal infections, within the 4 weeks before the onset of neurological symptoms (23). In addition, the pathogenesis of GBS is also related to the factors such as vaccination (24), ganglioside administration (25, 26), and surgery (27). Studies have shown that 50–70% of cases occur 7–14 days after infection or immune stimulation, which would induce an abnormal autoimmune response to the peripheral nerve and its spinal nerve roots (28–30). The molecular mimicry between pathogen antigens and neural antigens is currently considered to be one of the most important mechanisms leading to the pathogenesis of GBS (3). This theory holds that some components of pathogens have the same structure as some components of peripheral nerves, and the body's immune system recognizes them incorrectly. Autoimmune cells and autoantibodies conduct immune attacks on normal peripheral nerves, resulting in peripheral nerve demyelination. Studies have currently supported the vital role of molecular simulation in GBS pathogenesis (31). As a type of immune stimulation, immune checkpoint inhibitors may also induce abnormal autoimmune responses in the body, resulting in peripheral nerve demyelination.

Immune checkpoint inhibitor-induced GBS usually develops after three courses of ICIs, and the disease progresses rapidly (2). CSF analysis showed albuminocytological dissociation, and electrophysiological studies supported demyelinating neuropathy (32). The mechanism of ICI-induced GBS is currently unclear. It may be due to the abolition of self-tolerance that activates cytotoxic T lymphocytes while reducing the inhibition of antibody-producing B lymphocytes (2). It is worth noting that the treatment of ICI-induced GBS is different from that of classic GBS. Although corticosteroids are not recommended for classic GBS, they can significantly improve clinical symptoms of ICI-induced GBS (33).

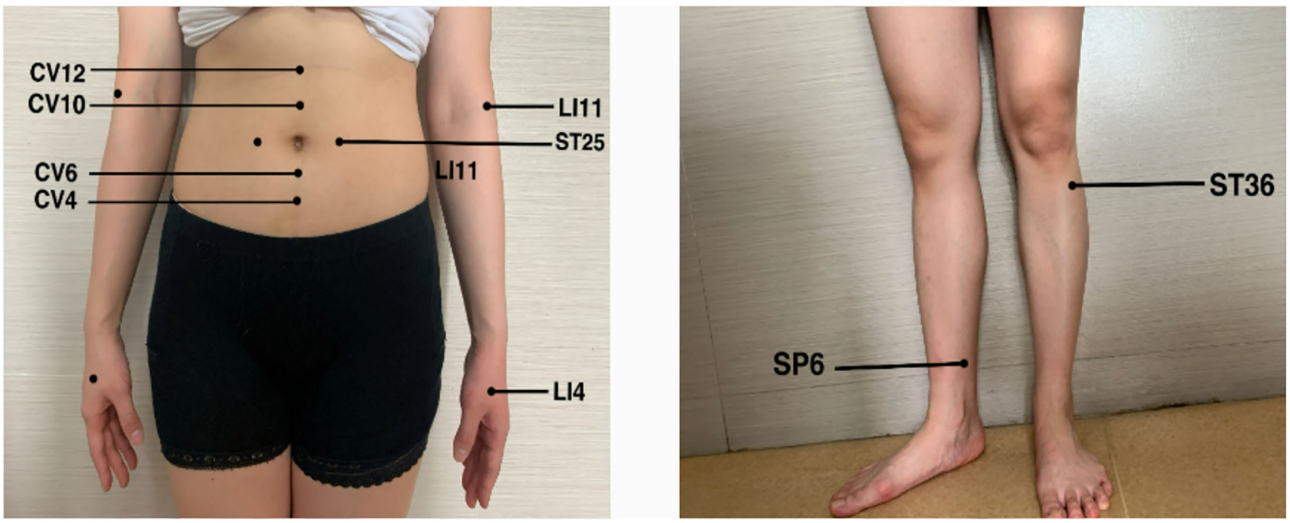

FIGURE 1 | The selected acupoints bilateral Tianshu (ST25), Zhongwan (CV12), Xiawan (CV10), Qihai (CV6), Guanyuan (CV4), bilateral Quchi (LI11), bilateral Hegu (LI4), bilateral Zusanli (ST36) and bilateral Sanyinjiao (SP6).

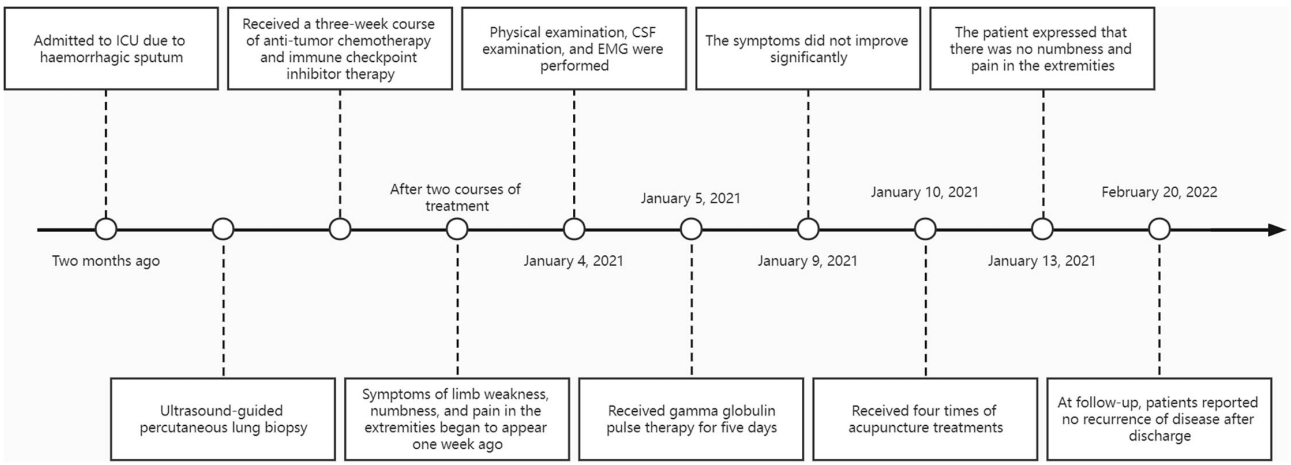

FIGURE 2 | Timeline with relevant data from the episode of care.

Through reviewing the previous literature on GBS related to ICIs, we found that the majority of patients (44%) had a 73% improvement in clinical symptoms when receiving IVIg and steroids concurrently. In contrast, the clinical efficacy of PE is uncertain due to the small number of effective cases (33). The American Society of Clinical Oncology (ASCO) clinical practice guidelines state that in the treatment of GBS associated with ICIs, IVIG 0.4 g/kg/day should be used for 5 days in combination with (methyl)prednisolone 1–2 mg/kg/day (34). The National Comprehensive Cancer Network (NCCN) guidelines recommend high-dose intravenous methylprednisolone 1 g/d for 5 days with concurrent IVIG and PE (35). However, the European Society for Medical Oncology (ESMO) considers that 1–2 mg/kg/day of (methyl)prednisolone is sufficient for general ICIs-related GBS. IVIG and PE are recommended when symptoms do not improve or worsen (36). According to the guideline recommendations and previous literature, once ICIs-related GBS is diagnosed, immunotherapy should be stopped immediately. First-line treatment is recommended to use IVIg 0.4 g/kg/day for 5 days, and concurrently use (methyl)prednisolone 1–2 mg /kg/day. Second-line treatment is PE, which should be considered when symptoms do not improve or when the condition worsens (33).

In this case, the patient only received IVIG therapy and was not assigned corticosteroid therapy, which could not effectively relieve the clinical symptoms caused by ICI-related GBS. After four times of acupuncture treatments, the patient's symptoms of limb weakness and numbness and pain were successfully relieved, the quality of life was improved, and there were no adverse

reactions. The patient expressed that he was satisfied with the curative effect of acupuncture.

As the primary treatment modality of East Asian medicine, acupuncture and moxibustion have received extensive attention worldwide (37). In the clinical application of acupuncture, the functional connection and communication between acupuncture points, the brain (the heart of ancient medicine), and the gut are essential (38), similar to the gut–brain axis in modern medicine. The gut–brain axis represents bidirectional communication between the gut and the brain (39, 40) and plays an important role in neurodegenerative diseases. Dysbiosis of the gut microbiota will result in an imbalance of the gut–brain axis, which will induce an increase in inflammatory signaling factors and epithelial permeability (38). The vagus nerve has been reported to be important in gut microbiota–brain axis communication, and acupuncture may exert immunomodulatory effects through the vagus nerve-mediated regulation of the brain–gut axis (41), further exerting neuroprotective effects (42).

In this case, the acupuncturist selected Tianshu (ST25), Zhongwan (CV12), Xiawan (CV10), Qihai (CV6), Guanyuan (CV4) as the local abdominal acupoints, Zusanli (ST36), Sanyinjiao (SP6), Quchi (LI11), and Hegu (LI4) were selected as the distal points of the limbs. Studies have shown that acupuncture at Zusanli (ST36), Sanyinjiao (SP6), and Tianshu (ST25) can regulate the gut–brain axis and treat diseases with gut–brain interaction disorders (43). Studies have confirmed that acupuncture at Zusanli (ST36) can enhance immunity and improve exercise capacity, which may be related to the modulation of gut microbial dysbiosis, thereby inhibiting neuroinflammation (38). Zhongwan (CV12), Xiawan (CV10), Qihai (CV6), and Guanyuan (CV4) are all on the route of the conception vessel. The digestive tract is a tubular object located on the midline of the human body in the early stage of embryogenesis, which is the route of the conception vessel. We believe that acupuncture at these acupoints may regulate the gut–brain axis by stimulating the conception vessel to achieve immune regulation and neuroprotection effects. In addition, previous studies have shown that acupuncture at Quchi (LI11), Hegu (LI4), Zusanli (ST36), and Sanyinjiao (SP6) can alleviate the symptoms of limb numbness effectively (44). However, the specific mechanism is not precise. It may be due to the vital nerve distribution where these acupoints are located, and stimulating them can effectively alleviate numbness, pain, and other paresthesias caused by neuropathy. Still, we need further research to clarify it.

It should be noted that the patient also used mecobalamin and pregabalin while using IVIG to nourish the nerves and improve the symptoms of limb weakness, numbness, and pain. At this point, the effect of acupuncture on relieving symptoms may be questioned. Relevant studies have pointed out that acupuncture has synergistic and attenuating impact in managing cancer-related symptoms and adverse reactions of anticancer therapy (45, 46). In this case, the effects of acupuncture, mecobalamin, and pregabalin are synergistic, and acupuncture can increase their efficacy in nourishing nerves and improving symptoms, which provides a reference for our clinical treatment. In the process of routine use of western medicine, acupuncture can be considered to make the onset time of the medicine faster and the effect better.

According to the latest published reviews and clinical studies, there is no literature to collect and evaluate the clinical evidence of acupuncture for GBS (47). There is only one related article in the English literature, which is a clinical case of acupuncture for the treatment of CIDP (48). Most of the cases and clinical studies of acupuncture in the treatment of GBS are published in Chinese literature. The sample size of these related clinical studies is relatively small, the research center is single, and the quality of the research is low. Therefore, from the perspective of evidence-based medicine, if we want to obtain clinical evidence that acupuncture effectively treats GBS, it is necessary to carry out large-sample, multi-center, high-quality clinical research and basic research.

CONCLUSION

In conclusion, our case shows that acupuncture eliminated the symptoms of weakness and numbness and pain in ICI-related GBS patient's limbs and improved their quality of life. Recent research shows that acupuncture has advantages in treating neurological disorders (49). Based on our experience, we believe that acupuncture may be an effective, economical, and safe complementary therapy for treating GBS. However, we still need high-quality, large-sample clinical research and basic research to demonstrate the mechanism of action and efficacy of acupuncture for GBS.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine and obtained ethical approval (Ethics Batch Number: K-2022-018). The patients/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

JL and DX conceived the idea, conceptualized the research, and prepared the manuscript. YC and YL collected and analyzed

the data. JH and ML reviewed by Manuscript. All authors contributed to the article and approved the submitted version.

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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.2022.908282/full#supplementary-material

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Investigating Acupoint Selection and Combinations of Acupuncture for Tic Disorders: An Association Rule Mining and Network Analysis Study

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Objective: Tic disorders (TDs) are common mental disorders in children and adolescents, and the clinical application of acupuncture for treating TDs is becoming increasingly widespread. However, the criteria for selecting acupoint prescriptions and combinations have not been summarized. Therefore, data mining was used herein to determine the treatment principles and the most effective acupoint selection and compatibility criteria for the treatment of TDs.

Methods: Clinical studies and observations of the efficacy of acupuncture treatment for TDs were obtained from the PubMed, Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and Chinese Biomedical (CBM) databases. The data on the acupoint prescriptions applied in these studies were collected, and network and association analyses were used to reveal the relationships between acupoints and to identify acupoint combinations. Additionally, the principles of acupuncture for TDs were determined through cluster analysis. Subgroup analysis of acupuncture prescriptions based on specific categorical diagnoses was performed to further assess the selection of acupoints.

Results: Eighty-six trials were identified, and 257 groups of effective prescriptions involving 121 acupoints were extracted. Bai-hui (DU20), Feng-chi (GB20), Tai-chong (LR3), He-gu (LI4), and San-yin-jiao (SP6) were the most regularly used acupoints for treating TDs. The Governor Vessel, gallbladder, and large intestine meridians were more commonly used than other meridians. Moreover, most acupoint sites focused on the head and neck. Network analysis revealed potentially effective acupoint prescriptions for their commonly used acupoints, namely, Bai-hui (DU20), Si-shen-cong (EX-HN1), Feng-chi (GB20), Nei-guan (PC6), Shen-men (HT7), He-gu (LI4), Zu-san-li (ST36), San-yin-jiao (SP6) and Tai-chong (LR3). Association rule mining indicated that potential point combinations that should be prioritized in TD treatment are Bai-hui (DU20), Neiguan (PC6) and Sanyinjiao (SP6). Cluster analysis revealed the treatment principle of "coordinating yin and yang, tonifying qi and blood, dispelling pathogenic wind and eliminating phlegm". The

core acupoint prescription of TS treatment comprised He-gu (LI4), Feng-chi (GB20), Tai-chong (LR3), Bai-hui (DU20), Yin-tang (EX-HN3), Si-shen-cong (EX-HN1), San-yin-jiao (SP6), and Nei-guan (PC6). The core group included He-gu (LI4) and Feng-chi (GB20). Proximal points were usually used in TS as an additional method of point selection.

Conclusion: Using data mining analysis of published studies, this study provides valuable information regarding the selection of the most effective acupoints and point combinations for clinical acupuncture practice for treating TDs.

Keywords: acupuncture, tic disorders acupoint, data mining, association rule, cluster analysis

INTRODUCTION

A tic disorder (TD) is a neuropsychiatric disorder that occurs mostly in childhood (1). The clinical manifestations of TDs are several motor and at least one phonic tic, which may be accompanied by attention deficit hyperactivity disorder, sleep disorders, mood disorders and other neuropsychiatric disorders (2). The pathogenic mechanisms of TDs are currently unknown. Several studies have shown that TDs are mainly associated with neurotransmitter imbalance, whiplash brain injury, and imbalance in micronutrient intake (1). Currently, typical antipsychotics, atypical antipsychotics, painkillers and other medications are commonly used as treatments in clinical practice. Unfortunately, these medicines cannot cure TD and are accompanied by adverse effects such as drowsiness and weight gain. Other main treatments are neuromodulation therapy and psychobehavioral therapy (3). TD is characterized by tics as the main symptom and are characterized as disorders of the Endogenous Liver Wind in traditional Chinese medicine (TCM). The pathogenesis of TD is mainly due to the deficiency of the five zang organs, the imbalance of yin and yang, and the interlocking of Wind-phlegm. Previous research has shown that TCM therapies such as acupuncture, massage and Chinese herbal treatment can be used to treat TDs (4–7). Over the years, the application of acupuncture in the treatment of TDs has become increasingly widespread and has achieved good efficacy (8). We used data mining techniques to analyze and explore the regularity of clinical acupuncture point selection for treating TDs to provide a reference for the standard treatment of TDs with acupuncture.

MATERIALS AND METHODS

Literature Source and Search Strategy

The electronic literature databases PubMed, the Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang, VIP, and Chinese Biomedical (CBM) were searched for research on acupuncture treatments for TDs published from the inception of the database to 10th October 2021, with the language restricted to English and Chinese. The search strategy used subject terms related to acupuncture and TDs, such as convulsion disorder, acupuncture, and electroacupuncture.

Literature Screening

Two researchers independently screened the eligible articles according to the inclusion and exclusion criteria; if these two researchers disagreed about an article, the article was screened by a third researcher. After reading the titles and abstracts, we deleted duplicate and irrelevant articles. Then, according to the inclusion and exclusion criteria, the remaining articles were further screened.

Inclusion Criteria

The inclusion criteria were as follows:

(i) Randomized controlled trials (RCTs) and self-control and retrospective studies (NRSIs) were included.
(ii) The participants described in the studies met one of the following diagnostic criteria for TDs: American Handbook of Diagnostic Statistics of Mental Disorders, Chinese Classification Scheme and Diagnostic Criteria of Mental Disorders, Practical TCM Pediatrics, TCM Pediatrics, Chinese Society of Traditional Chinese Medicine Guidelines for the Treatment of Common Pediatric Disorders, Neurology. The age of the participants was <20 years old, with no restrictions on sex, race, or duration of illness.
(iii) There were recognized evaluation criteria for efficacy, and the therapeutic group efficacy was clearly reported. Acupuncture therapy was defined as manual acupuncture or electroacupuncture points, moxibustion, acupuncture and moxibustion with simultaneous intervention, massage, cupping, acupoint injection, acupoint needle embedding, acupoint catgut embedding, and a combination of two or more of these therapies. In addition, a clear acupoint prescription that matched the acupoint trigger points was reported.
(iv) The primary outcome indicators were recognized efficacy evaluation criteria, such as the Yale gestalt gross severity scale (YGTSS) score, open illness scoring method score, and quantitative TCM evidence grading score. The efficacy of the intervention group was clearly reported.
(v) Republished articles retained only the most recent article.

Exclusion Criteria

The exclusion criteria were as follows:

(i) Newspapers, conference papers, degree papers, research on mechanisms, animal experiments, systematic reviews or meta-analyses, case reports and theory categories were excluded.
(ii) Studies with ambiguous acupoint prescriptions, inability to extract clear acupoint prescriptions that matched the

acupoint trigger points, and no significant efficacy in the intervention group were excluded.

(iii) The study records were not clearly reported, and the evaluation criteria were not standardized.

Data Extraction and Quality Assessment

One reviewer extracted informational data for all the eligible studies, including the name of the first author, time of issue, title of the article, type of study, sample size, diagnostic criteria, age of the participants, interventions, principle acupoints and additional acupoints, and outcome measures. Valid prescriptions were extracted *via* the "one group of main acupoints and one group of minor acupoints with one group of acupoint prescriptions" strategy. Another reviewer checked for the accuracy and completeness of the input information. The names of all the acupoints included in the prescription were standardized according to the World Health Organization's Standard Acupuncture Point Location in the Western Pacific Region and the China National Standard "Naming and Positioning of Acupoints" (GB/T 12346-2006). The meridians, positioning of acupoints and special points were extracted. Finally, we established a dataset of acupuncture treatment for TDs and entered all the data into a Microsoft Excel 2019 workbook.

Using the revised Cochrane risk-of-bias tool for randomized trials (ROB 2) to assess the risk of RCT bias, the quality of the included RCTs was assessed based on the following five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Next, The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) was used to assess the risk of NRSI bias based on the following seven domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result.

Data Mining Analysis

Descriptive Analysis

Frequency statistics of the extracted valid prescriptions were performed using the Microsoft Excel 2019 workbook and included the frequency of point application, frequency of meridian application, frequency of special point application and frequency of positioning distribution.

Network Analysis

To generate association rules more effectively and obtain the core acupoint prescriptions of the acupuncture treatments for TDs, the interconnection network of acupoints in all the included prescriptions was analyzed and visually constructed using IBM SPSS Modeler 18.0. Acupoints (defined as the "nodes" of the network) were connected by "lines" in the network. The more frequently used acupoints had thicker connecting lines.

Cluster Analysis

First, the acupoints that were used more than 20 times were converted into dichotomous variables, where "1" indicates the occurrence of an acupoint and "0" indicates the absence. Then, cluster analysis was carried out by using "cluster" in IBM SPSS Statistics 26 statistical software. The clustering method was intergroup linking, and the squared Euclidean distance (SED) was used as a measure of relational distance between acupoints to obtain the classification relationship of high-frequency acupoints.

Association Rule Mining Analysis

To obtain the high-frequency acupoint pairs, we used the Apriori algorithm of the IBM SPSS Modeler 18.0 software to analyze the association rules. An association rule is expressed in the form A→ B. Itemset A represents the "antecedent," and itemset B represents the "consequent". The strength of an association rule can be measured by its support, confidence level and lift. The support of A→ B refers to the frequency with which itemset A and itemset B appear together in the transactions. The confidence of A→ B refers to the conditional probability that itemset A appears in the presence of itemset B. The lift is used to verify that two itemsets are dependent on one another, which makes the rule valuable when the lift's value is larger than 1. We used the support level to determine the probability that A and B occurred simultaneously.

Subgroup Analysis

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies TD as transient tic disorder (TTD), persistent (chronic) tic disorder or vocal tic disorder (CTD), Tourette syndrome (TS), and other specific or unspecific tic disorders. Only one type of motor tic or vocal tic in TTD and CTD occurs during the disease course. A disease course of <1 year is considered TTD and that of more than 1 year is considered CTD. TS is defined by the presence of both motor and vocal tics. According to the disease course and specific diagnosis of the subjects included in the literature, we performed subgroup analyses of acupuncture prescriptions based on the specific classified diagnosis to further discuss the selection of acupoints for a classified diagnosis.

RESULTS

Eligible Studies

The research process is shown in **Figure 1** according to the search results. We retrieved a total of 2,100 related articles and removed 961 duplicated studies. Then, we extracted 323 eligible studies by screening the titles and abstracts of the remaining 1,139 studies. Finally, a total of 86 trials were identified based on the inclusion criteria. In all included studies, including 73 RCTs and 13 NRSIs, the overall quality of bias of the RCTs was assessed as low risk (4.1%), some concerns (78.1%), and high risk (17.8%). Because of insufficient allocation concealment and missing outcome data, 94.6% of all RCT studies were rated as high or moderate risk of bias in outcome measures, and 17.8% were rated as high or

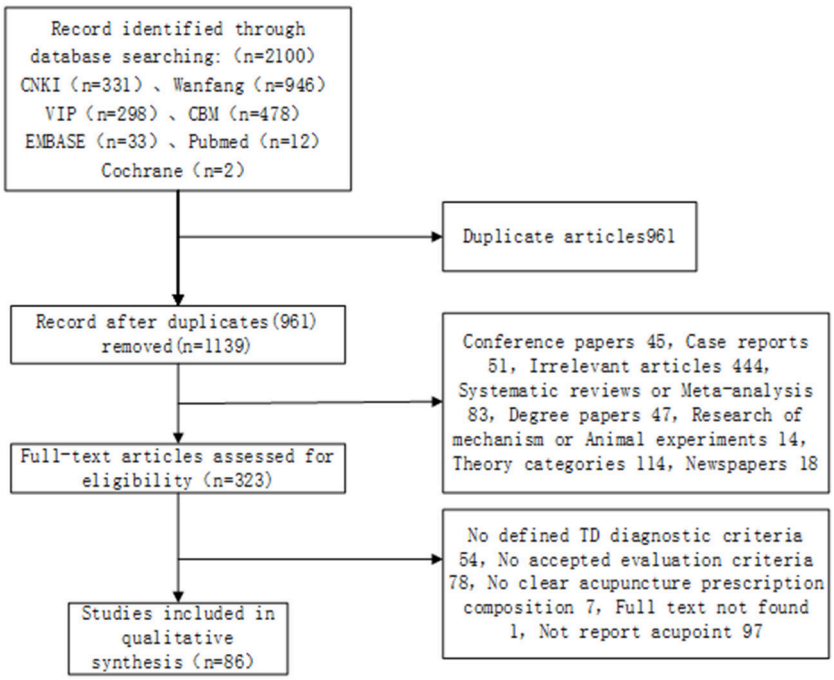

FIGURE 1 | PRISMA flow diagram.

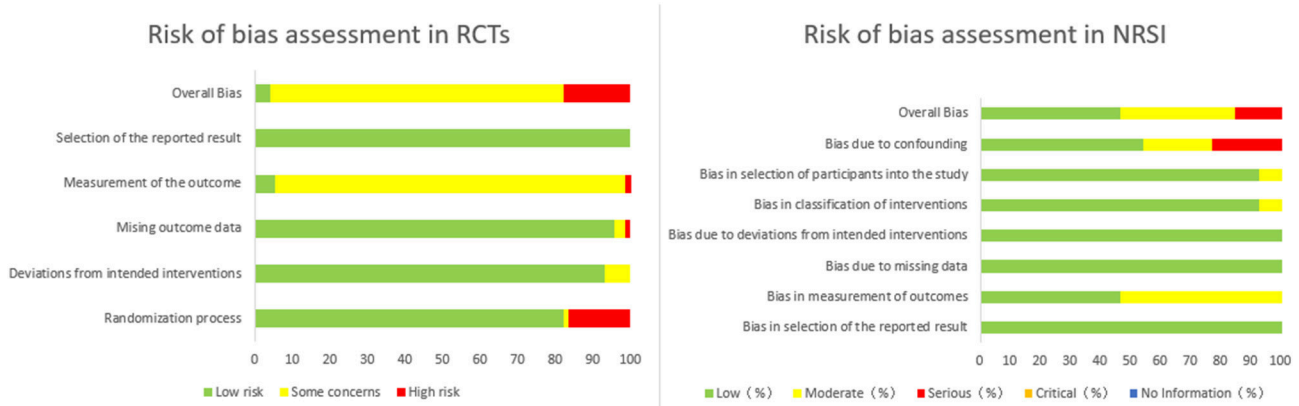

FIGURE 2 | Risk of bias assessment.

moderate risk of bias due to randomization process. The overall bias quality of NRSIs was rated as low risk (46.1%), moderate risk (38.5%), and serious risk (15.4%). Higher risks of bias were confounding bias and measurement bias at 46.2 and 53.9%, respectively. The results are shown in **Figure 2**.

Frequency of Acupoint Analysis

In all, 257 prescriptions were identified involving 121 acupoints with a total frequency of 2,032; 107 of these were traditional acupoints, 11 were extra points, and 3 were the experience acupoint that was not part of any traditional meridian. The five most commonly used acupoints were Bai-hui (DU20), Feng-chi (GB20), Tai-chong (LR3), He-gu (LI4), and San-yin-jiao (SP6) (**Table 1**; **Figure 3**). Bai-hui (DU20) was the most frequently used, with a frequency of 76.26% in 257 acupoint prescriptions.

Frequency of Meridian Analysis

Of the 257 acupoint prescriptions, 107 acupoints from the fourteen meridians were used in the treatment of TDs, with a total frequency of 1,794 (**Table 2**; **Figure 4**). The distribution detailed in the analysis showed that the Governor Vessel, including 13 acupoints, was the most frequently used at 354 times. The second most used meridian was the gallbladder

TABLE 1 | Frequency of acupoint application for TD treatment.

NO.	Acupoint	Frequency		Meridian	Site of the point	Specific points
1	DU20	196	9.65%	Du meridian	Points of head and neck	Crossing point
2	GB20	154	7.58%	Gallbladder meridian	Points of head and neck	Crossing point
3	LR3	147	7.23%	Liver meridian	Points of lower extremities	Five Shu points, yuan-primary point
4	LI4	128	6.30%	Large intestine meridian	Points of upper extremities	Yuan-primary point
5	SP6	104	5.12%	Spleen meridian	Points of lower extremities	Crossing point
6	EX-HN1	93	4.58%	Extra points	Points of head and neck	
7	PC6	85	4.18%	Pericardium meridian	Points of upper extremities	Luo-connecting point, eight confluent point, crossing point
8	EX-HN3	81	3.99%	Extra points	Points of head and neck	
9	HT7	73	3.59%	Heart meridian	Points of upper extremities	Five Shu points, yuan-primary point
10	ST36	71	3.49%	Stomach meridian	Points of lower extremities	Five Shu points, lower He-Sea point
11	DU24	41	2.02%	Du meridian	Points of head and neck	Crossing point
12	DU14	39	1.92%	Du meridian	Points of head and neck	Crossing point
13	LI11	31	1.53%	Large intestine meridian	Points of upper extremities	Five Shu points
14	EX-HN5	29	1.43%	Extra points	Points of head and neck	
15	ST4	28	1.38%	Stomach meridian	Points of head and neck	Crossing point
16	BL18	27	1.33%	Bladder meridian	Points of back	Back Shu point
17	KI3	26	1.28%	Kidney meridian	Points of lower extremities	Five Shu points, Yuan-primary point
18	DU16	24	1.18%	Du meridian	Points of head and neck	Crossing point
19	ST40	24	1.18%	Stomach meridian	Points of lower extremities	Luo-connecting point
20	KI6	24	1.18%	Kidney meridian	Points of lower extremities	Eight confluent point, crossing point

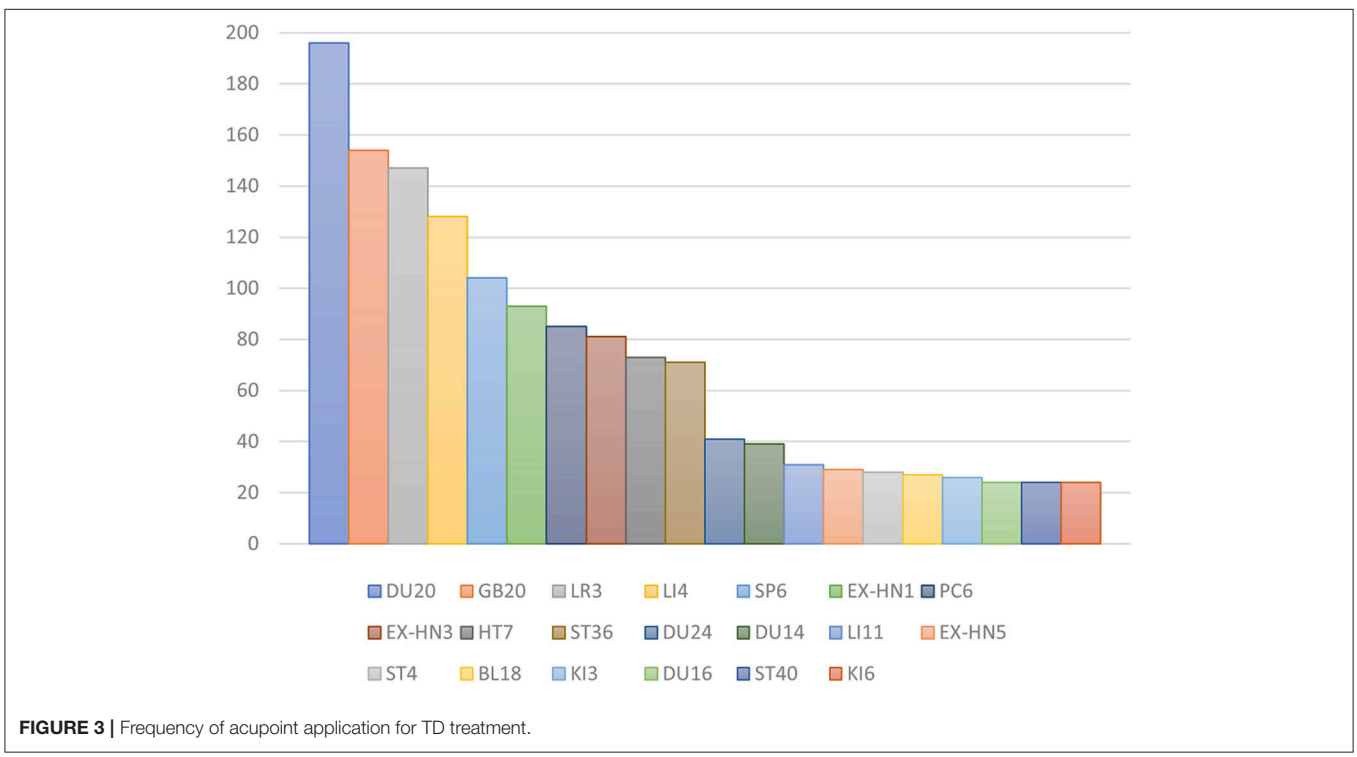

FIGURE 3 | Frequency of acupoint application for TD treatment.

meridian, which was used 227 times and involved 15 acupoints. The third most used meridian was the large intestine meridian, which was used 192 times and involved five acupoints. The meridian with the most acupoints involved was the bladder meridian, comprising 18 acupoints, but this meridian had a low frequency of use.

TABLE 2 | Frequency of meridian application for TD treatment.

Meridian	Frequency		Amount		Acupoints
Du meridian	354	17.42%	13	11.02%	DU20 196, DU24 41, DU14 39, DU16 24, DU26 15, DU8 13, DU23 12, DU11 3, DU25 3, DU22 3, DU12 3, DU17 1, DU21 1
Extra points	228	11.22%	11	9.32%	EX-HN1 93, EX-HN3 81, EX-HN5 29, EX-B2 8, EX-HN15 3, EX-HN12 4, EX-HN4 4, EX-HN13 3, EX-B1 1, EX-UE8 1, EX-UE11 1
Gallbladder meridian	227	11.17%	15	12.71%	GB20 154, GB13 13, GB34 11, GB26 8, GB14 8, GB7 6, GB39 6, GB21 5, GB6 5, GB15 3, GB8 2, GB16 2, GB1 2, GB19 1, GB17 1
Large intestine meridian	192	9.45%	5	4.24%	LI4 128, LI11 31, LI20 20, LI15 9, LI10 4
Stomach meridian	181	8.91%	14	11.86%	ST36 71, ST4 28, ST40 24, ST6 17, ST25 11, ST21 8, ST2 5, ST8 5, ST9 4, ST7 4, ST5 1, ST32 1, ST24 1, ST23 1
Liver meridian	161	7.92%	4	3.39%	LR3 147, LR13 8, LR14 4, LR2 2
Bladder meridian	136	6.69%	18	15.25%	BL18 27, BL20 23, BL23 17, BL12 12, BL10 11, BL15 10, BL62 9, BL2 7, BL13 6, BL17 2, BL4 2, BL21 2, BL19 1, BL58 1, BL1 1, BL60 1, BL49 1, BL52 1
Ren meridian	136	6.69%	14	11.86%	RN12 24, RN23 22, RN22 13, RN6 11, RN4 10, RN11 8, RN21 8, RN24 7, RN20 7, RN14 7, RN13 7, RN9 7, RN17 3, RN8 2
Spleen meridian	122	6.00%	5	4.24%	SP6 104, SP1 11, SP9 4, SP10 2, SP4 1
Pericardium meridian	91	4.48%	3	2.54%	PC6 85, PC8 4, PC7 2
Kidney meridian	79	3.89%	8	6.78%	KI3 26, KI6 24, KI18 8, KI21 7, KI26 7, KI1 3, KI4 2, KI7 2
Heart meridian	73	3.59%	1	0.85%	HT7 73
Sanjiao meridian	26	1.28%	4	3.39%	SJ23 11, SJ5 8, SJ17 4, SJ14 3
Lung meridian	11	0.54%	1	0.85%	LU7 11
Small intestine meridian	5	0.25%	2	1.69%	SI18 4, SI9 1

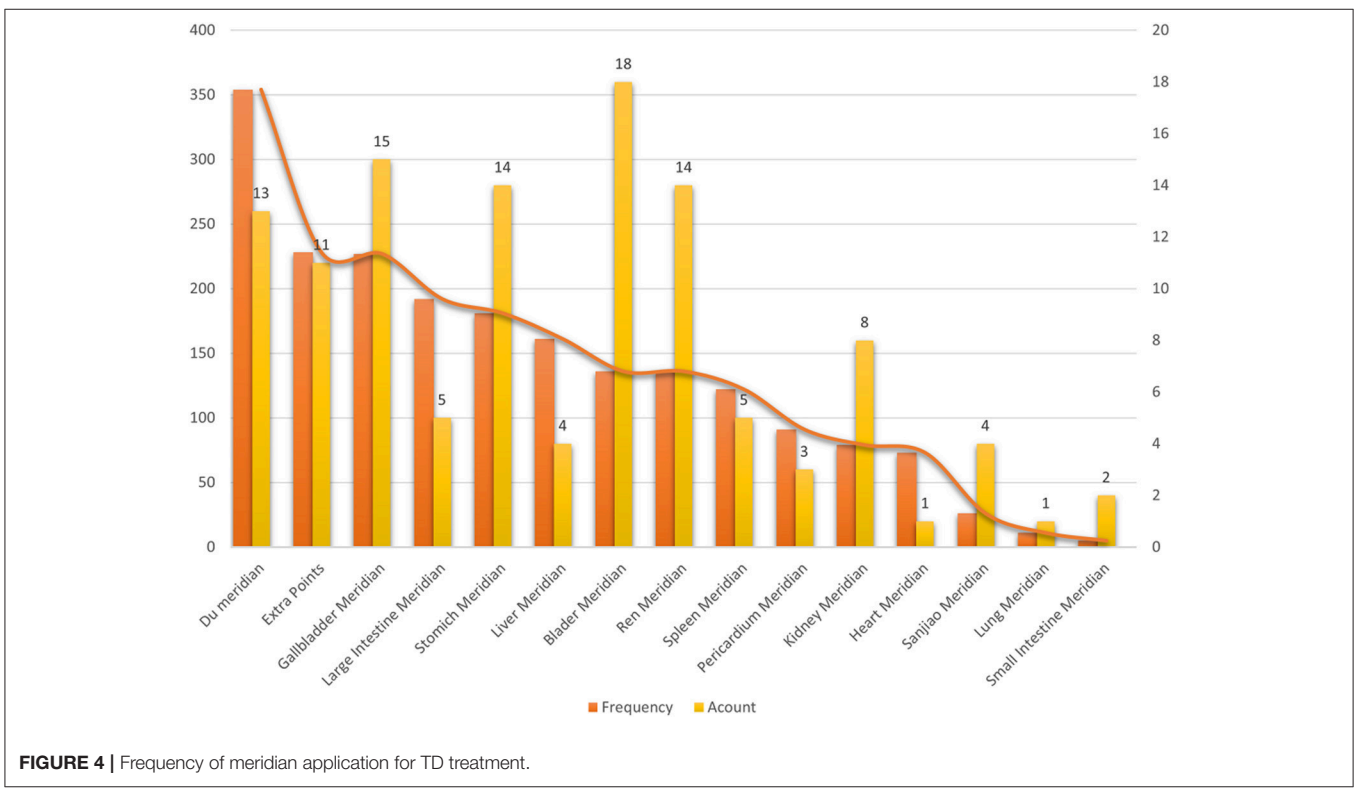

FIGURE 4 | Frequency of meridian application for TD treatment.

Specific Acupoint Analysis

A total of 67 acupoints were specific acupoints, 17 of which contained multiple attributes. For example, Tai-chong (LR3) is both a Shu point and a Yuan-primary point, and Nei-guan (PC6) is both a Luo-connecting acupoint and an eight confluent acupoint. The top five acupoints were Bai-hui (DU20), Feng-chi

TABLE 3 | Frequency of special point application for TD treatment.

Special point	Frequency	Amount	Acupoints
Crossing point	907	37	DU20 196, GB20 154, SP6 104, PC6 85, DU24 41, DU14 39, ST4 28, DU16 24, KI6 24, RN12 24, RN23 22, LI20 20, DU26 15, GB13 13, RN22 13, LU7 11, LI15 9, BL62 9, GB14 8, SJ5 8, LR13 8, RN24 7, RN13 7, GB7 6, GB21 5, ST8 5, GB6 5, SI18 4, LR14 4, GB15 3, GB8 2, GB16 2, GB1 2, BL1 3, DU17 1, GB19 1, SP4 1
Five Shu points	387	14	LR3 147, HT7 73, ST36 71, LI11 31, KI3 26, GB34 11, SP1 11, SP9 4, PC8 4, KI1 3, PC7 2, KI7 2, LR2 2, BL60 1
Yuan-primary point	376	5	LR3 147, LI4 128, HT7 73, KI3 26, PC7 2
Eight confluent point	138	6	PC6 85, KI6 24, LU7 11, BL62 9, SJ5 8, SP4 1
Luo-connecting point	132	7	PC6 85, ST40 24, LU7 11, SJ5 8, KI4 2, BL58 1, SP4 1
Back Shu point	86	7	BL18 27, BL20 23, BL23 17, BL15 10, BL13 6, BL21 2, BL19 1
Lower He-Sea point	71	1	ST36 71
Front Mu point	67	7	RN12 24, ST25 11, RN4 10, LR13 8, RN14 7, LR14 4, RN17 3
Eight influential point	48	5	RN12 24, GB34 11, LR13 8, RN17 3, BL17 2

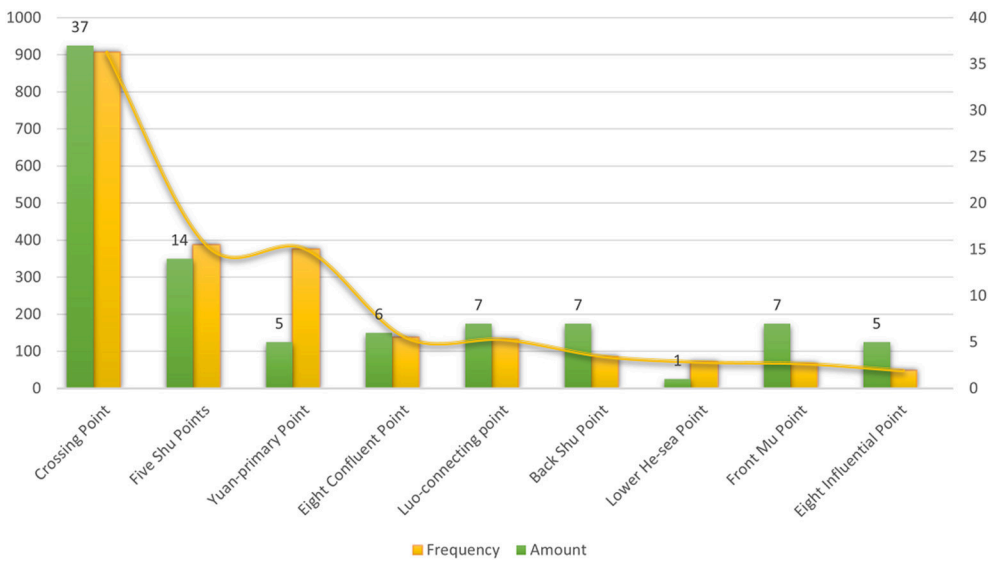

FIGURE 5 | Frequency of special point application for TD treatment.

(GB20), Tai-chong (LR3), He-gu (LI4), and San-yin-jiao (SP6). The frequency of the crossing acupoints, including 37 acupoints, was far higher than that of the others. The second most used special point was five Shu points, which was used 387 times and involved 14 acupoints (**Table 3**; **Figure 5**).

Distribution of Acupoint Analysis

The distribution of TD acupoints in acupuncture treatment is detailed in **Table 4** and **Figure 6**. The analysis showed that the acupoints of the head and neck were the main selected acupoints, and the frequency of use accounted for 45.62% of the total.

Cluster Analysis

Cluster analysis was performed on acupoints with frequencies of more than 20 times, resulting in an icicle chart (**Figure 7**) and tree charts (**Figure 8**) by using IBM SPSS Statistics 26 statistical software. Cluster analysis is a technique for classifying all subjects into the best homogeneous group based on a measure of similarity. This technique allows us to derive treatment directions and principles for the treatment of TD with acupuncture. By using a clustering algorithm with a distance scale of 15, 24 acupuncture points with frequencies >20 were clustered into a total of six major clusters as follows: Cluster 1, Nei-guan (PC6), Shen-men (HT7), San-yin-jiao (SP6), Zu-san-li (ST36), Zhong-wan (RN12), Bai-hui (DU20), Tai-yang (EX-HN5), and Qu-chi (LI11); Cluster 2, Feng-chi (GB20), Hei-gu (LI4), Tai-chong (LR3), Lian-quan (RN23), and Yin-tang (EX-HN3); Cluster 3, Zhaohai- (KI6) and Feng-long (ST40); Cluster 4, Da-zhui (DU14), Feng-fu (DU16), Si-shen-cong (EX-HN1), Shen-ting (DU24), and Ying-xiang (LI20); Cluster 5, Di-cang (ST4) and Tai-xi (KI3); and Cluster 6, Gan-shu (BL18) and Pi-shu (BL20).

Association Rule Mining Analysis

A total of 12 acupoint association rules were obtained using the Apriori algorithm by using IBM SPSS Modeler 18.0, in which the minimum support required was set to 15%, the minimum

TABLE 4 | Frequency of site of point application for TD treatment.

No.	Site of points	Frequency		Amount		Acupoints
1	Points of head and neck	927	45.62%	49	40.50%	DU20 196, GB20 154, EX-HN1 93, EX-HN3 81, DU24 41, DU14 39, EX-HN5 29, ST4 28, DU16 24, RN23 22, LI20 20, ST6 17, DU26 15, GB13 13, RN22 13, DU23 12, BL10 11, SJ23 11, EX-B2 8, GB14 8, RN24 7, BL2 7, GB7 6, ST2 5, ST8 5, GB6 5, EX-HN15 3, EX-HN12 4, SI18 4, ST9 4, ST7 4, EX-HN4 4, SJ17 4, DU25 3, GB15 3, DU22 3, EX-HN13 3, GB8 2, GB16 2, BL4 2, GB1 2, An-mian 1, ST5 1, BL1 1, DU17 1, GB19 1, Qian-zheng 1, DU21 1, GB17 1
2	Points of lower extremities	460	22.64%	21	17.36%	LR3 147, SP6 104, ST36 71, KI3 26, ST40 24, KI6 24, GB34 11, SP1 11, BL62 9, Lan-men 8, GB39 6, SP9 4, KI1 3, KI4 2, KI7 2, LR2 2, SP10 2, BL58 1, ST32 1, SP4 1, BL60 1
3	Points of upper extremities	366	18.01%	15	12.40%	LI4 128, PC6 85, HT7 73, LI11 31, LU7 11, LI15 9, SJ5 8, GB21 5, LI10 4, SJ14 3, PC8 4, PC7 2, SI9 1, EX-UE8 1, EX-UE11 1
4	Points of chest and abdomen	157	7.73%	21	17.36%	RN12 24, RN6 11, ST25 11, RN4 10, GB26 8, RN11 8, ST21 8, KI18 8, RN21 8, LR13 8, RN20 7, RN14 7, RN13 7, RN9 7, KI21 7, KI26 7, LR14 4, RN17 3, RN8 2, ST24 1, ST23 1
5	Points of back	122	6.00%	15	12.40%	BL18 27, BL20 23, BL23 17, DU8 13, BL12 12, BL15 10, BL13 6, DU11 3, DU12 3, BL17 2, BL21 2, BL19 1, EX-B1 1, BL49 1, BL52 1

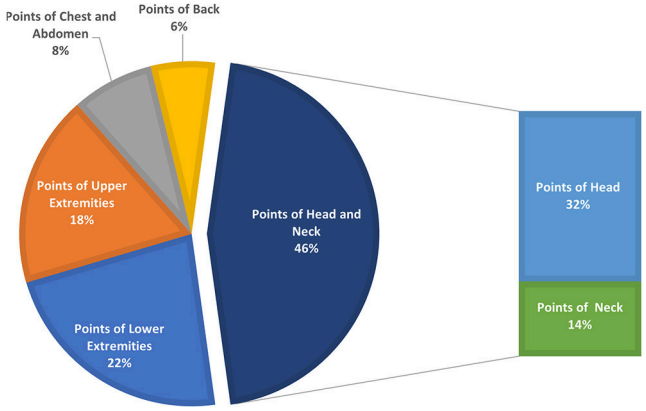

FIGURE 6 | Frequency of site of point application for TD treatment.

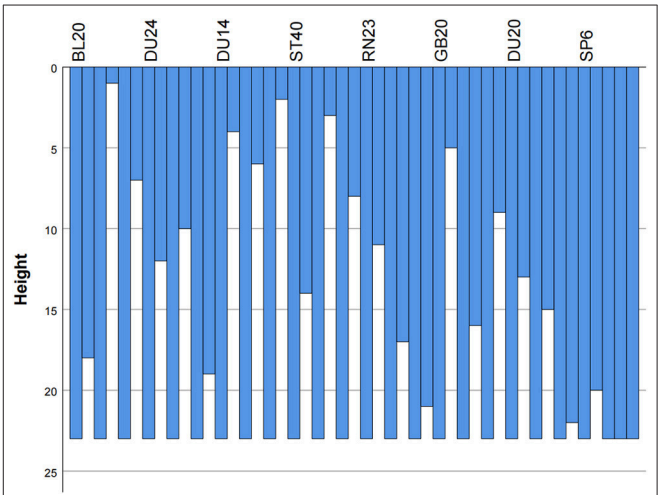

FIGURE 7 | Icicle chart of the cluster analysis of acupuncture for TDs.

confidence required was set to 95%, and the maximum number of lift-hand sides was set to 1. In terms of acupoint combinations, the top five combinations with the highest support were {Nei-guan (PC6), San-yin-jiao (SP6)} ≥ {Bai-hui (DU20)}, {Shen-men (HT7), San-yin-jiao (SP6)} ≥ {Bai-hui (DU20)}, {San-yin-jiao (SP6), Feng-chi (GB20)} ≥ {Bai-hui (DU20)}, {Shen-men (HT7), Zu-san-li (ST36)} ≥ {Bai-hui (DU20)}, and {Zu-san-li (ST36), Feng-chi (GB20)} ≥ {Bai-hui (DU20)}. The results are shown in **Table 5**. In addition, the network diagram drawn from the correlation analysis yielded the core acupoints selected for acupuncture treatment of TDs: Bai-hui (DU20), Si-shen-cong (EX-HN1), Feng-chi (GB20), Nei-guan (PC6), Shen-men (HT7), He-gu (LI4), Zu-san-li (ST36), San-yin-jiao (SP6) and Tai-chong (LR3). The results are shown in **Figure 9**.

Subgroup Analysis

Among the 86 included trials, 5 (5.81%) were clearly divided into TTD (0–1 year) according to the disease course. The remaining trials did not clearly distinguish the treatment according to the disease course. The disease course for the included subjects spanned 0–5 years in 48 (55.81%) and 0–10 years in 17 (19.77%); the remaining 16 (18.60%) did not specify a specific duration of disease. Forty-eight trials (55.81%) investigated TS, and the remaining 33 articles (38.37%) did not make a detailed classified diagnosis or included at least two types of diagnosis.

The TS treatment involved 144 prescriptions and 101 acupoints with a total frequency of 1,088; 89 were traditional acupoints, and 12 were extra points. The top five common acupoints were DU20 (111; 10.20%), LR3 (100; 9.19%), GB20 (98; 9.01%), LI4 (79; 7.26%) and EX-HN1 (53; 4.87%). The top 3 common meridians were stomach meridian (14; 13.86%), bladder meridian (14; 13.86%), and gallbladder meridian (13; 12.87%). We set the association rules to Confidence > 90, Support > 20, and Lift > 1, and the acupoint combinations with a high correlation degree were as follows (**Figure 10**): {Hei-gu (LI4)} ≥

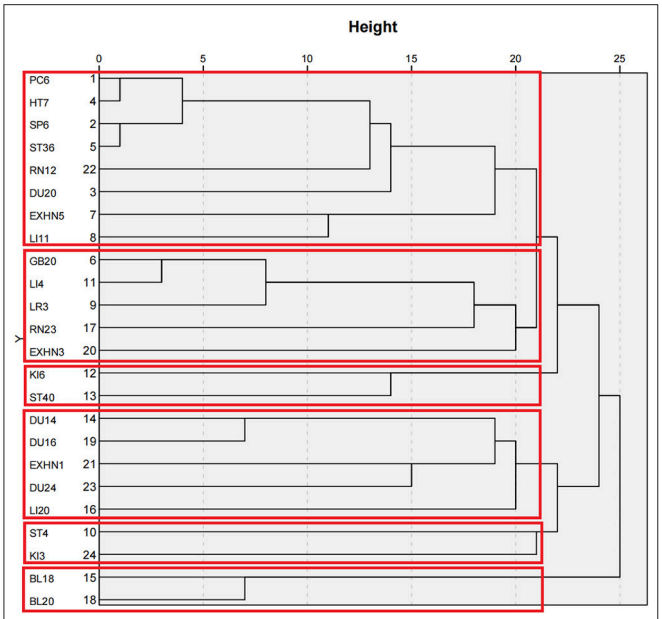

FIGURE 8 | Tree chart of the cluster analysis of acupuncture for TDs.

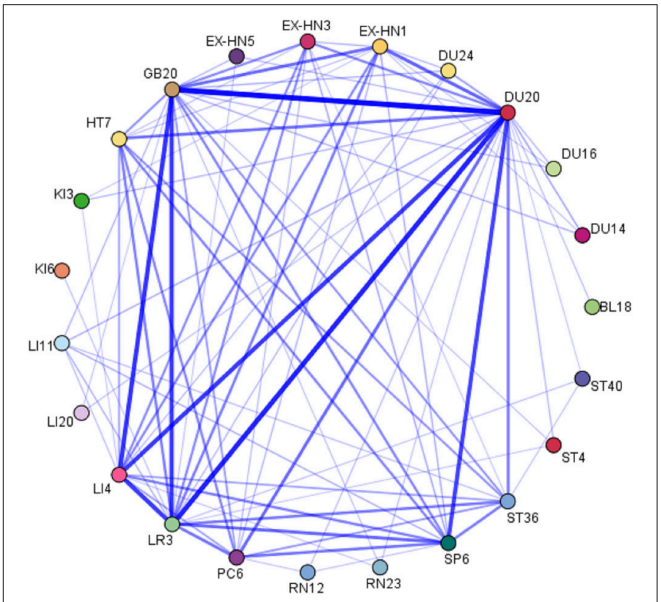

FIGURE 9 | Acupoints association network of acupuncture for TD treatment.

TABLE 5 | Association rules of acupoints for TD treatment.

Post-item	Ex-items	Confidence	Support	Lift
DU20	PC6 and SP6	100.00	25.29	1.32
DU20	HT7 and SP6	100.00	21.01	1.32
DU20	SP6 and GB20	98.15	20.62	1.29
DU20	HT7 and ST36	100.00	17.90	1.32
DU20	HT7 and GB20	97.83	17.51	1.29
DU20	ST36 and GB20	100.00	17.51	1.32
LR3	HT7 and ST36	95.65	17.12	1.70
SP6	ST36 and PC6	100.00	16.73	2.47
DU20	ST36 and PC6	100.00	16.73	1.32
LR3	ST36 and PC6	97.67	16.34	1.73
DU20	PC6 and GB20	100.00	15.56	1.32
DU20	DU24	95.12	15.18	1.25

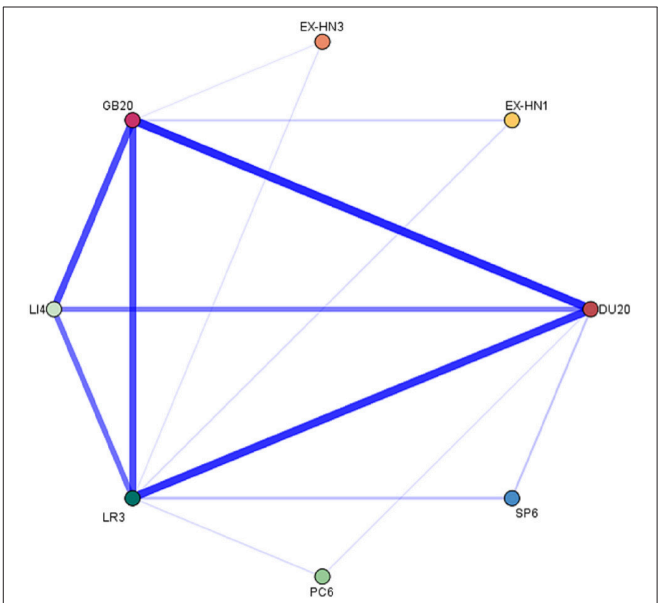

FIGURE 10 | Acupoints association network of acupuncture for TS treatment.

{Bai-hui (DU20)} (Conf 92.41, Supt 50.69, Lift 1.36), {San-yin-jiao (SP6)} ≥ {Tai-chong (LR3)} (Conf 100.00, Supt 33.33, Lift 1.45), and {San-yin-jiao (SP6)} ≥ {Bai-hui (DU20)} (Conf 95.83, Supt 31.94, Lift 1.25).

According to our study, additional acupoints were often used in the TS treatment with tic symptoms in different parts of the body. Forty-two prescriptions were used for facial tics (including frowning, blinking, nose shrugging, pouting, corner of mouth twitching, and drooling), 12 for vocal tics (including roaring and laryngeal ringing), 12 for limb tics, nine for accompanying mental symptoms (including inattention, poor sleep, and irritability), nine for neck tics (including head shaking, shoulder shrugging, and neck twitching), and two for abdominal tics. The acupoints often selected for facial tics were Di-cang (ST4), Tai-yang (EX-HN5), Ying-xiang (LI20), Jia-che (ST6), and Yin-tang (EX-HN3), with Stomach Meridian as the main meridian. When twitching of the limbs occurred, Jian-yu (LI15), Wai-guan (SJ5), and Feng-long (ST40) were often used, with Large Intestine Meridian as the main choice. Lian-quan (RN23) was often used when vocal tics were present. When mental symptoms were also present, Shen-men (HT7) and Nei-guan (PC6) were often selected. Tian-zhu (BL10), Ren-ying (ST9), and Lie-que (LU7) were often selected when neck tics occurred.

DISCUSSION

The overall quality of the 86 publications in this study was biased toward moderate to high risk, and 68 RCTs (93.2% of all RCTs) were deemed moderate to high risk of bias in outcome measures. The main reason is that acupuncture treatment is different from drug treatment. Additionally, achieving complete double-blindness in RCT studies is challenging. Most types of placebo acupuncture cannot make the experimenter single-blind, and most RCTs use drug control, making it impossible to achieve single blinding of subjects, resulting in a higher risk of bias in outcome measures due to unblinding. A moderate to high risk of bias in the randomization process was found in 17.8% of the studies because they used inappropriate allocation methods, such as allocation according to the order of patient visits, making the allocation concealment insufficient. The low risk percentages for bias in deviations from intended interventions and bias in missing outcome data were 93.1 and 95.8%, respectively. Thus, most of the patients showed good adherence to acupuncture treatment and completion of the treatment course; only a few studies had missing data results due to study withdrawal for reasons such as adverse reactions to control medications.

Only 1 of the 13 NRSIs was a retrospective study, and 92.3% had a low risk of bias in selecting participants. Additionally, all the subjects in the 13 NRSIs showed good compliance, and no omission of clinical data or selective reporting occurred. The overall risk of bias was low and medium, representing a good reference value. However, this study had many limitations. For example, six NRSIs, accounting for 46.2% of all NRSIs, were associated with confounding biases such as traditional Chinese medicine, and all NRSIs were self-control studies before and after. Differences in different individuals and stages of the same individual may have affected the study findings. Therefore, the control of confounding bias in clinical research must be further improved. Additionally, the use of blinding was not clarified in any of the NRSI outcome measures; thus, the bias in the outcome measures was evaluated as medium risk. Some clinical studies had certain flaws in the initial design; thus, the rigor of clinical study protocol design must be improved.

The evaluation of the efficacy of acupuncture clinical trials is closely related to the process of acupuncture treatment, which includes the selection and combination of acupoints, interventions and treatment protocols. The selection and combination of acupuncture points are based on channel diagnostics and the syndrome differentiation of channel theory. Therefore, the use of data mining techniques to analyze the use of acupuncture points in clinical trials of acupuncture helps improve the treatment protocols in clinical and experimental studies of acupuncture for TDs and provides more effective options for acupuncture point selection and combination selection.

This study shows that the treatment of TDs emphasizes the main treatment principles and concepts of coordinating yin and yang, tonifying qi and blood, dispelling pathogenic wind and eliminating phlegm. It focuses on the use of the Bai-hui (DU20) and the Governor Vessel and on the selection of the crossing acupoint and the five Shu points. The choice of the distribution of acupoints focuses on the head and neck. The potential point combinations were Bai-hui (DU20), Nei-guan (PC6), and San-yin-jiao (SP6).

In this study, we used data mining to systematically summarize the prescriptions of acupuncture therapy for TD. The results show that Bai-hui (DU20) was the core acupoint used for TD treatment. Bai-hui (DU20) was one of the main acupoints of 76.26% of all prescriptions assessed in this study. It belongs to the Governor Vessel and is the intersection of the triple energizer meridian, gallbladder meridian, bladder meridian, and liver meridian. Therefore, it is also known as "san yang wu hui". Bai-hui (DU20) is located on the top of the head. TCM holds the opinion that "all yang channels converge overhead". Lingshu Jing, an ancient Chinese literature, indicates that all qi channels circulate in the head and enter the brain. According to this theory, acupuncture at Bai-hui (DU20) can mobilize the Qi of the whole body into the brain. Several studies have demonstrated that the onset of TD is associated with decreased dopamine levels due to striatal dopaminergic neuronal hyperactivity or postsynaptic dopamine receptor hypersensitivity (9, 10). In contrast, acupuncture in Bai-hui significantly inhibited the expression of dopamine receptors in the striatum and substantia nigra by modulating the dopamine system in the striatum, substantia nigra, and prefrontal cortex to control tics (11).

Another commonly used point was Feng-chi (GB20), with a total frequency of 154. Feng-chi (GB20) belongs to the bile meridian and is located under the occipital bone, flush with Feng-fu (GU16), between the sternocleidomastoid and oblique muscles, 1 inch into the hairline. Feng-chi (GB20) is anatomically located at the projection of the vertebral artery on the body surface. Stimulation of the neck muscles by acupuncture with Feng-chi (GB20) improves blood supply to the vertebral-base artery system and accelerates blood flow to the brain, achieving the effect of improving blood supply to the brain. It is now believed that there is a correlation between the onset of TD and reduced 5-HT and that acupuncture with Feng-chi (GB20) can increase central 5-HT levels and reduce the release of 5-HT in peripheral blood.

According to TCM theory, the twitching symptom in TD is considered to be tendon injury (12), and tendons are closely related to the liver and involve the remaining four organs. In the Su Wen, it is believed that yang qi can replenish shen qi and nourish tendons and that the Governor Vessel is the master of the yang vessel. Therefore, all muscles along twelve regular channels need to be warmed and pushed through the yang qi of the Governor Vessel to function. In our study, the Governor Vessel was also the most frequently used meridian. It travels along the posterior midline of the human body, borders the Conception Vessel and closely connects to all the zang-fu organs. At the same time, it regulates the yin and yang qi and blood of the whole body. The Great Compendium of Acupuncture and Moxibustion documents that the Governor Vessel crosses the top of the head and enters the brain. Therefore, it can be assumed that the Governor Vessel has a therapeutic effect on brain diseases, especially in patients who also have mental disorders. Therefore, we believe that the use of the Governor Vessel meridian has a therapeutic effect on brain disorders, which has a positive effect on TD patients with concomitant mental disorders.

In addition, the crossing acupoints, including Bai-hui (DU20), Feng-chi (GB20), and San-yin-jiao (SP6), are specific acupoints commonly used in the treatment of TDs, accounting for 44.6% of the total frequency of acupoints. The crossing acupoint is the acupuncture point where the meridians meet, which can take all the main functions of the intersecting meridians. The crossing acupoints selected in this study mostly intersect with the Governor Vessel and the gallbladder meridians. According to this result, it can also be reverified that acupuncture treatment for TDs attaches importance to the Governor Vessel. The top 3 acupoints of the crossing acupoint were Bai-hui (DU20), Feng-chi (GB20), and San-yin-jiao (SP6). We identified these three acupoints as the most commonly used acupoint combinations in TD treatment by using association rule mining techniques. Feng-chi (GB20) belongs to the gallbladder meridian, which intersects with the triple energizer meridian and the Yang Heel Vessel. It is on the posterior side of the head, located in the depression between the bilateral sternocleidomastoid muscles and the trapezius muscles. It treats muscle twitches of the head and improves blood circulation in the brain. San-yin-jiao (SP6) is the place where qi and blood substances meet in the three yin meridians of the foot, which can strengthen the spleen and blood and tonify the liver and kidneys. After the crossing acupoint, the five Shu points have the highest frequency of application. The top 3 acupoints were Tai-chong (LR3), Shen-men (HT7), and the Yuan-Source acupoint of the liver meridian and the heart meridian. The original qi of the internal organs starts from the kidney and is injected into five zang organs and six fu organs through Sanjiao. The Yuan-Source acupoint is the node through which the original qi of the organs passes and remains. Therefore, it can be used to treat the disease of the corresponding organs. TCM considers that liver lesions cause TD, and the heart, spleen and kidneys are also affected. Choosing the corresponding yuan primary points can replenish the qi of the organs.

From the study, acupuncture treatment of TD mainly uses acupoint sites in the head and neck. On the one hand, acupuncture at points of the head will stimulate the corresponding functional areas of the brain, which can improve blood circulation in the brain, improve the oxygen carrying capacity of brain cells, and finally promote the repair of neuronal cells (13). Stimuli of the thalamus and the globus pallidus are effective in controlling twitching episodes (14). Nerve fibers emanating from the thalamus project to the frontal and parietal cortices of the brain. This coincides with the findings of our study. On the other hand, ∼58% of TD patients have recurrent neck twitches (15). Repeated hard stretching of the neck in jerks can lead to spinal cord damage. Therefore, TD patients are more likely to suffer from cervical spine disorders than the general population (16). Studies have demonstrated that TD affects the medulla oblongata and has a high potential for subsequent progression to severe cervical spondylosis (17–21). In addition to head acupuncture points, our study indicated that neck acupoints such as Feng-chi (GB20) and Da-zhi (DU14) were also used. We believe that acupuncture of the neck may have a better effect in regulating the action of the medulla oblongata and blocking the progression of TDs.

By using a clustering algorithm, 24 acupoints with a frequency >20 were clustered into six major clusters, signifying the main treatment principles and concepts of coordinating yin and yang, tonifying qi and blood, dispelling pathogenic wind and eliminating phlegm.

The TCM pathogenesis of TDs has been summarized by some scholars (22). TCM distinguishes two general pathogeneses of TD, a "deficiency" pathogenesis and an "excess" pathogenesis. The former appears in TD as an imbalance in qi, blood, yin and yang due to the weakening of the five zang organs and six fu organs. The other one occurs in TDs caused by wind-phlegm, which causes tendon injuries and weakness of yin and yang. The wind-phlegm is twisted and reaches the head and face, flies to the limbs, and migrates to the airway. Thus, TDs manifest as facial muscle twitching, limb twitching, mouth salivation and others. According to the above article, the pathogenesis of TD is mainly the deficiency of the five zang organs, imbalance of yin and yang, and wind-phlegm strangulation, matching the treatment direction we have concluded. Thus, acupoint Cluster 1, Nei-guan (PC6), Shen-men (HT7), San-yin-jiao (SP6), Zu-san-li (ST36), Zhong-wan (RN12), Bai-hui (DU20), Tai-yang (EX-HN5), and Qu-chi (LI11), and Cluster 6, Gan-shu (BL18) and Pi-shu (BL20), were chosen to invigorate the heart, liver and spleen, benefit both qi and blood and achieve the effect of dispelling wind-evil. Cluster 2, Feng-chi (GB20), Hei-gu (LI4), Tai-chong (LR3), Lian-quan (RN23) and Yin-tang (EX-HN3), was used to dispel pathogenic wind for resolving convulsions. Cluster 3, Zhaohai- (KI6) and Feng-long (ST40), and Cluster 5, Di-cang (ST4) and Tai-xi (KI3), were used to invigorate the spleen and kidney and dissipate phlegm. Cluster 4, Da-zhui (DU14), Feng-fu (DU16), Si-shen-cong (EX-HN1), Shen-ting (DU24), and Ying-xiang (LI20), was used to coordinate yin and yang and draw qi and blood into the brain.

Network diagrams derived from association rule mining analysis yielded the core acupuncture points with the strongest associations, which revealed potentially effective acupoint prescriptions for TD treatment; these points were Bai-hui (DU20), Si-shen-cong (EX-HN1), Feng-chi (GB20), Nei-guan (PC6), Shen-men (HT7), He-gu (LI4), Zu-san-li (ST36), San-yin-jiao (SP6), and Tai-chong (LR3) (**Figure 8**).

We used association rule mining technology to identify the most commonly used combinations of acupuncture points for the treatment of TDs. The core group is Bai-hui (DU20), Nei-guan (PC6), and San-yin-jiao (SP6). As mentioned earlier, TCM considers the deficiency of the five zang organs and the imbalance of yin and yang as the mechanism of TD attacks. Nei-guan (PC6) is the Luo-connecting point of the pericardium meridian, and it is also one of the eight influential acupoints. It is connected to the Yin Link Vessel. It has the function of nourishing blood and resolving stagnation for tranquilization. San-yin-jiao (SP6) belongs to the spleen meridian. It tonifies the spleen and kidneys and the innate deficiency. Experimental studies have shown that acupuncture with Nei-guan (PC6) and Shui-gou (DU26) protects neuronal cells by reducing the abnormally elevated mRNA expression of IL-1RI and TNFR-I in brain tissue (23). Acupuncture with Nei-guan (PC6), Shui-gou (DU26), and San-yin-jiao (SP6) improves the reperfusion function of the brain and reduces the occurrence of neuronal cell apoptosis (24). Therefore, we believe that the combined use of Nei-guan (PC6) and San-yin-jiao (SP6) regulates the flow of qi and blood in the body.

When paired with Bai-hui (DU20), they combine yin and yang to harmonize qi and blood. However, a three-acupoint combination was seldom used as the prescription in the treatment of TDs. We therefore conclude that acupoint prescriptions for the treatment of TDs often consist of different combinations of commonly used acupoints on commonly used meridians.

Only five trials explicitly included only participants in the short-term disease course, while others included participants in both the short- and long-term disease course. Participants with a disease course of 0–5 years accounted for 61.63% of the trials, and participants with a disease course >5 years numbered fewer than those with a disease course of <5 years. This finding might be related to the benign prognosis of TD patients who usually have symptoms that gradually lessen after puberty. Although we have not found strong evidence that the earlier is the treatment, the better is the effect, a few trials suggest that acupuncture with a short-erm disease course is more effective than that with a long-term disease course.

The TS trials accounted for 55.81% of all trials. The core acupoint prescription of TS treatment with the strongest correlation included He-gu (LI4), Feng-chi (GB20), Tai-chong (LR3), Bai-hui (DU20), Yin-tang (EX-HN3), Si-shen-cong (EX-HN1), San-yin-jiao (SP6), and Nei-guan (PC6), which is essentially the same as the core acupuncture point prescription for TD treatment. Yin-tang (EX-HN3) is a new core point that is also the most frequently used point when facial tics occur. It is located in the center of the eyebrow and belongs to the Governor Vessel, which is considered by TCM to induce resuscitation. Unlike TD treatment, its core group includes He-gu (LI4) and Feng-chi (GB20). He-gu (LI4) is the Yuan-Source acupoint of the large intestine meridian, where the qi and blood gather. In TCM theory, the large intestine meridian is also considered a meridian rich in qi and blood; therefore, He-gu (LI4) significantly affects the body's regulation of qi and blood throughout the body and its combination with Feng-chi (GB20) is ideal.

As mentioned previously, the clinical picture of TS is complex and varied, with both motor and vocal tics occurring during the disease course. TS treatment was often used with specific additional acupoints at different local sites where tics occur. For example, the most commonly used additional acupoint for facial tics is Di-cang (ST4). Acupuncture Di-cang (ST4) raises precentral gyrus and postcentral gyrus signals (25) and may achieve the effect of controlling the motor sensation of the face. Lian-quan (RN23) is often used for vocal tics. It is located between the thyroid cartilage and hyoid bone. Its deep part comprises branches of the sublingual nerve and swallowing nerve. Studies have reported that acupuncture with Lian-quan (RN23) stimulates the laryngeal muscles (26), which may control vocal tics to some extent. The acupoint in the human being has two functional states—sensitization state and rest state. When the human body has disease, the acupoints on the surface of the body will be sensitized. When the sensitized acupoints are stimulated externally, they trigger larger internal stimulation (27) and may reflect the significance of local acupuncture at the location where the tics occur. In summary, TS treatment is often performed with proximal points in the selection of additional acupuncture points.

LIMITATIONS

The present study has several limitations that need to be considered. First, the methodological quality of the included studies was relatively low. This is because it is extremely difficult to achieve complete double-blindness for acupuncture treatment and sufficient concealment of treatment allocation, resulting in incomplete outcome data. Some studies utilized treatment groups that combined other treatments, such as head and hand acupuncture, all of which led to potentially biased efficacy results. More rigorous clinical studies of acupuncture for TD need to be developed in the future to improve the quality of evidence. Second, all trials included participants with at least two levels of severity and did not delineate these levels more carefully, and most trials did not make a careful distinction in the selection of the timing of the intervention. Thus, further studies are required. Third, the more common criteria to evaluate the efficacy of this disease are mainly based on rating scales such as the YGTSS score, which are subjective, possibly leading to biased results. More objective indicators of acupuncture for TD will be needed in the future to enhance the quality of the evidence. Finally, the potential prescriptions extracted through data mining are the result of data integration. Further animal experiments and clinical trials are still needed to verify whether these prescriptions are practical and feasible.

CONCLUSION

In summary, the current study investigated the potential acupoints and combinations for TD treatment based on a data mining analysis of published studies. Bai-hui (DU20), Feng-chi (GB20), Tai-chong (LR3), He-gu (LI4), and San-yin-jiao (SP6) appeared to be the most frequently used acupoints for TD treatment. The Governor Vessel was the more commonly selected meridian, which demonstrates a significant role in the treatment of TD. Additionally, the selection of the crossing acupoint and the five Shu points was found to be important. The selection of acupuncture points focused on the head. Cluster analysis indicated the treatment principle of harmonizing yin and yang, tonifying qi and blood, dispelling wind and resolving phlegm. The potentially effective acupoint prescriptions were revealed by a network analysis. There were Bai-hui (DU20), Si-shen-cong (EX-HN1), Feng-chi (GB20), Nei-guan (PC6), Shen-men (HT7), He-gu (LI4), Zu-san-li (ST36), San-yin-jiao (SP6), and Tai-chong (LR3). Association rule mining demonstrated that the combination of Bai-hui (DU20) + Nei-guan (PC6) and San-yin-jiao (SP6) was a potential acupoint combination that should be selected with priority in TD treatment. The core acupoint prescription of TS treatment comprised He-gu (LI4), Feng-chi (GB20), Tai-chong (LR3), Bai-hui (DU20), Yin-tang (EX-HN3), Si-shen-cong (EX-HN1), San-yin-jiao (SP6), and Nei-guan (PC6). The core group comprised He-gu (LI4) and Feng-chi (GB20). Additionally, the treatment is often performed with proximal points in the selection of additional acupuncture points. Overall, this study provides valuable

information for the selection of acupoints for the clinical acupuncture treatment of TDs.

AUTHOR'S NOTE

Data mining is a technology that has emerged in recent years with the development of the Web, artificial intelligence, and database technology. It is used to conditionally filter out valid and credible information from abundant random source data and derive regular and potential information after advanced processing to achieve efficient learning. Tic disorders are neuropsychiatric disorders occurring primarily in children and adolescents. They can cause physical and psychological harm to the patient. The relationship between the efficacy of the clinical acupuncture treatment of tic disorders and the acupuncture treatment process and the selection and combination of acupoints based on meridian and acupoint theory must be evaluated. The volume of literature on acupuncture for treating tic disorders has been increasing recently. Using data mining techniques to analyze the use of acupuncture points in the clinical treatment of tic disorders and to explore the potential patterns may enable the selection of more effective acupuncture points and combination protocols for the clinical acupuncture treatment of tic disorders and provide new therapeutic ideas.

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

JC analyzed and visualized the data and wrote the original manuscript. YX conceived and designed the study protocol and wrote the original manuscript. QL was involved in the visualization of the data. QL, WC, and YW searched the articles and screened the eligible literature. YC and ZG extracted the data. JZ was involved in the revision of the manuscript. ZQ and JF were responsible for the review process and participated in the critical revision of the manuscript. All the authors read and approved the final manuscript.

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Effects of Acupuncture in Ischemic Stroke Rehabilitation: A Randomized Controlled Trial

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Background: Acupuncture is a well-known treatment option for ischemic stroke recovery, but evidence of its effectiveness remains limited. This is a randomized controlled trial to evaluate the effectiveness of acupuncture treatment for ischemic stroke rehabilitation.

Methods: Rehabilitation training was provided to the control group. In acupuncture arm 1, these acupoints were derived from the ancient books, including GV20 (*baihui*), GV26 (*shuigou*), PC9 (*zhongchong*), ST6 (*jiache*), ST4 (*dicang*), LI15 (*jianyu*), LI11 (*quchi*), LI4 (*hegu*), GB30 (*huantiao*), GB31 (*fengshi*), GB34 (*yanglingquan*), and GB39 (*xuanzhong*). In acupuncture arm 2, the acupoints used were GV20 (*baihui*), PC6 (*neiguan*), LI11 (*quchi*), LI10 (*shousanli*), SJ5 (*waiguan*), LI4 (*hegu*), GB30 (*huantiao*), ST36 (*zusanli*), GB34 (*yanglingquan*), SP6 (*sanyinjiao*), ST41 (*jiexi*), and LR3 (*taichong*), which were extracted from *Acupuncture and Moxibustion Science*. After acupuncture, the needles were left in for 30 min and manually manipulated every 10 min. The three groups received treatment once a day, 5 times a week for 2 weeks. The primary outcome was the National Institutes of Health Stroke Scale (NIHSS), and the secondary outcomes were the Barthel Index (BI) and the Modified Ashworth Scale (MAS). Outcomes were measured in patients both before and after treatment.

Results: A total of 497 patients with ischemic stroke were randomized into either arm 1 (159 cases), arm 2 (173 cases), or the control group (165 cases). After 2 weeks of treatment, the NIHSS scores for arm 1 were lower than those of the control group ($P = 0.017$); the BI scores were higher in arm two than that in the control group at T2 ($P = 0.016$) and follow-up ($P = 0.020$). Additionally, there was no significant difference between arm one and the control group for either the BI scores or the MAS scores ($P > 0.05$) and no significant difference between arm two and the control group for the MAS scores or the NIHSS scores ($P > 0.05$).

Conclusion: The clinical efficacy of arm 1 and arm 2 (acupuncture groups) was superior to that of the control group, but there was no difference between the effects of the two acupuncture groups.

Clinical Trial Registration: http://www.chictr.org.cn/index.aspx, identifier: ChiCTR-IOR-16008627.

Keywords: acupuncture, ischemic stroke, randomized controlled trial (RCT), rehabilitation, clinical trial

BACKGROUND

Stroke is widespread around the world. According to recent reports (1–3) the incidence of stroke in China is 274–379 per 100,000 people, of which ischemic stroke accounts for 60–70%. Three-fourths of stroke survivors are left with disability of varying degrees and about 40% are severely disabled. In China, the care for patients with stroke imposes heavy economic burdens on both the state and many families.

Ischemic stroke is the common term for cerebral infarction, which disrupts cerebral artery blood flow through several pathways, such as cerebral arteriosclerosis or cerebral artery thrombosis, causing hypoxia and ischemic necrosis in local brain tissue. This results in corresponding neurologic deficits (4). The clinical manifestations of ischemic stroke are focal neurological deficits such as hemiplegia, aphasia, dysphagia, visual impairment, and mental disturbances. Ultra-early thrombolysis has been used widely in the acute phase of stroke. However, due to its time-restricted application, the probability of thrombolysis is only 2.4% (5). This leaves intravenous or oral medications, rehabilitation training, and prevention of complications as the primary treatment measures for most patients with stroke.

Acupuncture has been used for the treatment of stroke since ancient times. The stroke symptoms and acupoints were recorded in the earliest Chinese medicine canon named the Yellow Emperor's Inner Classics (Huang-Di-Nei-Jing in Chinese), while the syndrome differentiation of stroke and its treatment were described in the Comprehensive Achievements of Acupuncture and Moxibustion (Zhen-Jiu-Da-Cheng in Chinese). This provides a theoretical basis for the treatment of apoplexy by acupuncture. At present, new acupuncture theories and techniques are still being developed. These include body acupuncture, scalp acupuncture, electrical acupuncture, and eye acupuncture. Effective treatment is dependent on the proper choice of acupuncture points. The acupoints in this study were selected based on ancient literature and Acupuncture and Moxibustion Science (6). They were chosen because of their wide application, frequent use, and direct curative effect. These acupoints possess the following characteristics: they are connected to the yang meridians. The Du Meridian, the Large Intestine Meridian, the Stomach Meridian, and the Gallbladder Meridian are the most relevant yang meridians in this regard. Since GV20 is the meeting of various yang meridians, it is the most frequently selected acupoint, which has the effect of awakening the brain and pacifying the spirit (Xingnaoanshen) and expelling wind to open the orifices (Qufengkaiqiao) (7). The Stomach Meridian and the Large Intestine Meridian have the functions of harmonizing Qi and blood and relieving limbs and joints. The Gallbladder Meridian is related to tendons and has the function of stimulating the circulation of the blood and relaxing the muscles and joints. In Chinese medicine, yin and yang balance is important to maintain the physiological equilibrium of the human body. The acupoints on the yang meridians have the effect of replenishing yang qi. However, patient with apoplexy often shows symptoms such as paralysis and aphasia that belong to Yin syndrome. This is in line with the viewpoint of treating yin disease with Yang. The other feature of the selected acupoints in this study is that they have a unique therapeutic effect and a specific name. The main ones are the convergence points (Jiao-hui-xue) and the He acupoints, in which Jiao-hui acupoints enable the Qi and blood of meridians to communicate with each other for the treatment of the disease of intersecting meridians. The He acupoint is one of the five Shu points (Wu-shu-xue) and it is the acupoint with the greatest Qi and blood. Therefore, it is easier to mobilize Qi and blood in the treatment of apoplexy by needling such acupoints. This provides a sound theoretical basis for effective stroke treatment (8–10). However, acupuncture's clinical efficacy needs further validation in clinical trials.

A prospective randomized controlled trial was conducted to explore an effective scheme for acupuncture treatment of ischemic stroke and to provide scientific evidence for the effectiveness of acupuncture for stroke rehabilitation.

METHODS

Settings and Subjects

This study was a randomized controlled trial, conducted by the Affiliated TCM Hospital of Guangzhou Medical University, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, and the Liwan District Hospital of Chinese Medicine. In this study, patients were randomly divided into three groups: the ancient books acupoint group (treatment group 1), the modern literature acupoint group (treatment group 2), and the rehabilitation group (control group). The random assignment operation was completed by the personnel of the Key Research Laboratory of Clinical Research Methodology of Guangdong Hospital of traditional Chinese medicine using SAS version 9.2 software. At the same time, the personnel responsible for the efficacy evaluation will be hired separately and will not know the grouping of patients. The personnel for the final data analysis will also be hired separately and will not participate in the specific clinical implementation work and design scheme of the subject. Doctors and patients are aware of the study interventions. The study reporting was in compliance with the requirements of the CONSORT 2010 statement (11).

Abbreviations: NIHSS, National institutes of Health Stroke Scale; BI, Barthel index; MAS, Modified Ashworth Scale; STRICTA, Reporting Interventions in Clinical Trials of Acupuncture; WHO, World Health Organization.

Patients were randomly divided into arm 1, arm 2, or the control group. The randomization was performed by personnel from the Key Research Laboratory of Clinical Research Methodology at the Guangdong Provincial Hospital of Chinese Medicine. SAS version 9.2 was used to complete the randomization. The trials were single-blind as the outcome evaluators and data analysts were unaware of the groupings. Neither patients nor the acupuncturists performing the interventions were blinded. To avoid bias, individuals responsible for the evaluation of the efficacy were hired separately and were unaware of patient groupings. Analysts did not participate in the clinical procedure or the design of the project. The control group used the basic treatment plan, including baseline medications and rehabilitation training.

The trial was conducted between July 2016 and July 2017 and patients who met the following criteria were included in this study:

(1) Diagnosed with the ischemic cerebrovascular disease by either CT or MRI (12);
(2) With a period of 2 weeks to 12 months after acute stroke;
(3) With a number of strokes $\leq$3;
(4) Aged between 40 and 75 years (men or women); and
(5) Had clear cognitive faculties, stable vital signs, no obvious dementia, no obvious hearing impairment, and ability to cooperate with rehabilitation training.

Exclusion criteria were those patients who:

(1) Had already received other treatments that were not part of this study plan;
(2) Suffered from transient ischemic attack or reversible ischemic neurological deficit (RIND);
(3) Had neurological deficit, which was not related to ischemic stroke;
(4) Suffered from mental disorders or other severe diseases;
(5) Had severe aphasia, sleep apnea, deafness, or severe cognitive impairment;
(6) Patients with severe heart, liver, kidney, and other important organ diseases;
(7) Those with diabetes or endocrine diseases. Complicated with serious lesions of important organs;
(8) Before onset, there are malnutrition diseases, intestinal diseases, or stress ulcers with bleeding; and
(9) Those who are unwilling to participate in this study or withdraw from this study.

Treatment Process

The standards of this study met the requirements of the *Standards for Reporting Interventions in Clinical Trials of Acupuncture* (STRICTA) 2010 (13). Ethics approvals were obtained from the Ethics Committee of the Guangzhou Chinese Medicine Hospital, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, and the Liwan District Chinese Medicine Hospital (Reference no. 2016NK001) before conducting this study. All the patients also received rehabilitation training (12–14). Rehabilitation training followed the guidelines of the *Rehabilitation Treatment Guide 2011 of Stoke in China* (15) and *Practical Rehabilitation* (16). The members of the rehabilitation team examined the patient to determine the nature and extent of the disorder. The rehabilitation team also held review meetings to integrate patient care, formulate a rehabilitation plan, and implement treatment. According to the specific conditions of patients, they were trained to sit, balance, stand, shift their center of gravity, walk, feed themselves, change clothes, or go to the bathroom. They also received systemic coordination training, which included balancing, practical walking, using a walking stick, and going upstairs and downstairs.

Acupoints

The optimal acupoint scheme for this test was determined based on a consensus of acupuncture experts and *Acupuncture and Moxibustion Science* (17). Treatment for arm 1 was based on an acupoint summary from ancient literature (18, 19) and treatment for arm 2 followed the composition of the acupuncture points in the textbook. The most frequently used twelve acupoints in the ancient books and *Acupuncture and Moxibustion Science* were determined based on the consensus of acupuncture experts. In arm 1, these acupoints included GV20 (*baihui*), GV26 (*shuigou*), PC9 (*zhongchong*), ST6 (*jiache*), ST4 (*dicang*), LI15 (*jianyu*), LI11 (*quchi*), LI4 (*hegu*), GB30 (*huantiao*), GB31 (*fengshi*), GB34 (*yanglingquan*), and GB39 (*xuanzhong*). In arm 2, the acupoints used were GV20 (*baihui*), PC6 (*neiguan*), LI11 (*quchi*), LI10 (*shousanli*), SJ5 (*waiguan*), LI4 (*hegu*), GB30 (*huantiao*), ST36 (*zusanli*), GB34 (*yanglingquan*), SP6 (*sanyinjiao*), ST41 (*jiexi*), and LR3 (*taichong*). Bilateral acupoints were needled on PC9 and PC6, while all the remaining acupoints were selected from the affected side.

Acupuncture Intervention

The acupuncture treatment was performed by 16 different acupuncturists (with between 2 and 7 years of experience) at three different hospitals. Seven of the acupuncturists had Bachelor's level education, six had Master's degrees, and three had doctorates and all of them were registered Chinese medicine practitioners in China. All the researchers and acupuncturists were required to undergo a 4-day training session before the trial.

Appropriate positioning of the needles is crucial to obtaining good acupuncture results. Patients in this study were asked to lie in a lateral position with the affected side facing up. The hemiplegic shoulder stretched forward, with the shoulder joint flexed at 90° and the paraplegic upper limb resting on a pillow at a 100° angle to the trunk. The elbow was straightened, with arm, wrist, and fingers extended and palm facing up. Next, the paraplegic side of the lower extremity was placed on the pillow, revealing a step-like shape (with hips and knees flexed). The disposable sterile acupuncture needles used had varying specifications (0.30 mm × 25 mm, 0.30 mm × 40 mm, 0.30 mm × 50 mm, or 0.30 mm × 75 mm). Conventional disinfection with 75% alcohol was employed after acupuncture point positioning in accordance with *Standard Acupuncture and Moxibustion Positioning by the WHO* (20). During the acupuncture session, patients would feel soreness, numbness, distension or heaviness around the point, or an electric shock feeling during needling, indicating effective needling. To stimulate needle sensation, the

needles were inserted flat and backward, 25 mm into DU20, and 8–15 mm obliquely and upward into DU26. Then, a reducing method was used for 30 s, rotating at a small amplitude and high frequency. The other acupoints utilized the reinforcing-reducing method 2.5 mm deep into PC9; 15–20 mm vertically into ST6, ST4, GB39, ST41, and LR3; 15–25 mm perpendicularly into LI4, PC6, and SJ5; 25–40 mm obliquely and downward into LI15; 25–40 mm perpendicularly into LI11, GB34, GB31, LI10, ST36, and SP6; and 50–70 mm perpendicularly into GB30. After insertion, the needles were left *in situ* for 30 min. The course of treatment was five times a week for consecutive 2 weeks. All the necessary precautions were taken to prevent any adverse events that occurred during treatment (e.g., fainting and broken needles). All the adverse events were recorded.

Control Intervention

The control group used the basic treatment plan, including baseline medications and rehabilitation training. The rehabilitation plan is mainly determined by the rehabilitation team.

Outcomes

The treatment effect of this trial was evaluated by three scales at different time points (baseline = T0, week 1 = T1, week 2 = T2, and follow-up = T4). The primary outcome was expressed using the National Institutes of Health Stroke Scale (NIHSS). It ranged from 0 to 40 and included 11 items: consciousness, limb movement, eye movement, vision, facial paralysis, feeling, language, dysarthria, and neglect. It also measured the improvement in neurological function of patients (i.e., the lower the score, the lesser the patient's neurological deficit). The secondary outcomes were the Barthel Index (BI) scale and the Modified Ashworth Scale (MAS). The BI scale is typically used to assess patient self-care ability and if the score is below 20, this means that the patient's self-care ability had been seriously impaired. A score of over 60 indicated patients had been able to care for themselves. The improvement and difference in muscle tension within the three groups were determined by the changes in the Modified Ashworth Scale, both before and after treatment—the higher the score, the higher the patient's muscle tone. Since returning to the hospital after discharge is not an easy task for patients with stroke, only BI data for these three observations could be obtained in a remote setting such as a telephone conversation. Thus, only BI was measured four times.

Sample Size

Referring to previous studies (21, 22),after 15 days of treatment, the NIHSS score variances before and after treatment for simple stroke rehabilitation was-3.95 ± 4.05, for acupuncture combined with rehabilitation was -6.07 ± 3.99, and for another acupuncture group combined with rehabilitation was -5.93 ± 4.08. Setting α to 0.05, β to 0.1, and substituting the sample size formulae of one-way ANOVA, the results showed that 76 patients were necessary for each group to complete the trial. Considering the similar curative effect between the two treatment groups, the two treatment groups need to be compared with the control group separately. According to Zhou (21), after 15 days of treatment, the NIHSS score for simple stroke rehabilitation was 8.86 ± 3.15 and the NIHSS score for acupuncture combined with stroke rehabilitation was 7.54 ± 2.68. Setting α to 0.05, β to 0.1, and substituting the sample size formulae of the two independent samples *t*-test, the results showed that 105 patients were necessary for each group to complete the trial. Assuming a 20% dropout rate per group, each group was adjusted to 126, with a total of about 378 patients. Finally, we determined that a sample size of at least 378 can better meet the statistical requirements.

Statistical Analysis

An intention-to-treat (ITT) population was surveyed before the analyses, which included those patients undergoing baseline assessment and at least one evaluation after treatment. The NIHSS, the BI, and the MAS scores, along with changes over time, were compared by using repeated measures designed for the three groups. We also employed ANOVA to define the among-group differences at each measurement time point. The chi-square test or Fisher's exact test was used to analyze categorical variables, including categorical baseline variables and incidence of adverse events. The last observation carried forward (LOCF) was used in the ITT analysis to address missing data due to attrition and shedding. Statistical significance was defined as a two-tailed $P < 0.05$. Statistical analysis was performed with PASW version 20.0 (IBM SPSS Incorporation, Armonk, New York, USA).

RESULTS

Baseline Data

Between July 2016 and July 2017, a total of 2,369 patients were assessed for eligibility. 497 of them participated in the trial (Guangzhou Hospital of Chinese Medicine = 200, First Affiliated Hospital of Guangzhou University of Chinese Medicine =247, and Liwan District Hospital of Chinese Medicine = 50). They were randomly divided into the three groups (arm 1 = 159, arm 2 = 173, and the control group = 165). Ten patients dropped out before the completion of the trial, six patients stopped treatment because of sudden serious diseases such as heart failure or lung infection, and three patients could not comply with the treatment schedule. One patient was lost due to a change in the contact phone number (**Figure 1**).

Table 1 shows the basic information for patients involved in this study, totaling 311 men and 186 women, all aged around 65 years. Most of the patients were not college-educated and most lived in urban areas. Twenty-five point eight percentage of patients had a history of smoking and 15.5% of patients had a history of moderate to heavy alcohol consumption. No statistical significance was found in the general variables (e.g., sex, age, education, and career) among the three groups. No statistically significant difference was found in ischemic stroke characteristics (disease course, number of strokes, infarct size, and family history, see **Table 2**).

Mean scores and changes in the NIHSS, the BI, and the MAS at different time points in the three study arms are shown in **Table 3**. In the statistical analysis of the above three items, no difference was found among the three groups in the repeat measurement design.

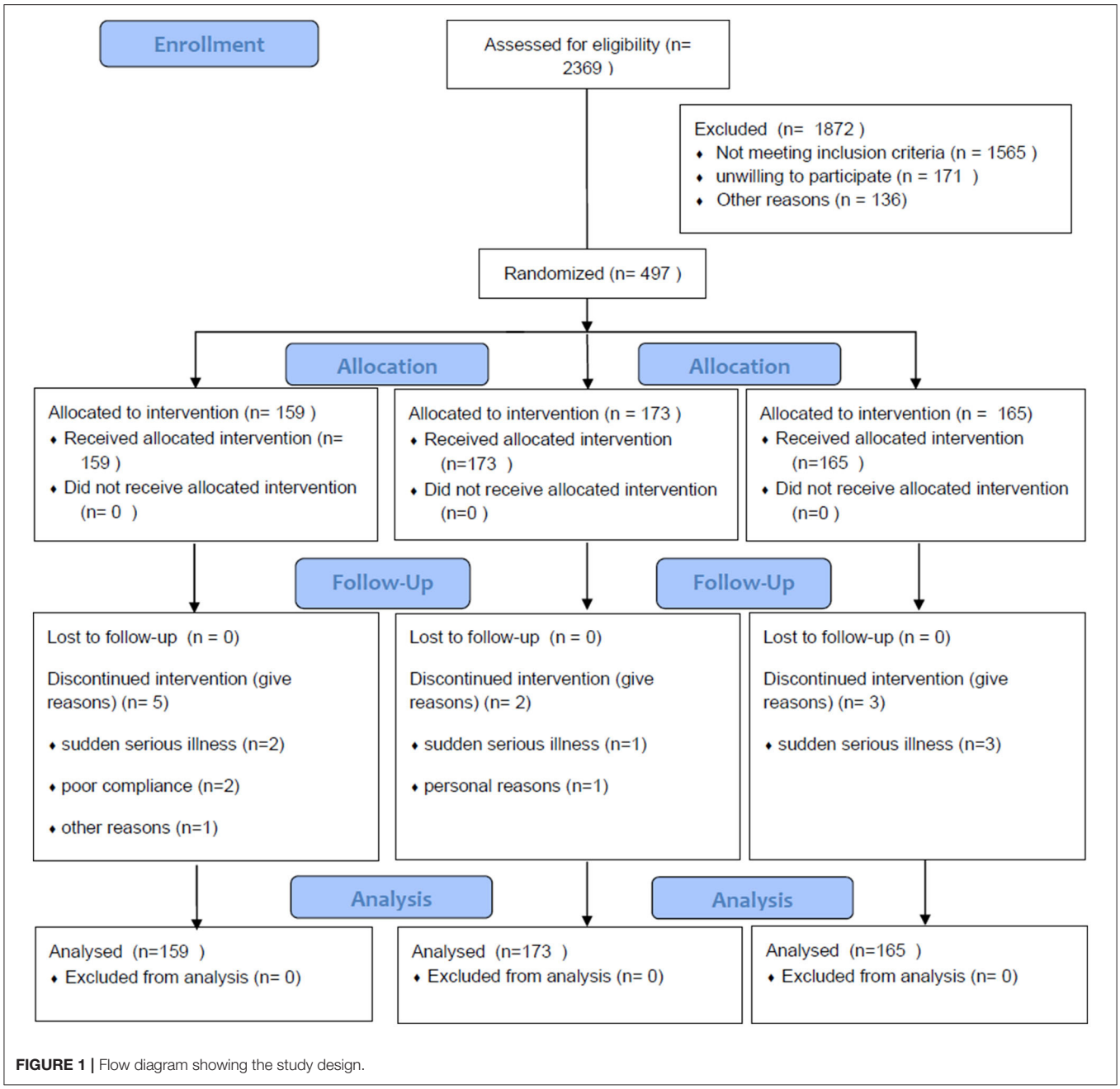

FIGURE 1 | Flow diagram showing the study design.

The NIHSS scores of the three groups at each time point were analyzed and the results showed no significant difference in the NIHSS scores, at either T0 or T1 ($P > 0.05$). However, the difference between the NIHSS scores at T2 was statistically significant ($P = 0.014$). Further between-group comparisons found that there was a statistically significant difference between arm 1 and the control group ($P = 0.017$). As shown in **Figure 2A**, the NIHSS score in arm 1 had the largest reduction.

During the treatment and follow-up period, the BI scores of the three groups were accentuated. ANOVA showed that there were no significant differences either at T0 or T1 ($P > 0.05$), while the difference between the BI scores at T2 and follow-up was statistically significant ($P = 0.014$ and $P = 0.017$). Between-group comparisons showed a statistically significant difference in the arm 2 BI scores at T2 ($P = 0.016$) and follow-up ($P = 0.020$). However, we found no other marked differences at other time points (see **Figure 2B**).

Although there was an obvious decrease in the MAS scores during the treatment period, no statistically significant difference across the three groups was found at any time point (see **Figure 2C**).

TABLE 1 | Baseline characteristics of patients ($n = 497$).

General information	Arm 1 ($n = 159$)	Arm 2 ($n = 173$)	Control group ($n = 165$)	Total
Sex				
Male	107(67.3)	107(61.8)	97(58.8)	311
Female	52 (32.7)	66(38.2)	68(41.2)	186
Age	64.3± 8.3	65.2 ± 8.5	65.4 ± 6.9	64.98 ± 0.3
Education				
Primary school or illiterate	31(19.5)	31(18.0)	36(22.0)	98(19.8)
Secondary school	53(33.3)	68(39.5)	62(37.8)	183(37.0)
High school	61(38.4)	61(35.5)	61(35.5)	176(35.6)
University	14(8.8)	12(7.0)	54(32.9)	38(7.7)
Master's or above	0(0)	0(0)	0(0)	0(0)
Career				
Office clerk	23(14.5)	23(13.3)	18(10.9)	64(12.9)
Manual worker	22(13.8)	27(15.6)	31(18.8)	80(16.1)
Student	0(0)	0(0)	0(0)	0(0)
Retired	84(52.8)	99(57.2)	87(52.7)	270(54.3)
Unemployed	11(6.9)	13(7.5)	12(7.3)	36(7.2)
Other	19(11.9)	11(6.4)	17(10.3)	47(9.5)
Residence				
Town	132(83.0)	150(86.7)	137(83.0)	419(84.3)
Village	27(17.0)	23(13.3)	28(17.0)	78(15.7)
Smoking				
None	114(71.7)	123(71.1)	132(80.0)	369(74.2)
Former smoker	31(19.5)	27(15.6)	20(12.1)	78(15.7)
Current smoker	14(8.8)	23(13.3)	13(7.9)	50(10.1)
Alcohol				
None	130(81.8)	151(87.3)	139(84.2)	420(84.5)
Former user	19(11.9)	13(7.5)	17(10.3)	49(9.9)
Current user	10(6.3)	9(5.2)	9(5.5)	28(5.6)

TABLE 2 | Ischemic stroke characteristics.

General information	Arm 1 ($n = 159$)	Arm 2 ($n = 173$)	Control group ($n = 165$)	F/ X^2	*P*
Disease course					
Month	3.49 ± 3.11	4.12 ± 4.10	3.83 ± 3.25	1.097	0.335
Times of stroke	1.26 ± 0.53	1.25 ± 0.44	1.28 ± 0.50	0.134	0.857
Infarct size					
Lacunar	28(17.7)	29(17.8)	45(27.4)	6.467	0.373
Multiple	81(51.3)	87(53.4)	78(47.6)		
Large area	16(10.1)	15(9.2)	13(7.9)		
Other	33(20.9)	32(19.6)	28(17.1)		
Family history of stroke					
No	129(81.1)	134(77.9)	123(74.5)	4.635	0.324
Unknown	26(16.4)	36(20.9)	35(21.2)		
Yes	4(2.5)	2(1.2)	7(4.2)		

SAFETY ASSESSMENT

Over the course of acupuncture treatment for the three groups, there were no obvious changes in blood counts, routine urine tests, liver function, renal function, or heart enzymes. There were 5 adverse events in arm 1, 7 adverse events in arm 2, and no adverse events in the control group. Of these adverse events, nine were cases of bleeding, and three were cases of sticking of the needle. We stopped the bleeding by applying pressure with a sterile swab for 10 s and gently poking

TABLE 3 | Scores and changes for the National Institutes of Health Stroke Scale (NIHSS), the Barthel Index (BI), and the Modified Ashworth Scale (MAS) in the three study arms (x ± SD).

	Group	T0=baseline	T1 = 1 week	T2 = 2 weeks	Follow up = 4 weeks
NIHSS	Arm 1	7.13 ± 4.91	5.98 ± 3.72	4.59 ± 3.47[ab]	
	Arm 2	6.88 ± 4.08	6.11 ± 4.01	4.88 ± 4.11	
	Control group	6.98 ± 3.93	6.62 ± 4.03	5.81 ± 4.11	
BI	Arm 1	54.94 ± 27.01	60.00 ± 27.92	67.50 ± 28.22[a]	69.54 ± 27.69[a]
	Arm 2	57.82 ± 27.40	61.84 ± 27.58	69.26 ± 8.64[c]	71.15 ± 28.73[c]
	Control group	54.34 ± 27.52	56.62 ± 28.31	60.52 ± 28.69	62.68 ± 28.69
MAS	Arm 1	2.17 ± 1.32	2.03 ± 1.18	1.78 ± 0.99	
	Arm 2	2.34 ± 1.38	2.06 ± 1.24	1.80 ± 1.06	
	Control group	2.18 ± 1.37	2.09 ± 1.24	1.96 ± 1.17	

[a]*There were significant differences between the three groups.* [b]*A comparison between arm 1 and the control group was statistically significant.* [c]*A comparison between arm 2 and the control group was also statistically significant.*

the needle handle, thus facilitating needle removal, tapping the needle handle to relieve muscle tension, and eliminating needle stagnation. No patients withdrew from the trial due to adverse events.

DISCUSSION

We have successfully completed a multicenter randomized controlled clinical trial on the effectiveness and safety of acupuncture for ischemic stroke rehabilitation. Acupuncture and moxibustion, as traditional treatment methods of traditional Chinese medicine, have long been confirmed for patients with stroke. It has the advantages of wide indications, obvious curative effect, convenient operation, economic safety, and so on. Acupuncture and moxibustion can improve the elasticity of patients' cerebral arteries, reduce their tension, dilate blood vessels, increase blood flow, promote the establishment of collateral circulation, improve the blood pressure circulation of the brain, and promote the repair of brain tissue. Studies by foreign scholars have also confirmed that acupuncture and moxibustion can maximize the activation of the motor cortex and promote the recovery of motor function by improving the plasticity of motor function. This method has been used in the treatment of stroke in China and East Asia for thousands of years. We found that compared with the control group, arm 1 and arm 2 were clinically effective and safe. The study has shown that acupuncture treatment after ischemic stroke can generate neuroprotective and neuroregenerative effects that increase cerebral blood flow, regulate oxidative stress, maintain blood–brain barrier integrity, inhibit apoptosis, and increase growth factor production (23). This may be the basis for acupuncture treatment of ischemic stroke. At present, ischemic stroke treatment is mostly performed in the setting of stroke units, which are considered to be the most effective way to deal with the disease (24–26). In many stroke units, various therapies and techniques are combined to provide patients with therapeutic medications and physical, language, and psychological rehabilitation, and also health education (27). In China, acupuncture also plays an indispensable role in the clinical rehabilitation of stroke (28, 29).

In stroke diseases, the occurrence and gradual development of limb paralysis in patients will lead to damage to the cortex and problems in the basal ganglia and brain cadres. Hemiplegia is mainly due to the damage to patients' upper motor neurons, which leads to related diseases. When the upper motor neuron is damaged, the inhibition of pivot reflex will be relieved and large muscle tension will be generated; in the case of combined with other diseases, it will hinder the movement of patients. From the perspective of traditional Chinese medicine, the limb hemiplegia of patients with stroke is the category of "spasm" or "contracture," which needs to dredge the blood stasis in time, i.e., acupuncture points and act on the patient's central nervous system through acupuncture and moxibustion, so as to weaken the promoting effect of the descending central nervous system of the patient's spinal cord and to alleviate the symptoms of muscle spasm.

GV20 is located on the top of the head and can adjust the medullary sea. Modern studies have confirmed that stimulating Baihui acupoint can inhibit the oxidative stress state of the chronic stress rat model, improve cerebral hypoxia and blood circulation, enhance brain antioxidant capacity, delay neuronal apoptosis, and have a brain-protective effect on depressed rats. DU26 belongs to the category of thirteen ghost acupoints, also known as the Shuigou acupoint. It is the intersection of the Yangming Meridian of hand and foot and the governor vessel. Modern studies have proved that the Shuigou point contains branches of the facial nerve and trigeminal nerve, with a rich blood supply and a rich distribution of nerve fibers. Stimulating this point can improve cerebral blood supply. According to the study results, the function of the above acupoints and the correctness of acupoint selection were confirmed.

The NIHSS is an important scale for stroke assessment. It comprehensively evaluates the consciousness, movement, sensation, and advanced neurological function of patients with stroke. In this trial, arm 1 was superior to the control group in treating neurological deficits; however, there was no marked difference between arm 2 and the control group. The reduction

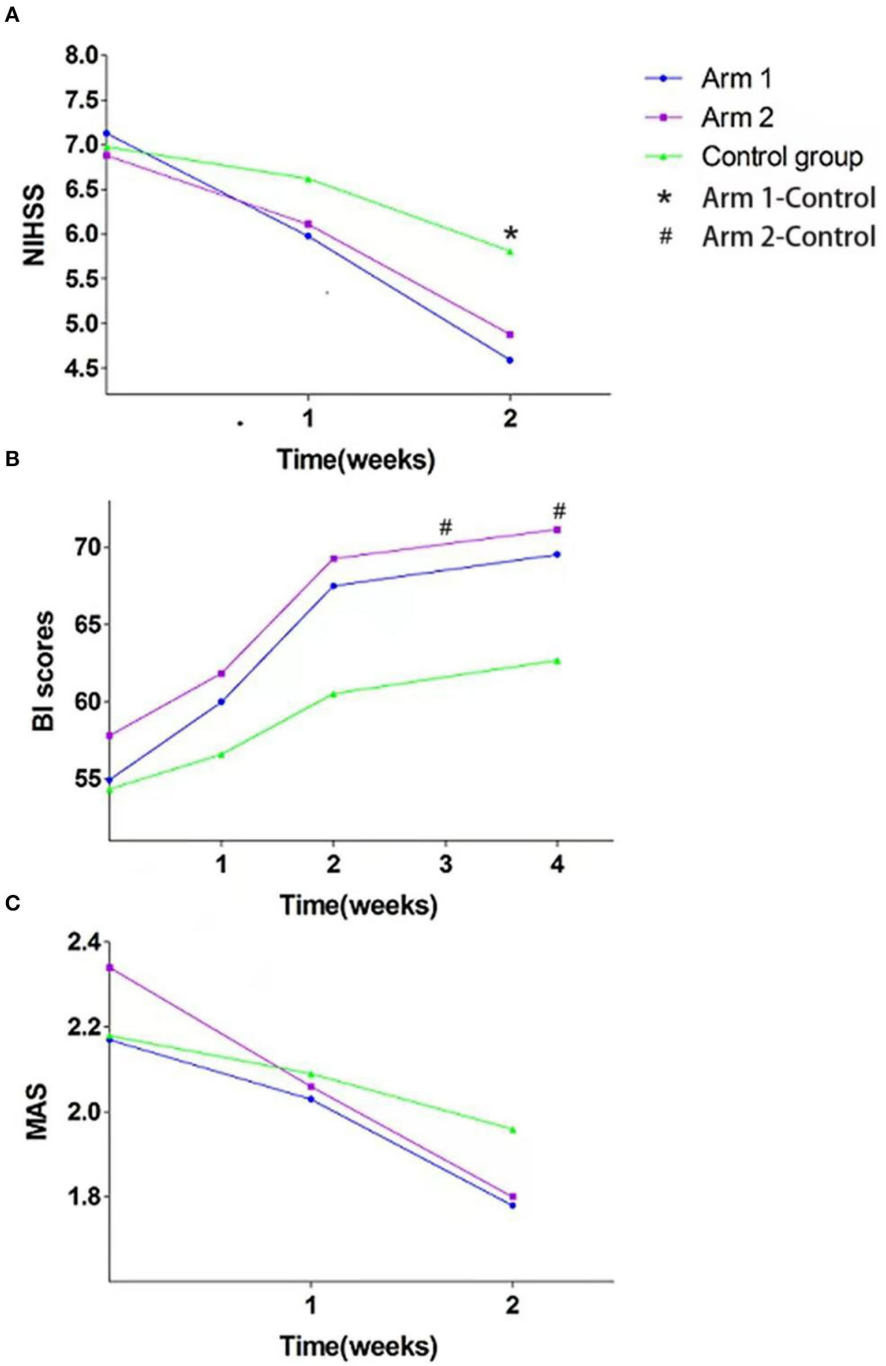

FIGURE 2 | Scores of the **(A)** National Institutes of Health Stroke Scale (NIHSS), **(B)** the Barthel Index (BI), and **(C)** the Modified Ashworth Scale (MAS) in the three groups. *, # denotes significant difference.

in the NIHSS score predicts that the degree of neurological impairment was better than before, indicating that the treatment was beneficial to the disease recovery. Previous studies have shown that GV20-based acupoint combination together with rehabilitation is more effective than simple rehabilitation in reducing the NIHSS scores after eight courses of treatment (21), largely owing to the fact that these acupoints can balance the body's *yin* and *yang* and dredge the *qi* and blood of the meridians. In terms of improving patient self-care ability, the effect of arm 2 was better than that of the control group, but there was no significant difference between arm 1 and the control group. Increased BI scores mean that patients have improved

their lives in terms of eating, dressing, walking, and going to the bathroom. While a multicenter RCT revealed that the BI scores of patients with subacute stroke were significantly higher after 6 months of body and scalp acupuncture treatment, no obvious improvements were found when compared with the rehabilitation group (30). In the authors' opinion, this negative result was due to the acupoints in the program deviating from the viewpoint of TCM syndrome differentiation. Thus, we should not only focus on the proximity to afferent nerve fibers but also select points according to the specific conditions of patients. The acupoints in this study were derived from a combination of multiple clinical trials and the experience of several seasoned acupuncturists. The two treatment groups exerted a similar effect to that of the control group in terms of improving muscle tension. However, many experiments have shown that acupuncture or electroacupuncture combined with rehabilitation can improve muscle tone and release spastic limbs (31–34). In our opinion, this is likely related to insufficient treatment or observation time. Further clinical studies are needed to confirm this hypothesis.

In designing the trial's scheme, considering the adjustment of multicentric effect and multiple independent variable effects in statistical models, we determined to include more samples besides 378 to obtain more statistical power. During the trial process, the control group also received basic treatment and rehabilitation without violating ethics.

This experiment is different from other similar trials. One is a multicenter participation and a large sample size. The other is a selection of acupoints by not only referring to ancient books but also by paying attention to modern literature and comprehensively evaluating the curative effect of acupuncture on stroke. This experiment proves that acupuncture has positive significance for the recovery of patients with ischemic stroke and promotes the popularization and application of acupuncture in patients with stroke.

LIMITATIONS OF THIS STUDY

Although this trial is one of the few random, multicenter, and large-sample trials of acupuncture treatment for stroke (35), some limitations were observed and require attention in the future. First, the course of treatment was relatively short. After two courses of treatment, acupuncture has achieved a good curative effect and positive effects may emerge in the treatment group with the passage of treatment time. Second, our study was not double-blinded. Although clinical trials on acupuncture are mostly conducted in a single-blind state, the possible risk is that the acupuncturists are affected by them after communicating with patients, that is, the experimenter's own preferences are passed onto the participants and cause experimental deviation. This may have led to treatment outcome bias.

CONCLUSION

Acupuncture treatment for ischemic stroke demonstrated better recovery results than the simple rehabilitation group. Specifically, group 1 was better than the control group in improving the degree of neurological impairment, while group 2 was preferred in improving patients' ability of daily living. But there was no difference between the effects of the two acupuncture groups.

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 human participants were reviewed and approved by the Ethics Committee of the Guangzhou Hospital of Chinese Medicine (Reference No. 2016NK001). The Affiliated TCM Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LLi, CC, and GL designed and led the study. WZ, DT, XW, WL, and SL analyzed and interpreted the patient data to generate the study results. LLu and LX drafted the manuscript. All authors have read and approved the final version of the manuscript.

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CASE REPORT
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Electroacupuncture on Hemifacial Spasm and Temporomandibular Joint Pain Co-Morbidity: A Case Report

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Hemifacial spasm (HFS) and temporomandibular joint (TMJ) pain are common facial diseases which cause depression, anxiety, insomnia, and poor quality of life. However, currently there are still no effective therapies to treat HFS and TMJ. Electroacupuncture (EA) has advantages of safety, rapid work, easy operation and convenience. Here, we reported a case of a 50-year-old woman who presented with irregular spasm of eyelids and facial muscles on the left side, and TMJ pain on the right side. The patient had been treated with carbamazepine (20mg per day) and alternative therapies for a year, but still not much improvement in the symptoms. The scores of the Jankovic Rating Scale (JRS), global rating scale (GRS), and visual analog scale (VAS) were 7, 60, and 7 points, respectively. The EMG test showed that the spastic side had higher R1 amplitude, longer R2 duration, and larger R2 area than the non-spasmodic side, and the occurrence rate of the lateral spread responses (LSR) in the Orbicularis oris and the Orbicularis oculi muscle was 60% and 40%, respectively. We considered this patient had left HFS and right TMJ pain. EA was successfully undertaken for two periods over 30 weeks. After EA, JRS and VAS were reduced sharply, and the symptoms of HFS were stable without recurrence. However, the frequency of the lower eyelid increased gradually during the 6-month follow-up. These findings reveal that EA with the frequency of 2 Hz and intensity of ∼ 1–2 mA may be a benefit for alleviating symptoms of HFS and TMJ pain without adverse reaction. The potential mechanisms of EA in HFS and TMJ pain co-morbidity involve brain stem mechanism and DNIC mechanism for distal acupuncture and segmental mechanism for local acupuncture analgesia.

Keywords: electroacupuncture, hemifacial spasm, temporomandibular joint pain, co-morbidity, case report

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HIGHLIGHTS:

- A total of 30 weeks of EA has benefits for relieving the spasm of HFS and reducing the pain of TMJ, and lasts for 3 months.
- Sensory input from the hand may be *via* the medial lemniscus, then inhibiting afferent from the face in the trigeminal nucleus (TN).

- Diffuse noxious inhibitory controls (DNIC) and segmental mechanisms play an important role in acupuncture analgesia effect.

INTRODUCTION

Hemifacial spasm (HFS) is a frequent disorder characterized by involuntary contractions of those muscles innervated by the facial nerve on one side of the face. The symptoms can appear as tonic or clonic and intermittent or permanent. The incidence rate of HFS was about 1 per 10,000 people (1). To date, the gold standard for the diagnosis of HFS is still lacking. Clinicians diagnose mainly based on clinical symptoms. HFS can cause depression, anxiety, insomnia, poor quality of life, and so on (2, 3).

At present, clinicians mainly use drugs, surgery, and other methods to treat HFS; however, the effects of these therapies are relatively limited and accompanied by some adverse reactions. For example, carbamazepine and clonazepam may be effective in some mild patients, but there are some side reactions, such as drowsiness, headaches, and dizziness (4). The botulinum toxin type A is another therapy to reduce the symptoms of HFS, but its effect can only last up to 3–6 months and long-term use requires increased doses (5, 6). Previous studies reported that botulinum toxin type A can paralyze facial nerves and cause artificial facial paralysis (7, 8), leading to a main long-term side effect of facial asymmetry (9). Surgery (e.g., facial nerve decompression and microvascular decompression) is the most commonly used method for radical HFS, but always rejected by patients due to the adverse effects, such as facial palsy and transientor permanent cranial nerve deficits (10, 11).

Temporomandibular joint (TMJ) disorder is the most common disease of the oral and maxillofacial region, of which the main clinical manifestations are pain in the TMJ, joint snapping during exercise, mandibular movement disorder, ear pain, tinnitus, dizziness, neck pain, and headache (12, 13). It affects ∼15%−20% of the population (14). Previous MRI-based studies have demonstrated that TMJ pain is associated with multiple factors including joint effusion, bone marrow edema, and osteoarthritis (15, 16). The treatment protocols for TMJ

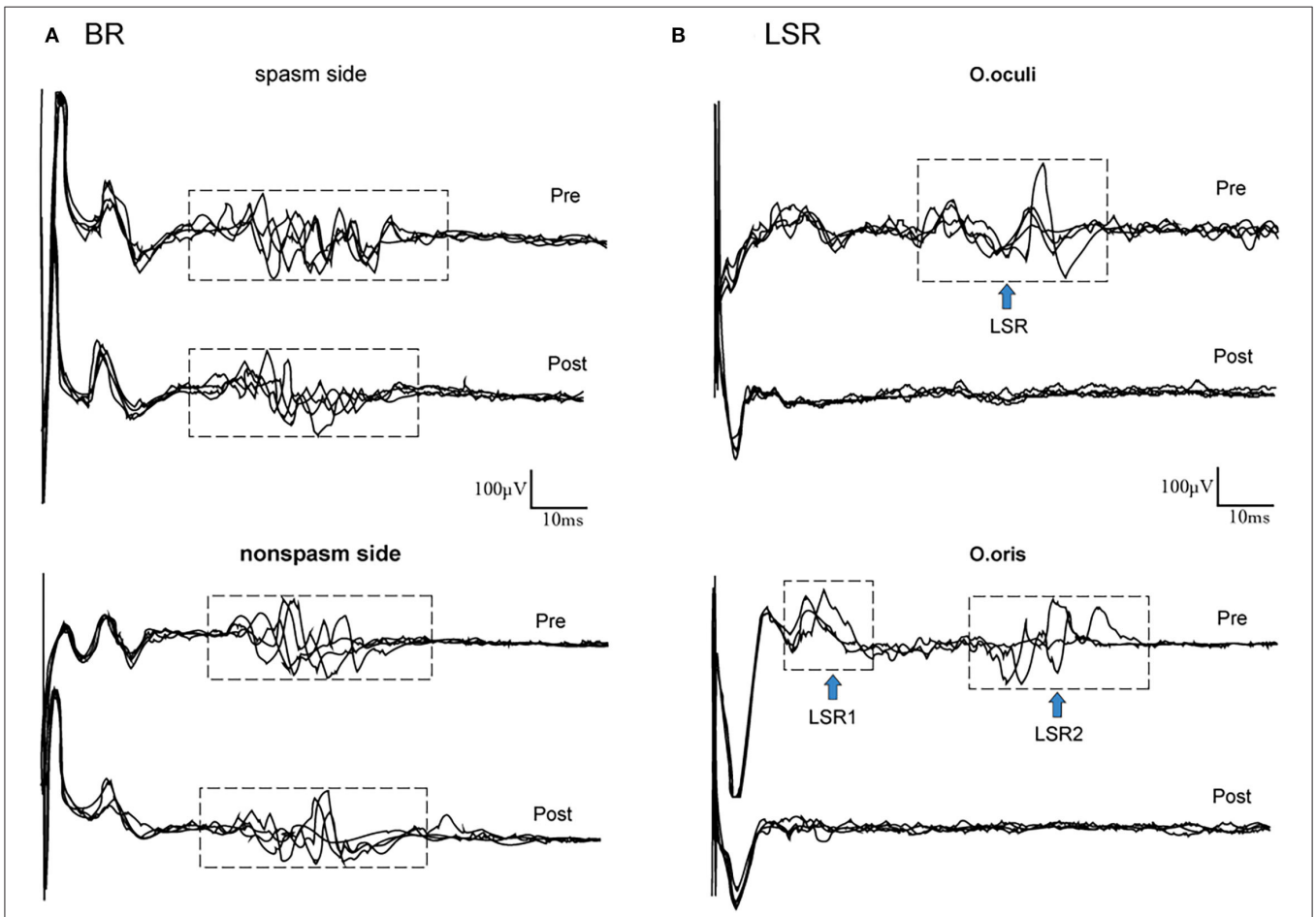


FIGURE 1 | Raw data of BR and LSR. **(A)** Changes in BR. Compared to nonspasm side at baseline, the amplitude of R1 was higher, the duration of R2 was longer, and the area of R2 was larger in the spasm side. After 30 weeks of EA treatment, the duration of R2 was shortened and the area of R2 was reduced in the spasm side, and there were no changes in the nonspasm side. **(B)** Occurrence of LSR in O.oc and O.or (the blue arrow). After EA, no LSR was found in the facial muscles. BR, blink reflex; LSR, lateral spread responses; O.oc, Orbicularis oculi muscle; O.or, Orbicularis oris muscle.

disorders vary over the years (17). Pharmacotherapies were used to reduce pain and improve function, such as anti-inflammatory drugs, muscle relaxants, and Botulinum toxin, for mild to moderate TMJ disorder (18). Moreover, in terms of surgical treatment, arthroscopic therapy is more popular because of its higher success rate (17).

Electroacupuncture (EA) is a combination of conventional acupuncture with electrical stimulation on acupoints, which can enhance the sensory input from peripheral system (19). EA has the advantages of safety, rapid work, easy operation, and convenience, which has been widely used in the management of neurological and arthrosis diseases (20, 21). We report a case of HFS and TMJ pain co-morbidity treated successfully by the peripheral EA. This study was approved by the Ethics committee of the Guangdong Provincial Hospital of Chinese Medicine (AF/04-07.0/10.0).

CASE DESCRIPTION

A 50-year-old female patient, who had suffered from hemifacial spasm (HFS) for nearly 6 years, came to the acupuncture clinic on 16 February 2021. She complained of irregular spasms of the eyelids and facial muscles on the left side, and the occurrence of TMJ pain on the right side, accompanied with tinnitus, dizziness, neck pain, and headache, which seriously affected her health and daily life. Before her first visit to our hospital, she was diagnosed with primary HFS in another hospital in 2015. In the following 5 years, her symptoms worsened when she was stressed, tired, and fatigued, with increased frequency and severity of intermittent twitching of the left lower eyelid and lower face. Hereafter, she had been treated with carbamazepine (20 mg per day) and alternative therapies (e.g., Chinese herbal medicine, moxibustion, Guasha therapy, facial massage, etc.) for a year, but still not much improvement in the symptoms.

Physical examination showed that there was obvious twitching of the left facial muscles, the eyes could not be opened due to spasms on the upper face, the degree of spasm on the lower face was less than that on the upper face, the facial muscles on both sides were not symmetrical, there were tenderness and clicking sounds at the right temporomandibular joint without redness and swelling, and no joint deformation. Her Jankovic Rating Scale (JRS) was 7 points, 4 points for the severity and 3 points for the frequency, and her global rating scale (GRS) and visual analog scale (VAS) were 60 points and 7 points, respectively.

Considering the recurrent symptoms and long course of HFS, we conducted relevant detection of the facial nerve, including blink reflex (BR) and lateral spread responses (LSR). We recorded the EMG activities in the Orbicularis oris (O.or) or the Orbicularis oculi (O.oc) muscle by stimulating the mandibular or zygomatic branches of the facial nerve, respectively. EMG test showed that the spastic side had higher R1 amplitude, longer R2 duration, and larger R2 area than the non-spasmodic side (**Figure 1A, Supplementary Table S1**). In ten stimuli, the occurrence rate of the LSR in O.oc was 60% and in O.or was 40%.

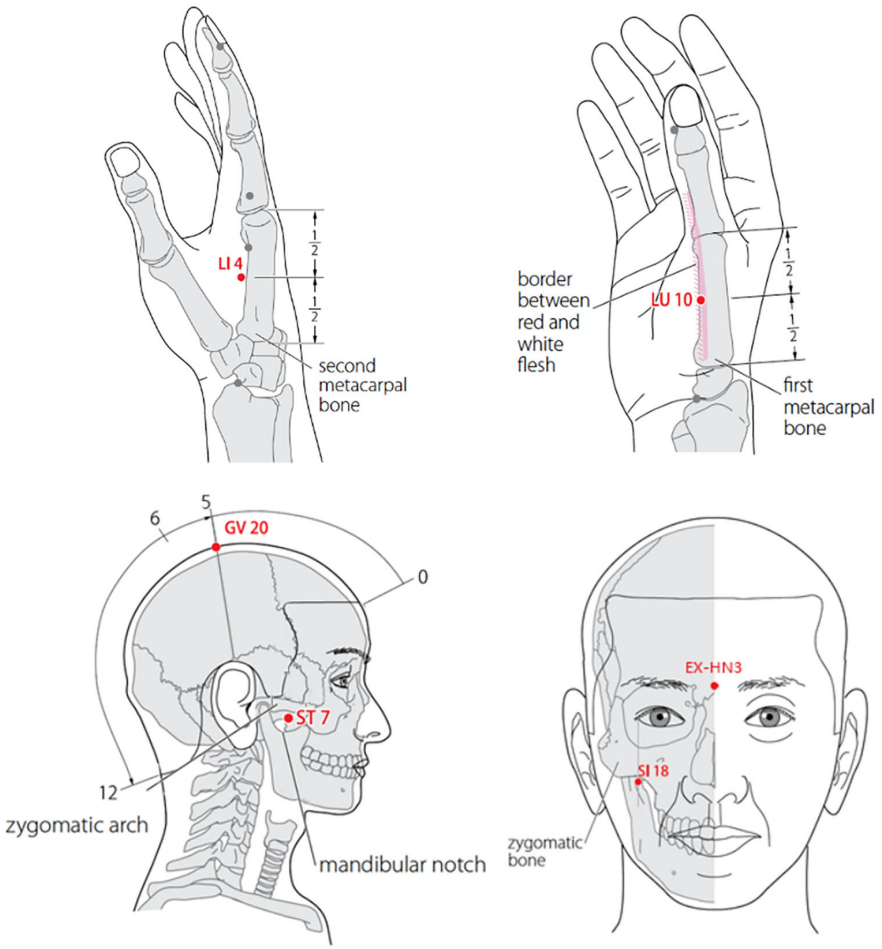
We considered this patient had left HFS and right TMJ pain based on the symptoms, physical examination, and EMG test. The onset stages of co-morbidity were severe. Her main pathological mechanism may be related to the hyperexcitability of the facial motor nucleus. Given her previous treatment protocols and her refusal to take medicines, we used EA to reduce her symptoms. According to the classical TCM theory "the treatment of ora-facial diseases by acupuncture at Hegu (LI4) acupoint," which means Hegu acupoint can effectively treat the ora-facial diseases, such as toothache, facial paralysis, etc. So, we selected the following acupoints (22): LI 4 (Hegu), LU 10 (Yuji), SI 18 (Quanliao), ST 7 (Xiaguan), EX-HN 3 (Yintang), and GV 20 (Baihui). The locations of the above acupoints are shown in (**Figure 2**). Manipulate program: The patient is made to lie supine on the treatment bed and the acupuncturist stands on his right side to locate the acupoints. After skin disinfection, the acupuncturist inserts a stainless steel needle (0.25 × 25 mm, Hwato, Suzhou, China) to a 1.5-cm subcutaneous depth at an appropriate angle according to the acupoints. When the patient had a feeling of Deqi (namely soreness, numbness, warmth, heaviness, or distention around the acupoints), a constant-current (direct current). EA (HANS-200A, Nanjing, China) was applied to LI 4 and LU 10 (positive pole), SI 18 and ST 7 (positive pole), respectively. The frequency was 2 Hz and intensity was set at ∼1–2 mA for 30 min, preferably with the muscle shivering mildly but without pain. The duration of EA was 30 min each session, two sessions a week, 20 sessions for the first 10 weeks, and then changed to 30 min each session, once a week, 20 sessions for the next 20 weeks. EA was performed by the same experienced acupuncturist registered in China. During treatment, no additional medications were used and no adverse events were found.

At the 10th week of treatment, the severity and frequency of the patient's facial spasms were relieved. The JRS was 4 scores (2 scores for severity and frequency, respectively), the GRS was 30 scores, and the VAS was 2 scores (**Table 1**). Also, she still felt mild tinnitus, dizziness, neck pain, and headache. By the 30th week of treatment, not only had her lower facial spasms gone, but her tinnitus, dizziness, neck pain, and headache had also reduced significantly. Meantime, her GRS and VAS were 20 and 0 score, respectively. However, she still had mild spasms on her lower eyelid. The JRS of her lower eyelid was 2 scores (1 score for severity and frequency, respectively; **Table 1**). The duration of R2 was shortened by 5.35ms, the area of R2 was reduced by 13.56%, and the LSR of O.oc and O.or disappeared on the spasm side (**Figure 1B**).

Telephone follow-up was conducted in the 3rd month after the end of EA, and the symptoms of HFS were stable without recurrence, but the TMJ pain occurred intermittently. At the 6-month follow-up, the frequency of spasms (lower eyelid) increased gradually, but the severity remained stable (**Table 1**). The timeline of the intervention and outcomes is shown in (**Figure 3**.)

DISCUSSION

Electroacupuncture therapy is the method that adds an electrical stimulation pulse to acupuncture needles. It is safe and



Acupoints	Side	Angle	Locations
Hegu (LI 4)	left side	90°	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone
Yuji (LU 10)	left side	90°	On the palm, radial to the midpoint of the first metacarpal bone, at the border between the red and white flesh
Quanliao (SI 18)	right side	90°	On the face, inferior to the zygomatic bone, in the depression directly inferior to the outer canthus of the eye.
Xiaguan (ST 7)	right side	90°	On the face, in the depression between the midpoint of the inferior border of the zygomatic arch and the mandibular notch.
Yintang (EX-HN3)	middle	15°	On the head, at the root of the nose and between the eyebrows
Baihui (GV 20)	middle	15°	On the head, 5-cun superior to the anterior hair line, on the anterior median line.

FIGURE 2 | Locations of acupoints. (WHO (22)).

TABLE 1 | Clinical assessments for HFS and TMJ pain at each time points.

Outcomes	Before treatment (T0)	During treatment (T1)	After treatment (T2)	3-month follow-up (T3)	6-month follow-up (T4)
JRS-Severity	4	2	1	1	1
JRS-Frequency	3	2	1	1	2
JRS total scores	7	4	2	2	3
GRS score	60	30	20	20	40
VAS score	7	2	0	1	1

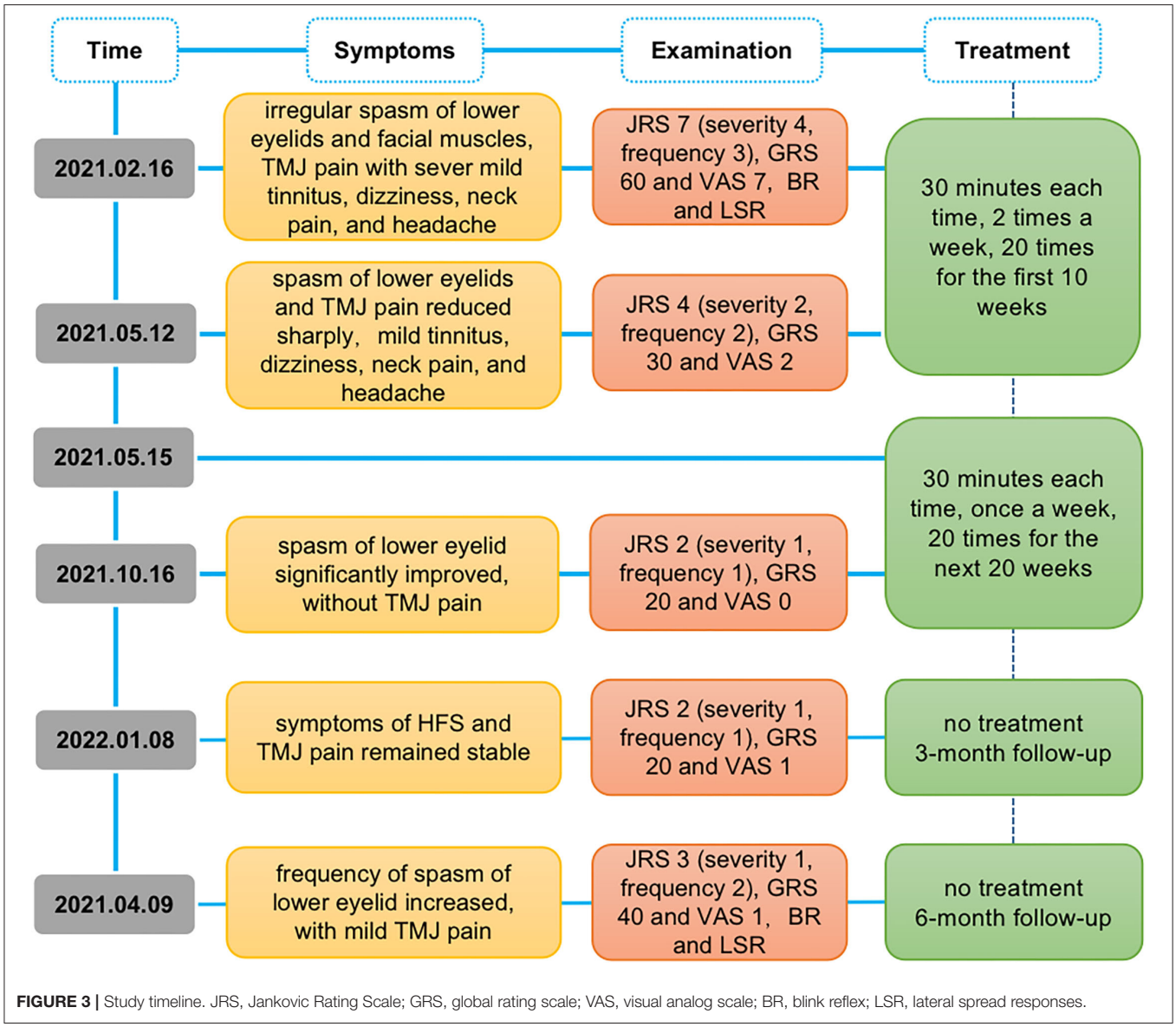


FIGURE 3 | Study timeline. JRS, Jankovic Rating Scale; GRS, global rating scale; VAS, visual analog scale; BR, blink reflex; LSR, lateral spread responses.

convenient. In this case, we showed that a peripheral electrical acupuncture stimulation can alleviate symptoms of HFS and TMJ pain, remaining stable for the following 3 months. Generally, in one way, it showed significant decreasing scores of JRS and GRS for HFS and VAS for TMJ pain, and in the other way, it declined the excitability of BR and LSR in spasm muscles.

For HFS, JRS and GRS are widely used for evaluating the symptoms (23, 24). The higher the scores, the more severe symptoms in the patient. The JRS is rated by a physician and is made up of two subscales, severity and frequency. Each of the subscale ranges from 0 to 4, where 0 indicates no symptoms and 4 indicates the most severe or frequent symptoms. GRS is

a self-reported measure rated by the patient to show whether the symptoms improved or worsened after the treatment. In the beginning, the scores of the severity and frequency of spam showed a severe level, and after 30 weeks of EA treatment, the overall scores decreased, mild symptoms were found and kept stable at the 3rd month follow-up. At the 6th month follow-up, the frequency, but not the severity of spasms increased only in the eyelid, caused by the lack of sleep due to stress and anxiety.

Besides, we applied BR and LSR for a neurological test. BR is for the assessment of excitability changes at the brainstem inter-neuronal level, consisting of two components: R1 and R2. R1 is an oligo synaptic circuit from the principal trigeminal nucleus (PTN) to the facial nucleus, while R2 is mediated by a multi-synaptic circuit between the spinal trigeminal nucleus (STN) and facial nucleus with a chain of brainstem interneurons extending in the lateral reticular formation (25). After 30 weeks of EA treatment in the ipsilateral hand, the R1 component (amplitude) and the R2 component (duration and area) in the spasm side decreased, suggesting that the sensory input from the hand may inhibit that from the face in the trigeminal nucleus (TN). But no effect was found in the contralatral BR, indicating that the EA effect is mediated by the medial lemniscus. LSR (a facio-facial reflex), which is elicited by stimulating one branch of the facial nerve on the affected side, causing co-contraction of muscles innervated by other branches of the facial nerve (26), is an important monitoring tool for HFS, indicating hyperexcitability of the facial motor nucleus. The use of LSR is chosen for predicting the effectiveness of treatments, i.e., microvascular decompression (MVD) (27). In most of the studies, the occurrence rate of LSR is about 87% (28), and after MVD, the recovery rates have reached upto 90% (29). After 30 weeks EA treatment, the facial nerve examination of LSR disappeared, suggesting that the hyperexcitability of facial motor nucleus decreased, which was consistent with clinical symptoms and revealed a good prognosis. Hence, we thought that somatosensory inputs from the ipsilateral hand may *via* the medial lemniscus inhibit the facial inputs in the TN, so that it attenuated hyperexcitability of the facial motor nucleus and finally reduced the excitability of the facial nerve, then improved the symptoms.

For TMJ pain, the intensity of pain was assessed by VAS, which included scores from 0 (no pain at all) to 10 (strongest pain) (30). The level of the pain scores reduced to mild after 10 weeks of EA treatment, and without any related symptoms when treatments finished, suggesting that local acupuncture has a strong analgesic effect. The underlying mechanisms of acupuncture-induced pain relief were unclear, and several theories have been discussed, such as the endogenous opioid system (31), gate control theory (32), diffuse noxious inhibitory controls (DNIC) (33), and so on. Among these, the segmental mechanism is modulated by noxious stimulation at the local (34), while the DNIC can also be activated by stimulating in a distant area of the body (35). DNIC refers to the response from a noxious stimulus at a distance that attenuates pain from the second focal stimulus. Studies showed that patients with fibromyalgia (36), irritable bowel syndrome, or TMD disorder (37) have a reduced ability to inhibit pain, possibly due to the impaired DNIC. It has been proved that the analgesic effects are triggered by the activation of peripheral receptors carried by Aδ- and C-fibers (38), which is the same as the electrical acupuncture by activating the afferent nerve fibers innervating both the skin and muscles (39). So, we speculated that the segmental mechanism and DNIC may be the possible mechanism of acupuncture analgesia for TMJ pain.Overall, this is the first report of HFS and TMJ pain co-morbidity. The etiology and pathogenesis of this oral-facial disease co-morbidity are still unclear. However, it can be treated under the same principle from the perspective of meridian theory. Here, the local and distal acupoints were used for the treatment of facial and oral diseases, such as facial paralysis and trigeminal neuralgia (40–42). Studies have shown that acupuncture has a good effect on facial spasms and TMJ pain, respectively. Professor Chen used ipsilateral local acupoints combined with distal acupoints to treat primary and secondary hemifacial spasms, each lasting 30 min once in 2 days, for a total treatment of 12 days (43). Besides, another study on 127 HFS patients showed that local fire needle therapy with distal acupuncture also showed relieving on the symptoms of HFS (44). However, local stimulation, i.e., chronic electrical stimulation on the facial nerve induced hyperactivity of the facial nucleus (45), which may aggravate spasms. In terms of pain relief, local and distal stimulation with acupuncture (46), transcutaneous peripheral nerve stimulation (47), or vibratory stimulation (48) also showed a strong analgesic effect, but differed in stimulus parameters, such as intensity and frequency (47, 48). What's more, stimuli at distal or local acupoints can change the excitability in specific brain regions. For example, EA at LI 4 increased fMRI signal in the precentral gyrus (49) in healthy subjects, while EA at ST2 can induce interaction between face and hand representations of contralateral motor cortex in facial paralysis (50).

Compared with the other treatments (i.e., medical therapy, botulinum toxin type A and facial nerve decompression, and microvascular decompression), peripheral EA treatment showed few side effects and was more safe. It is easy to be accepted by patients in China. In this case, we applied ipsilateral distal acupoints (LI 4 and LU 10) to inhibit hyperexcitability of the spastic side, ipsilateral local acupoints (SI 18 and ST 7) for relieving TMJ pain, and improve blood circulation and other acupoints (EX-HN3 and GV 20) for regulating emotion, relieving anxiety, and stress. A 30-week EA treatment alleviated most of the symptoms of HFS and TMJ pain, but some symptoms might recur at the 6th follow-up, such as the frequency of eyelid spasms and pain in the TMJ. These recurrence symptoms do not affect a patient's daily life, but still disturb the patient and might cause mental stress. On the one hand, the instability of symptoms may be related to the complex pathogenesis of the disease itself, and on the other hand, long-time activities of facial expression muscles (such as smiling, chewing, talking, etc.), emotional disorders (51, 52), and insomnia may be important factors to induce the recurrence of the disease. Notably, the effects of EA lasted only a few months after treatment, revealing that EA is transient and reversible. Therefore, it needs a long-term EA treatment to maintain the effects.

It is important to note some limitations to the current findings of this case. First, the lack of radiological evidence, such as MRI,

can be used as an auxiliary indicator to evaluate the changes in nerves, blood vessels, and joints in these two diseases. Second, the EA effect for relieving pain is obvious compared to attenuated spasms, which is essential to carry out further studies to verify the mechanisms of acupuncture in treating HFS and TMJ pain separately. Last, less was known about whether there was related interaction between the two types of facial disease. We are planning studies to address these limitations.

CONCLUSION

In this study, we present a case of HFS and TMJ pain successfully treated with EA. EA with a frequency of 2 Hz and an intensity of ∼1–2 mA showed effects of spasmolysis and analgesia for HFS and TMJ pain co-morbidity, which benefit for alleviating symptoms. Both distal and local acupoints play an important role in the treatment of co-morbidity. The potential mechanisms of EA on HFS and TMJ pain co-morbidity involved: (1) brain stem mechanism for distal acupuncture, where sensory input from the hand may inhibit facial afferent in the trigeminal nucleus *via* medial lemniscus; (2) segmental mechanism and DNIC for local and distal acupuncture analgesia.

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 human participants were reviewed and approved by Ethics Committee of the Guangdong Provincial Hospital of Chinese Medicine. The patients/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

J-hL and W-bF designed and drafted the manuscript. J-pH wrote the article and revised the manuscript. Z-mL and Q-wZ conducted the scale evaluation. W-tL and JZ conducted the EMG. SL and KL assisted in clinical treatment. All authors have read and agreed to the published version of the manuscript. All authors contributed to the article and approved the submitted version.

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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.2022.931412/full#supplementary-material

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Caffeine Attenuates Electroacupuncture Effect on Pressure Pain Threshold and Tolerance in Healthy Individuals: A Randomized Controlled Trial

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Introduction: The effect of caffeine on acupuncture analgesia in humans is unclear. This study aimed to investigate whether caffeine-containing beverage intake influences the effect of electroacupuncture (EA) on static quantitative sensory testing (QST) and dynamic QST in healthy subjects.

Methods: A total of 40 healthy subjects were enrolled and randomly assigned to receive coffee containing moderate doses of caffeine (coffee group) or non-caffeinated juice (juice group) for 4 weeks. The primary outcome measures were the pressure pain threshold (PPT), pressure pain tolerance (PPTo), and heat pain threshold (HPT) as static QST parameters. Numerical rating scales (NRS) of heat stimulus and nociceptive flexor reflex (RIII reflex), as parameters of dynamic QST, were also examined. EA stimulation with tolerance intensity was performed at ST36 (Zusanli)-GB34 (Yanglingquan) points at weeks 0, 2, and 4. PPT, PPTo, and HPT were detected pre- and post- EA. The NRS scores were examined pre-, during, and post-EA, and 1 min after EA was completed. The RIII reflex was examined pre- and 1–5 min post-EA.

Results: At week 0, both groups showed increased PPT and PPTo and decreased NRS scores of heat stimuli and RIII reflex after EA, but HPT was not affected. After 4 weeks, the effects of EA on PPT and PPTo were attenuated in the coffee group compared to the juice group, whereas the effect of EA on the NRS scores and RIII reflex were not influenced. There was no significant difference found at week 2 for these indications. EA also did not affect the HPT in both groups at week 4.

Conclusion: Moderate caffeine intake reduced the effects of EA on PPT and PPTo in healthy subjects.

Keywords: coffee, electroacupuncture, quantitative sensory testing, sensory perception, conditioned pain modulation

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INTRODUCTION

Acupuncture, which has been practiced in China for thousands of years, is widely used to alleviate both acute (1) and chronic pain (2, 3) and is currently practiced in 160 countries and regions worldwide. Studies on the physiological, anatomical, and neurochemical mechanism of the analgesic effect of acupuncture have shown that the same and adjacent segmental acupuncture analgesia is attributed to the spinal gate control theory, in which the painful site activates Aβ fibers to suppress Aδ or C fiber activation (4). The supraspinal structures involved in the endogenous descending inhibitory system in the CNS contribute to heterosegmental acupuncture analgesia. This diffuse noxious inhibitory control (DNIC) system exerts its effect through the activation of C-fibers from high-intensity stimulation that in turn induces an analgesic effect (5). Many signal molecules are involved in acupuncture analgesia, and these are mostly known as opioid peptides (μ-, δ-, κ-receptors). Human and rodent studies have revealed that different frequencies of electroacupuncture (EA) increase the levels of different opioid peptides. For example, EA stimulation at 2 Hz increased enkephalins and endorphins in the CSF content, whereas 100 Hz stimulation increases the release of dynorphins in parabrachial nuclei (6, 7).

In addition, adenosine is reported to suppress acute and chronic pain in both preclinical animal models and human subjects. Activation of the A1 adenosine receptor (A_1AR) plays an anti-nociceptive effect in spinal, supraspinal, and peripheral neurons, as well as glial cells (8–11). Other subtypes of adenosine receptors involved in pain modulation include the A2a adenosine receptor (A_{2a}AR) and A2b adenosine receptor (A_{2b}AR), which exhibit pro-nociceptive role in the periphery and spinal anti-nociceptive effects (8). Meanwhile, the role of the A3 adenosine receptor (A_3AR) in pain conditions is complicated, but the use of A_3AR agonists produces beneficial effects in neuropathic pain (12, 13).

Caffeine is a non-selective adenosine receptor antagonist. Coffee is a widely consumed caffeine-containing beverage that functions as a stimulatory agent in the central nervous system to increase alertness and decrease fatigue. The estimated daily consumption of caffeine is 168–410 mg/day in Western countries, while people in Eastern countries consume only 14 mg/day of caffeine. High, moderate, and low caffeine consumption is defined as consumption of 200–1,000, 100–200, and $<$100 mg/day, respectively (14, 15). Clinically, low doses of caffeine have an adjuvant analgesic effect that can inhibit A_{2a}AR and A_{2b}AR (16). Meanwhile, moderate to high doses of caffeine can block A_1AR and reduce the anti-nociceptive effects of analgesics (17). Some clinic or preclinic studies have reported the anti-nociceptive effect of adenosine on acupuncture analgesia (18). Peripheral and central A_1AR activations play a role in the anti-nociceptive effects of acupuncture (19, 20).

An animal study has shown that oral or local administration of caffeine during acupuncture eliminated acupuncture analgesia in acute and chronic animal pain models (21). In addition, a study of human subjects found that traditional acupuncture at Zusanli increased local interstitial adenosine concentration (22). In contrast, other studies have also shown that caffeine does not attenuate experimentally induced ischemic pain, and daily caffeine consumption does not influence acupuncture analgesia in healthy subjects (23, 24). Therefore, the effect of caffeine on pain in animal and human subjects is still unclear, and no systematic investigation has been conducted on the influence of caffeine on acupuncture analgesia in humans.

Quantitative sensory testing (QST), also called psychophysical testing, involves static and dynamic QSTs. Static QST further comprises the pressure pain threshold (PPT), pressure pain tolerance (PPTo), and heat pain threshold (HPT), while dynamic QST comprises conditioned pain modulation (CPM). CPM is used to experimentally assess endogenous pain inhibition and can be assessed using different methods. PPT, PPTo, and HPT are well-suited to provide confirmatory results on the mechanisms underlying acupuncture (25).

This study aimed to investigate whether caffeine-containing beverage intake influence the effect of electroacupuncture (EA) on static QST and dynamic QST in healthy subjects. Based on previous research on the biological effects of caffeine, we hypothesized that moderate doses of caffeine intake may inhibit the analgesic effects of acupuncture. Static and dynamic QST and CPM were assessed. The nociceptive flexion reflex of the lower limb (RIII reflex, a spinally mediated withdrawal reflex as a physiological correlate of spinal nociception processing) was also assessed to reflect the descending brain-to-spinal cord modulation of spinal nociception.

MATERIALS AND METHODS

Study Design and Participants

This interventional randomized parallel controlled trial was conducted at the Electrophysiological Laboratory of the Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences (IAM-CACMS). We enrolled healthy subjects from families, friends, colleagues who were familiar with acupuncture therapy, and postgraduate students at the Beijing University of Chinese Medicine and the China Academy of Chinese Medical Sciences. The inclusion criteria were aged between 20 and 40 years and no daily high caffeine-containing food or beverage (coffee, tea, chocolate, energy drinks, etc.) consumption habits. The exclusion criteria were (1) lactation or gestation; (2) a pacemaker; (3) lack of oral communication skills; (4) acute or chronic pain conditions or diabetes mellitus; (5) a history of chronic internal, dermatological, neurological, or psychiatric diseases; and (6) recent sleep deprivation or unusual physical exercise. Any kind of analgesic, anti-depressant, or cough suppressant was not allowed during the study period. All prospective subjects were asked for a medical history and underwent a comprehensive brief physical examination. If the subject met the study criteria, the nature of the study was explained and informed consent was obtained from the subject by our interviewer as in Step 1, **Figure 1**. Each participant scored the expectation value of acupuncture.

This study was approved by the China Ethics Committee of Registering Clinical Trials (No. ChiECRCT-20150031) and conducted according to the Declaration of Helsinki.

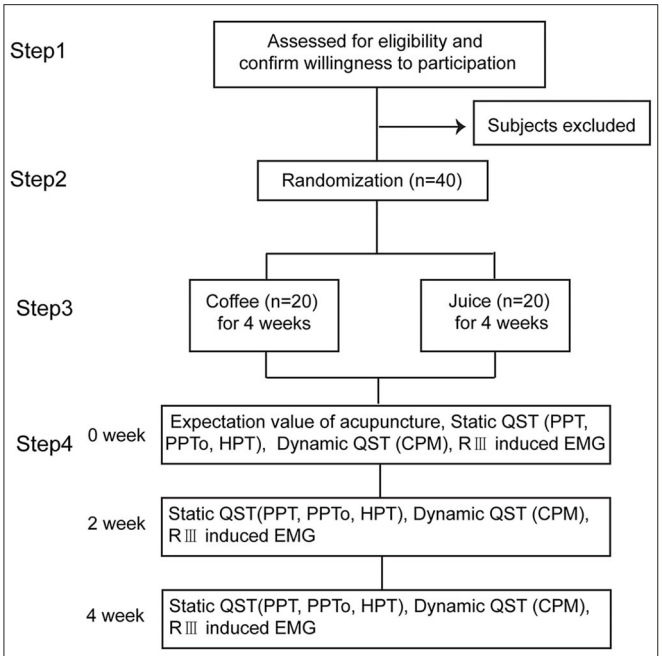

FIGURE 1 | Study design. The participants are randomized in a 1:1 ratio to either the juice or coffee group. The static QST, dynamic QST, and RIII induced EMG are measured before and after acupuncture and at 2 and 4 weeks after intervention in each group.

The details of the study are reported in the Acupuncture-Moxibustion Clinical Trial Registry (registration number: AMCTR-IOR-18000164; http://www.acmctr.org/index.aspx) = ChiCTR1800015994 (http://www.chictr.org.cn) in the Chinese Clinical Trial Registry.

Sample Size

The target sample size was calculated based on the ability to detect a PPT or PPTo difference between groups after a 4-week coffee intake or juice intake, given an expected PPT of 368.50 ± 119.14 kPa before acupuncture, 516.46 ± 207.41 kPa after acupuncture, 80% power, and 5% two-tailed significance level (26). The sample size was calculated using the STATA 14.0 software (Stata Corp., USA) for 10% attrition. In total, 40 participants were recruited (20 per group). The subject inclusion flowchart is shown in **Figure 1**.

Randomization and Masking

The participants were randomly assigned in a 1:1 ratio to receive coffee or juice according to a randomization sequence performed by an independent researcher not involved in the examination or data analysis. The randomization sequence was generated using a computerized, random number generator with the Microsoft Office Excel 2010 software package. Allocation concealment was ensured by opaque envelopes labeled by the study participant number conveyed to an interviewer.

The research coordinator, who was not involved in data collection and data analysis, provided the participants with the beverage they would drink daily for 4 weeks. This coordinator also supervised all the participants to drink coffee or juice during the trial. The subjects were instructed to prepare the coffee or juice powder into 200 ml of warm water and answer drinking forms after each drink to record the time of drinking. The daily videos or video calls of drinking through their cellphones were sent only to the coordinator. During the video call, the participants would show the drink to the coordinator and report the time and date before they drank it off. The examiner, data collection staff and data analysts in charge of examining the participant, and recording data or data analysis were blinded to group allocation during the study period. The interviewer, coordinator, and the data collection staff and analysts were instructed not to exchange information during the entire period of the trial. Allocation concealment was not performed until the completion of the study. The tests and measurements were conducted in the same shielded room of the Electrophysiological Laboratory under similar conditions (quiet atmosphere, room temperature: 20–25°C, and humidity 40–60%).

Intervention

The daily diet of the participants was maintained during the research except for the intake of coffee or juice. Subjects in the coffee group drank 2 bars of instant coffee (NESCAFE 1+2 original), with 50–60 mg caffeine/bar. Therefore, the daily consumption of caffeine in the coffee group was ∼100–120 mg per person as a moderate dose (27). Meanwhile, subjects in the juice group were asked to drink non-caffeinated juice powder (TANG, Kraft Foods (Mondelēz International), 15 g per person daily. The examination was conducted from 1:00 pm to 5:00 pm. The participants were asked to finish drinking at least 1 bar of the coffee or juice assigned before arriving at the laboratory on the examination day.

The acupoints for EA were ST36 (Zusanli) located on the anterior aspect of the leg, on the line connecting ST35 with ST41; 3 B-cun inferior to ST35; and GB34 (Yanglingquan) located on the fibular aspect of the leg, anterior and distal to the head of the fibula. The acupoints for PPT and PPTo measurement were the left point of BL25 (Dachangshu, in the lumbar region, at the same level as the inferior border of the spinous process of the fourth lumbar vertebra (L4), 1.5 B-cun lateral to the posterior median line) and BL57 (Chengshan, on the posterior aspect of the leg, at the connecting point of the calcaneal tendon with the two muscle bellies of the gastrocnemius muscle). The acupoint for HPT measurement was SP6 (Sanyinjiao) located on the tibial aspect of the leg, posterior to the medial border of the tibia, and 3 B-cun superior to the prominence of the medial malleolus (28). The schematic diagram of the acupoints stimulated and areas of QSTs tested were shown in **Figure 2**.

EA was performed by an acupuncturist certified in Chinese medicine, using disposable acupuncture needles (0.25 × 40 mm, Huatuo, Suzhou Medical Co. Ltd., Jiangsu, China). Two needles were inserted perpendicularly into the acupoints at the left ST36 and GB34 ∼25 mm in depth and then rotated clockwise and anticlockwise to induce a needle sensation. The EA current intensity induced a strong sensation within the subject's tolerance (15 Hz, 0.4 ms) to the HANS-200A analgesia apparatus (Nanjing Gensun Medical Technology Co. Ltd., Nanjing, China).

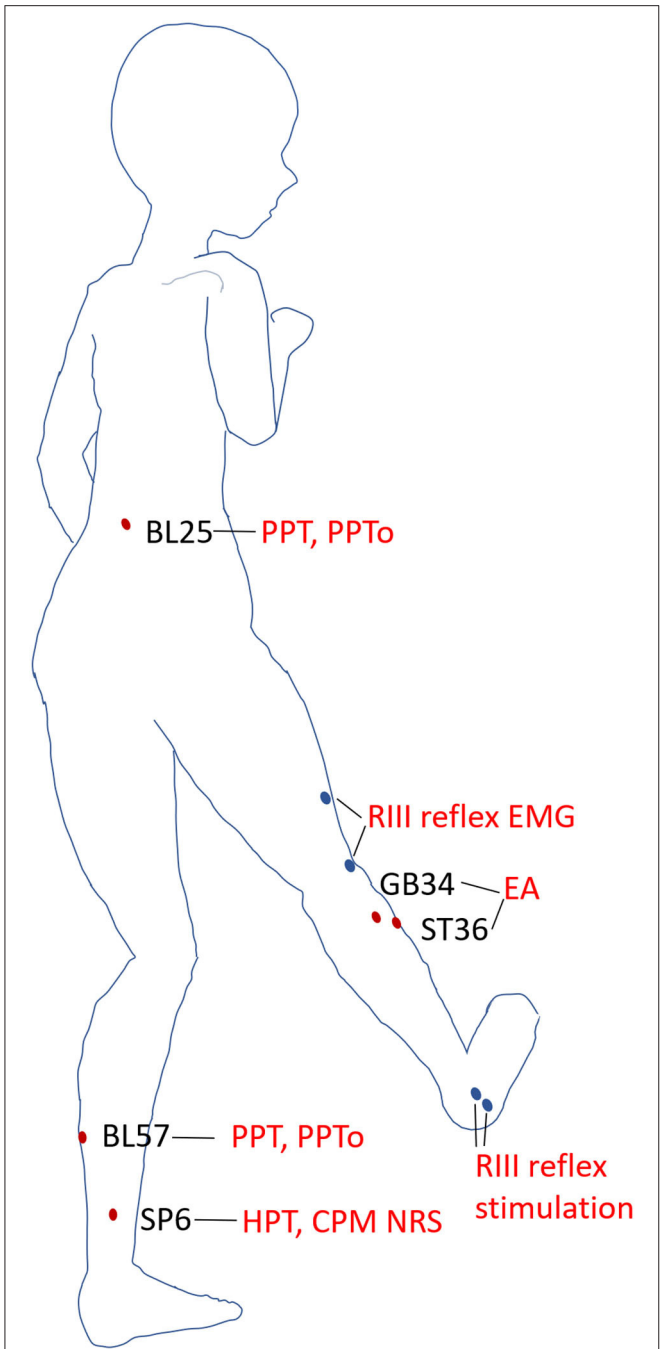

FIGURE 2 | Acupoints and areas of QSTs. Schematic diagram of the acupoints and areas tested in static and dynamic QSTs. Electroacupuncture (EA) was performed on ST36 and GB34. PPT and PPTo were examined at BL25 and BL57 in the prone position. HPT and NRS scores of heat stimulus were measured at SP6 when the subjects reclined relaxedly. The areas of RIII reflex stimulation and recording were blue dots in the diagram.

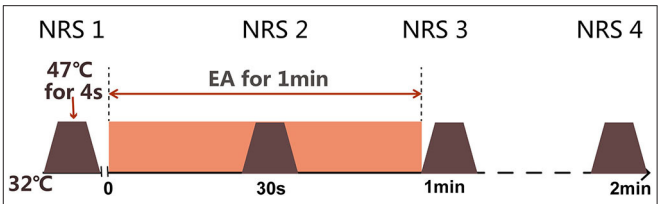

FIGURE 3 | Measurement of dynamic QST (CPM NRS). Numerical rating scale (NRS) scores are obtained under heat stimulus of 47°C at SP6 for 4 s before electroacupuncture (EA), during EA, immediately after EA, and 1 min after EA.

Before any beverage intake interventions, the numerical rating score (NRS) of heat stimulus was measured on SP6 at 0 weeks before, during (30 s), and 0 min and 1 min after EA on ST36-GB34 (**Figure 3**). PPT, PPTo, HPT, and RIII (**Figure 4**) were assessed before and after 20 min EA. PPT, PPTo, HPT, NRS, and RIII reflexes were examined at weeks 0, 2, and 4 (step 4 in **Figure 1**). The sequence of testing was that PPT, PPTo, HPT, and RIII reflex before 20 min EA. Then, NRS before, during, and 0 and 1 min after EA were examined. After 20 min EA, RIII reflex, PPT, PPTo, and HPT were reexamined. PPT, PPTo, and HPT were examined in the prone position, CPM NRS and RIII reflex were done when the subjects were reclined relaxedly. The examinations are described in detail below. The examiner was trained for 1 week to ensure correct and precise assessments according to the German Research Network on Neuropathic Pain (29).

Outcome Measures

The primary outcome measures were PPT, PPTo, and HPT. The subjects were placed in a prone position in a quiet room, and the static QST process was explained before the assessment.

PPT and PPTo

PPT and PPTo were measured using a pressure gauge device (FPIX25, Wagner Instruments, USA) with a contact probe (rubber tip) of 1 cm^2 area, a measuring range of 100 N/cm^2 (1,000 kPa), and a sensitivity of 0.1 N. The probe was perpendicularly pressed at a constant speed on BL25 or BL57. The PPT was read on the digital panel of the device if the subject verbally reported feeling pain, whereas PPTo was obtained if the subject reported intolerable pain. The same procedure was repeated three times for each subject.

HPT

Heat pain thresholds were detected using TSA 2001-II (Medoc, Ramat Yishai, Israel) with a thermode probe and a contact area of 16 * 16 mm^2. The probe was fixed to the left SP6 with a gentle and complete contact with the skin securely. The baseline temperature was set at 32°C with a heating rate of 1°C/s, and cut-off at 50°C. HPT was recorded using the computer software WinTSA 5.19 with the subject clicking a mouse when he or she felt heat pain. This measurement was repeated three times per subject. The computer screen was not visible to the subjects.

CPM NRS

NRS as dynamic QST in this study was measured using TSA 2001-II. Before the test, the subjects were informed that they will be exposed to a short heat stimulus (47°C) on left SP6 through the contact of thermode. This was the testing stimuli. EA at ST36 for

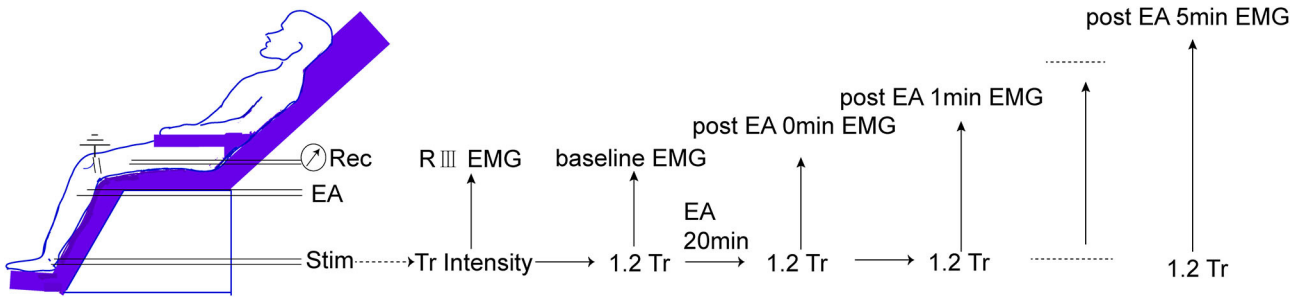

FIGURE 4 | Measurement of RIII reflex-induced EMG. The threshold of RIII reflex (Tr) is determined according to high intensities of peroneal nerve stimulation. Then, 1.2 Tr peroneal nerve stimulus is conducted every 1 min before and after 0–5 min of EA.

1 min as described in the intervention part was the conditioning stimuli. The base temperature was 32°C and was increased to 47°C at a rate of 2°C/s, which lasted for 4 s before decreasing to 32°C again (**Figure 3**). The subjects were then asked to give an NRS score from 0 to 10, according to the following criteria: 0 for no pain, 2.5 for uncomfortable feeling, 5 for pain at threshold, 7.5 for moderate pain, and 10 for unbearable pain (30, 31).

RIII Reflex

The RIII reflex was assessed to test the effects of caffeine intake on pain threshold and EA benefit. The subjects were reclined relaxedly as depicted in **Figure 4**. All electrode sites were shaved, cleaned, and abraded with NuPrep gel (Weaver and Company, USA). A reference (common ground) electrode was attached to the lateral condyle of the femurs. RIII reflex-induced electromyography (EMG) of the biceps femoris muscle of the left leg, 10 cm superior to the popliteal fossa, was recorded by surface electrodes [3 M Medical Devices Materials and Manufacturing (Shanghai) Co. Ltd, China].

The EMG signal was amplified using a bioelectric amplifier (ML135, AD Instruments, Australia) with high-cut 1 kHz and low-cut 10 Hz and recorded using Powerlab 8/30 acquisition system (ML870, AD Instruments, Australia), and online or offline analysis was processed with LabChart software (version 7.3.7) with a digital filter set between 25 and 450 Hz for noise screen with a sampling rate of 4 K/s.

The retromalleolar pathway of the sural nerve was stimulated using a stimulator (DS5—Isolated Bipolar Constant Current Stimulator, Digitimer Ltd., UK) with two Ag-AgCl surface electrodes placed 2 cm apart onto the shaved and degreased skin (eight pulses in 20 ms, and each pulse for a duration of 1 ms; for each time, four series of the above pulses were given at 0.2 Hz). The individual threshold of the RIII reflex (Tr) was the minimum stimulus intensity that evoked the EMG of the biceps femoris muscle. Baseline EMG for each subject was determined by a 1.2 Tr electric stimulus. The subjects then received EA stimulation as described in the intervention session. The EMG induced by 1.2 Tr was recorded every 1 min continuously at 0, 1, 2, 3, 4, and 5 min after EA. No change in the outcomes was made after the trial commenced.

Statistical Analysis

Data are presented as the mean and standard deviation. Data were first analyzed to determine whether they accorded to a normal distribution (Kolmogorov-Smirnov test: $P > 0.05$). All the baseline and change scores were found to be normally distributed in the sample. Baseline QST data between the two groups were analyzed by an independent *t*-test. To observe the change in analgesia efficacy of acupuncture, all data were calculated as the difference between post-EA and pre-EA. The difference in PPT, PPTo, and HPT was calculated by subtracting the baseline values from those after EA. The difference in CPM NRS scores and RIII reflex EMG integral was defined as the value during (30 s)/after (1–5 min) EA minus the value before EA. A general linear model was used to analyze group-by-time interactions. For PPT, PPTo, and HPT, the group was a fixed effect and the week was a random effect. For CPM and RIII reflex, the group was also a fixed effect and the time point was a random effect. The difference at the same week/time point between the groups was analyzed using the *t*-test. Data were analyzed using the Statistical Package of Social Science (SPSS, IBM SPSS Statistics for Windows, version 20.0; IBM Corp, USA) and SAS 9.3 (SAS Institute, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Participant Characteristics and Stimulation Parameters

All 40 subjects completed the intervention session, and no subject dropped out. There was no significant difference in the mean age and sex between the coffee and the juice group. The acupuncture expectancy scores were also not significantly different (**Supplementary Table 1**). No adverse events were reported. Sensory data obtained by QST and statistical differences are shown in **Tables 1**, **2** and **Supplementary Tables 2**, **3**.

Effect of Coffee on PPT and PPTo

The baseline PPT and PPTo values (kPa) for BL25 and BL57 showed no difference between the coffee and juice groups at 0 weeks initially (**Supplementary Table 2**).

TABLE 1 | Static QST change.

	Least square mean (SD)†		Mean score difference (95% CI)‡
	Coffee	Juice	
PPT (KPa)			
BL25 Baseline	43.77 (19.84)	42.48 (19.84)	1.29 (−54.35, 56.93)
2 wk	27.45 (19.84)	40.88 (19.34)	−13.43 (−68.36, 41.51)
4 wk	−46.40 (20.39)	72.23 (20.98)	−118.64 (−176.64, −60.65)***
BL57 Baseline	39.09 (17.96)	31.72 (18.42)	73.72 (−43.62, 58.37)
2 wk	34.20 (17.96)	22.91 (18.93)	11.29 (−40.43, 63.01)
4 wk	−30.80 (17.96)	51.10 (19.48)	−81.91 (−134.42, 29.40)***
PPTo (KPa)			
BL25 Baseline	55.43 (21.47)	16.46 (24.01)	36.47 (−23.71, 96.65)
2 wk	18.97 (21.47)	21.72 (22.03)	−27.53 (−63.72, 58.22)
4 wk	−35.01 (21.47)	37.10 (21.47)	−72.11 (−132.30, −11.94)
BL57 Baseline	41.60 (22.25)	2.60 (22.83)	39.00 (−24.15, 102.16)*
2 wk	20.17 (22.25)	35.12 (22.25)	−14.95 (−77.29, 47.39)
4 wk	−12.53 (22.25)	62.93 (22.25)	−75.47 (−137.80, −13.13)*
HPT (°C)			
Baseline	0.58 (0.37)	0.30 (0.37)	0.28 (−0.75, 1.32)
2 wk	−0.05 (0.37)	0.30 (0.37)	−0.36 (−1.39, 0.68)
4 wk	−0.11 (0.38)	−0.28 (0.43)	−0.18 (−0.95, 1.30)

† *General linear model for repeated measures with group as fixed effect, week as random effect.*
‡ *t-test.*
**Significant difference between Coffee and Juice group, *P < 0.05, ***P < 0.001.*

TABLE 2 | Statistical analysis: *P*-values from general liner models for repeated measure.

	Time	Group	Time × group
PPT			
BL25	0.317	0.009	0.007
BL57	0.374	0.164	0.021
PPTo			
BL25	0.289	0.507	0.043
BL57	0.969	0.336	0.042
HPT	0.317	0.538	0.777
CPM NRS			
0 wk	0.018	0.126	0.795
2 wk	0.024	0.387	0.976
4 wk	0.284	0.809	0.808
RIII reflex EMG integral			
0 wk	0.330	0.054	0.832
2 wk	0.992	0.001	0.935
4 wk	0.935	0.001	0.781

For the changes in PPT values (difference between post- and pre-EA), there was a significant time-by-group interaction in the PPT of BL25 ($P = 0.007$) and BL57 ($P = 0.021$) (**Table 2**). The change scores of PPT at week 4 were significantly different between the coffee and juice groups ($P < 0.001$, **Table 1**). After coffee consumption for 4 weeks, the effect of EA on PPT was attenuated.

As shown in **Table 1**, there was a significant time-by-group interaction in the PPTo of BL25 ($P = 0.043$) and BL57 ($P = 0.042$) (**Table 2**). After 4 weeks of beverages intake, the changes in PPTo (difference between post- and pre-EA) at BL25 and BL57 in the coffee group were significantly lower than those in the juice group ($P < 0.05$, **Table 1**). After coffee consumption for 4 weeks, the effect of EA on PPT was attenuated.

Effect of Coffee on Thermal Pain

There was no significant difference in baseline HPT between the coffee and juice groups ($P = 0.730$). Time-by-group interactions showed that coffee and juice intake did not affect the changes in HPT values before and after EA ($P > 0.05$, **Table 2**).

Effect of Coffee on CPM

As shown in **Supplementary Table 2**, the baseline average NRS scores in the coffee and juice groups had no significant difference between the two groups before EA ($P = 0.775$). In both groups, pain levels measured by CPM NRS were significantly lower during (T1) and after (T2 and T3) EA than at baseline (**Supplementary Table 3**). This indicated the CPM effect of EA at 47°C heat stimulus. However, there was no significant between-group difference in the CPM effect at weeks 0, 2, and 4. There was also no time-by-group point interaction ($P > 0.05$, **Table 2**).

Effect of Coffee on RIII Reflex

An example of an RIII reflex was shown in **Figure 5**. The latency of this reflex was 80 ms. The baseline threshold of RIII

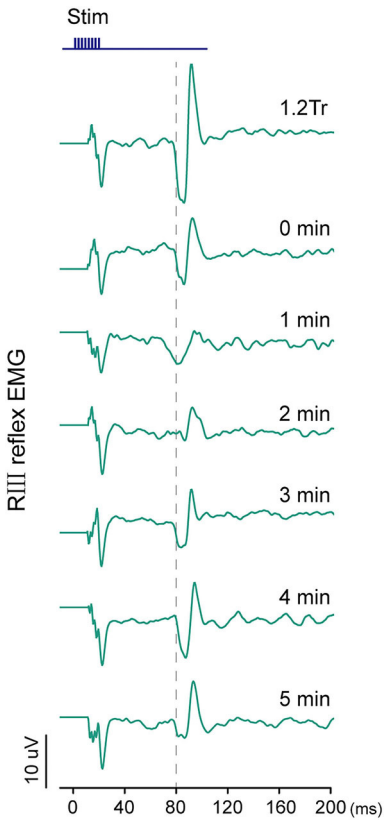

FIGURE 5 | Examples of the changes in RIII reflex EMG at baseline by 1.2 Tr, immediately after (0 min), and 1–5 min after electroacupuncture (EA) application in the juice groups at week 0.

reflex at week 0 showed no significant difference between the coffee and juice groups. At week 2, the difference in threshold was still not significant. Similar results were observed for the values at week 4 ($P = 0.805$; **Supplementary Table 2**). The baseline EMG integral of RIII reflex induced by 1.2 Tr at weeks 0, 2, and 4 had no significant difference between the two groups (**Supplementary Table 2**).

The difference in the EMG integral was calculated as the integral change in pre-EA minus post-EA application. Repeated measurements failed to show a significant group-by-time point interaction at weeks 0, 2, and 4. This indicated that caffeine intake did not influence the effect of EA on RIII reflex ($P > 0.05$, **Table 2**).

DISCUSSION

The effect of caffeine on acupuncture analgesia in humans is yet to be clarified. In this study, the difference in PPT and PPTo of BL25 and BL57 after and before EA was significantly lower in the coffee group than in the juice group. The NRS score obtained during the experimental heat pain paradigm post- and pre-EA showed no significant difference after coffee intake for 4 weeks compared with that of juice intake. The changes in EMG integral from baseline to after EA were also not significantly different between the coffee and juice groups.

PPT, PPTo, and HPT are the main measurement indices of the threshold that primarily reflects the state of the peripheral nervous system (32). The results of the current study confirmed that the PPT and PPTo of BL25 and BL57 are increased by tolerance intensities of EA at ST36 and GB34. Many clinical trials have recently shown that static QST parameters, such as PPT, PPTo, and HPT, could be markedly elevated after needling (26, 33). The spinal innervation of the points detected for PPT, PPTo (BL25: L2, 3; BL57: S1, 2), and HPT (SP6: L3, 4) are of the same or adjacent to those stimulated in EA (ST36 and GB34: L4, 5). This effect suggests a strong involvement of segmental inhibition through A-fiber signaling (26). "Tolerance intensity" was verbally described as "high to tolerable but sub-noxious" and higher than "strong but comfortable," and there were acupuncture sensations of fullness, heaviness, dull aching, or warmth (34, 35). The acupuncture sensation also suggests that Aδ and, possibly, C afferent fibers are activated. Stimulation of these fibers can elicit pain-modulating actions at the level of the dorsal horn as well as the release of endogenous opioids in the central nervous system, serotoninergic descending pain pathways, and diffuse noxious inhibitory controls (36–38).

The HPT is an index that reflects heat sensitivity. Most previous studies have indicated that HPT can be alleviated by acupuncture (32, 39) or adenosine (39, 40) in humans. However, some conflicting results have also been reported (41). In the current study, HPT was not significantly increased after EA, whereas PPT and PPTo were significantly increased. This may be explained as follows: First, the HPT is influenced by many factors (i.e., thermode area, ramp rate, anatomical site, glabrous or non-glabrous skin, and skin temperature) (42). Second, a systematic review and meta-analysis showed that 80% of the measured PPT were increased after acupuncture, while thermal detection findings were heterogeneous. Further, the assessments of pressure pain sensitivity may be more reliable than the assessment of heat pain sensitivity as the deeper tissues detected by PPT and PPTo may play an important role in many musculoskeletal pain conditions (33). One study reported a large variation in the statistical methods used when discussing the test-retest variability of the thermal threshold (43, 44). Conversely, good reproducibility of the mechanical thresholds has been reported (45).

The daily diet of the subjects was maintained, except that the coffee group consumed an extra 100–120 mg/day of caffeine, while the juice group did not consume extra caffeine. Low doses of caffeine exert an adjuvant anti-nociceptive effect in formulations containing aspirin, acetaminophen, and other non-steroidal anti-inflammatory drugs (NSAIDs) by inhibiting A_{2a}AR and A_{2b}AR (16, 46). Blockade of A1 receptors which occurs with moderate doses of caffeine can inhibit the anti-nociceptive effects of analgesics (47, 48). This effect on A1 receptors may lead to a decreased analgesic effect of acupuncture and transcutaneous electrical stimulation (49, 50), consistent with current study findings.

After 4 weeks of coffee consumption, PPT and PPTo were not significantly increased by acupuncture in the coffee group.

Furthermore, the difference in PPT and PPTo values at week 4 were smaller in the coffee group than in the juice group. The different interventions between the two groups were as coffee intake in the coffee group contained moderate (100–120 mg/day) caffeine compared with the juice group. This suggests that moderate caffeine intake attenuates acupuncture efficacy on PPT and PPTo through the blockade of adenosine receptors, which play a vital role in the analgesic effect of acupuncture. One study reported that adenosine is released during acupuncture in mice and its anti-nociceptive actions required A_1AR expression. Adenosine is degraded from ATP by several ectonucleotidases before the reuptake of ATP. Then, adenosine acts as an analgesic agent that suppresses pain through Gi-coupled A1-adenosine receptors. Adenosine was reuptaken by nucleoside transporters and degraded to inosine. The rapid clearance of adenosine in the extracellular space may shorten the anti-nociceptive effect of acupuncture (19, 50).

Consequently, we believe that acupuncture analgesia in humans is reversed after daily moderate caffeine intake (101–200 mg), consistent with previous results in animals (50). In North America, daily caffeine consumption ranges from 168 to 220 mg/day which is considered a high dose (51). Thus, our findings could provide some evidence to explain the different findings of acupuncture clinical trials between China and Western countries. A brief report showed that daily caffeine consumption did not influence the elevated PPT and HPT by acupuncture in healthy individuals (24). However, although, PPT and HPT were measured near the acupoints, they used manual acupuncture with a Deqi sensation, and the subjects were healthy individuals with low and high caffeine intake. Meanwhile, we used EA stimulation and the coffee group involved subjects with no habitual coffee habits and were given moderate doses of caffeine for 4 weeks. Thus, the heterogeneity between the two studies may be caused by differences in acupuncture stimulation and subjects (with or without coffee intake habits).

Changes in pain modulation processes, as reflected by dynamic psychophysical tests, are now being increasingly recognized as clinically relevant. The inhibition of experimental pain is tested at the bedside using the conditioned pain modulation (CPM) protocol, wherein the administration of two simultaneous painful stimuli typically results in pain inhibition. It is well-known that thermal, mechanical, or electrical pain stimuli used as the conditioning stimuli can inhibit a test stimulus. The current study showed that the changes from T1 to T3 were increased by EA intervention, and no group-by-time-point interaction was observed between the two groups at weeks 0, 2, and 4 (**Supplementary Table 3**).

CPM involves mechanisms at several levels, including modulation of the cerebral level *via* cortico-cortical interactions as well as modulation of the cerebrospinal level *via* descending pathways (52). Cerebral modulation has been shown to play a crucial role in the cognitive modulation of CPM through changes in attention, expectation, and emotion. In addition, modulation at the cerebral level plays a crucial role (53, 54). It is possible that caffeine cannot reduce the effects of acupuncture on the CPM NRS score because of the greater involvement of the central mechanisms in CPM modulation (55).

The nociceptive flexion reflex (NFR), composed of the RII and RIII reflexes, is widely used in pain research to investigate spinal and supraspinal influences on nociceptive processing in individuals with and without pain disorders. The European Federation of Neurological Societies guidelines stipulate that the RIII reflex is the most reliable nociceptive reflex for assessing treatment efficacy (56). Based on the observed EMG of the biceps femoris muscle response, the stimulation intensity required to elicit RIII is used as an objective index of the nociceptive threshold (56, 57). It is a polysynaptic and multi-segmental spinal reflex elicited by stimulation, which mainly activates nociceptive A-delta afferents.

In our previous study, transcutaneous EA of low intensities (below thresholds of RIII) on ST36 for 1 min reduced EMG induced by the RIII reflex in the ipsilateral leg. Activation of the endogenous opioid system could explain the "post-stimulus analgesic" effect (59). Moreover, some experimental evidence has revealed that neurotransmitters [e.g., serotonin (5-HT), dopamine, norepinephrine, gamma-aminobutyric acid, and glutamate] released by afferent fibers, descending terminations, or local interneurons in the dorsal horn modulate NFR in an inhibitory or excitatory manner (57). However, there are no reports on the relationship between neurotransmitters and caffeine. In this study, the RIII reflex also decreased from T0 to T6 by tolerant intensities of EA application for 20 min not only at week 0 but also at weeks 2 and 4. This supports that caffeine is not involved in the spinal nociceptive processing pathway and influences the effect of acupuncture on the RIII reflex. This could be because the targets for caffeine mainly focus on the peripheral adenosine receptor.

LIMITATIONS

This research provides evidence on the possible causes for the difference in the effect of acupuncture between Western and Eastern populations who consume caffeine more or less differently. However, this study also has some limitations. First, the effects of the study setting cannot be completely ruled out, although experiments were conducted in a calm environment with a stable room temperature, and examiners were intensively trained and blinded to group allocation. As a psychophysical measure, QST may be influenced by environmental factors and examiner (58). In addition, the placebo effect of acupuncture was not discussed in this research. The effects of subjective expectation could not be ruled out because the participants were not blinded to their drink intervention. Second, the study population was mainly medical students. They may have had previous experience with psychophysical experiments that may have influenced our results. Third, the comparison was performed for only 4 weeks. There may be some differences between long-term active caffeine consumption for years and short-term experimental caffeine intake for weeks. Further studies on patients with chronic pain are needed to validate our findings.

CONCLUSION

EA induces clinically relevant changes in the PPT, PPTo, CPM, and RIII reflexes in healthy adults. The effect of EA on PPT and PPTo was attenuated after caffeine intake, indicating a crucial role of adenosine mechanisms. This may also partially explain the difference in the analgesic effect of acupuncture between individuals who consume and do not consume caffeine.

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 human participants were reviewed and approved by China Ethics Committee of Registering Clinical Trials. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG and BZ designed the study. KL performed QST measurements. KL and XC drafted the manuscript and prepared the figures and tables. MZhi coordinated trial conductance and performed data analysis. MZha performed part of the dynamic QST measurements. TZ performed acupuncture intervention. All authors have contributed substantially to both the research and the manuscript and read and approved the manuscript.

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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.2022.859624/full#supplementary-material

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Brain Activities Responding to Acupuncture at ST36 (*zusanli*) in Healthy Subjects: A Systematic Review and Meta-Analysis of Task-Based fMRI Studies

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Purpose: Stomach 36 (ST36, *zusanli*) is one of the important acupoints in acupuncture. Despite clinical functional magnetic resonance imaging (fMRI) studies of ST36 acupuncture, the brain activities and the neural mechanism following acupuncture at ST36 remain unclear.

Methods: Literature searches were conducted on online databases, including MEDLINE, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang database, WeiPu database, and China Biology Medicine, for task-based fMRI studies of acupuncture at ST36 in healthy subjects. Brain regions activated by ST36 acupuncture were systematically evaluated and subjected to seed-based *d* mapping meta-analysis. Subgroup analysis was conducted on control procedures, manual acupuncture, electrical acupuncture (EA), and acupuncture-specific activations. Meta-regression analysis was performed to explore the effects of needle retention time on brain activities following ST36 acupuncture stimulation. The activated brain regions were further decoded and mapped on large-scale functional networks to further decipher the clinical relevance of acupuncturing at ST36.

Results: A total of sixteen studies, involving a total of 401 right-handed healthy participants, that satisfied the inclusion criteria were included in the present meta-analysis. Meta-analysis showed that acupuncturing on ST36 positively activates the opercular part of the right inferior frontal gyrus (IFG.R), left superior temporal gyrus (STG.L), and right median cingulate/paracingulate gyri (MCG.R) regions. Needle retention time in an acupuncture session positively correlates with the activation of the left olfactory cortex, as shown in meta-regression analysis. Subgroup analysis revealed

that EA stimulation may be a source of heterogeneity in the pooled results. Functional network mappings showed that the activated areas were mapped to the auditory network and salience network. Further functional decoding analysis showed that acupuncture on ST36 was associated with pain, secondary somatosensory, sound and language processing, and mood regulation.

Conclusion: Acupuncture at ST36 in healthy individuals positively activates the opercular part of IFG.R, STG.L, and MCG.R. The left olfactory cortex may exhibit positive needle retention time-dependent activities. Our findings may have clinical implications for acupuncture in analgesia, language processing, and mood disorders.

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Keywords: acupuncture, task-based fMRI, ST36 (zusanli), brain activation, systematic review

INTRODUCTION

Acupuncture, an ancient technique in traditional Chinese medicine, has been used to treat various conditions for thousands of years and has been widely accepted as an important modality of complementary therapy in modern medicine (1). Evidence has shown that acupuncture improves cerebral circulation, relieves pain, and modulates neural function (2, 3). The *deqi* sensation is the arrival of Qi, is the special feeling and reaction of the human body after filiform needles are inserted into an acupoint, and is also the key to the effect of acupuncture. It is believed that acupuncture excites afferent nerve receptors, stimulating signals that alter the central nervous system's signal integration (1). However, it is difficult to establish the central nervous effects of acupuncture in humans due to the diversity of acupoints for various clinical settings and inadequate trials.

In recent years, there has been increasing interest in studying acupuncture-related neural activities with advanced functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography, and electroencephalography (4, 5). fMRI measures the blood oxygenation level-dependent (BOLD) signals of the brain tissue, or more specifically, the oxygen demand surge in a brain region with increased neural activities, thus localizing the activity fluctuations of the brain (6). With a task-based design, fMRI is capable of measuring the temporal effects of acupuncture and capturing the activated brain regions' responses to stimulations (7).

It is important to identify the acupuncture-stimulated brain regions, which may help to elucidate the neural mechanisms of acupuncture. Among 720 acupoints on the human body, ST36 (Stomach 36, *zusanli*) is a commonly used acupoint in animal studies (8) and clinical practices for gastric disorders, stroke, pain, sleep disturbances, and some psychological diseases (9–11). Recent evidence from animal experiments has shown the neuroanatomical basis of ST36 in driving the vagal–adrenal axis, thus modulating anti-inflammatory responses in mice (12). Research in healthy individuals demonstrated the effects of ST36 in the somatosensory and motor areas, cerebellum, and limbic system (13, 14). A meta-analysis on block-design fMRI, including both patients and healthy individuals, demonstrated that acupuncture at ST36 with *deqi* sensation exclusively activates the right hemisphere of the brain, such as the right orbital part of the inferior frontal gyrus (IFG), right median cingulate, and paracingulate gyri, right supramarginal gyrus, and pons (15). Moreover, Bai et al. reported the time-varied effects of acupuncture at ST36 in fMRI (4, 16), indicating time-dependent modes of brain activity responses to acupuncture.

Without prior clinical conditions, healthy individuals are ideal subjects to identify the specific brain activities following acupuncture. Some studies have shown increased brain activities in the insula (17, 18), bilateral primary somatosensory area and the ipsilateral cerebellum, anterior cingulate cortex, superior temporal gyrus (STG) (18–20), primary visual cortex pons, medulla regions (20), and supplementary motor area (21) when acupuncture was performed on ST36 in healthy individuals; however, other studies have yielded heterogeneous results of attenuated signals in limbic and paralimbic structures, including the amygdala, anterior hippocampus, cortices of the subgenual and retrosplenial cingulate, ventromedial pre-frontal cortex, frontal, and temporal poles (17, 22), primary somatosensory (SI) cortex, secondary somatosensory (SII) cortex (21), and precuneus (13). Despite clinical fMRI studies of ST36 acupuncture, there is yet a consensus on the temporal neural activities following acupuncture at ST36 among healthy subjects.

In the present work, we summarized the current evidence of task-based fMRI studies of acupuncture at ST36 in healthy individuals with the seed-based *d* mapping (SDM) technique and functional network mapping and decoding analysis. Subgroup analysis was conducted to assess the sources of heterogeneity between manual acupuncture (MA) and electrical acupuncture (EA). Additional subgroup analysis was also conducted on control procedures (sham acupuncture, control point acupuncture, and sensory tactile stimulation) and

Abbreviations: fMRI, functional magnetic resonance imaging; BOLD, blood oxygenation level-dependent; ST36, Stomach 36, zusanli; STG, superior temporal gyrus; SI, primary somatosensory; SII, secondary somatosensory; SDM, seed-based d Mapping; MA, manual acupuncture; EA, electrical acupuncture; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MNI, Montreal Neurologic Institute; MINORS, methodological index for non-randomized studies; IFG, inferior frontal gyrus; MCG, median cingulate/paracingulate gyri; DMN, default-mode network.

acupuncture-specific activations to further understand the brain activation patterns of acupuncture at ST36. Meta-regression analysis was performed to explore the potential confounding effects of needle retention time in correlation with brain activities following ST36 acupuncture stimulation. Specifically, since many studies omitted cerebellar activations, the present study focused only on the activations located in the cerebrum.

MATERIALS AND METHODS

A systematic review and meta-analysis of the neural activities of ST36 acupuncture stimulation in healthy subjects was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and for Acupuncture (PRISMA-A) guidelines and published research protocol on INPLASY (INPLASY2021120035).

Search Strategy

We searched for studies indexed in the following online databases from inception to September 2021: MEDLINE, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang database, WeiPu database, and China Biology Medicine. The following terms were used for the search: ("ST 36" or "ST36" or "*zusanli*") and ("fMRI" or "functional MRI" or "functional magnetic resonance imaging"). Titles and abstracts were independently screened by two authors, and the bibliographies of the articles were checked for additional retrievable relevant studies.

Eligibility Criteria

Studies were selected if they met the following inclusion criteria: (1) published studies on single acupoint stimulation (c) conducted on at least 10 healthy subjects; (2) including the demographic information of the study sample; (3) conducting whole-brain analysis on task-based fMRI data; and (4) reporting the peak stimulation coordinates in standardized anatomic space, such as Talairach or Montreal Neurological Institute (MNI) space, with corresponding cluster size and statistics (voxel-wise *p*-values, *z* values, or *t* scores). Studies were excluded from the final analysis if they were (1) analyses of the region-of-interest level or (2) reviews, meta-analyses, or animal studies.

Outcome Measurement

Main Outcomes

The main outcomes are significantly activated brain regions in Talairach/MNI coordinates with corresponding cluster statistics (voxel-wise *p*-values, *z* values, or *t* scores) for baseline vs. activation comparison on ST36 acupuncturing or control procedures, for an instant, sham acupuncture, control point acupuncture, and sensory tactile stimulation.

Secondary Outcomes

The secondary outcomes are the two-sample (or group-level) comparison among acupuncture stimulation at ST36 and control procedures (sham acupuncture, control point acupuncture, and sensory tactile stimulation) regarding significantly activated brain regions (in Talairach/MNI coordinate) with corresponding cluster statistics (voxel-wise *p*-values, *z* values, or *t* scores) between groups.

Data Extraction

There were two authors independently extracted data from the original studies using a predesigned data extraction form. The following information was collected: first author's name, publication year, studied region, ethnicity, sex, sample size, dominant hand of the participants, experimental design, intervention, MRI acquisition protocols, neuroimaging processing software, and the coordinate system used in reporting of the results, as well as the correction method. Any discrepancies were resolved by referring to the original articles or consulting the lead author.

Meta-Analysis Procedures

For the SDM meta-analysis, peak stimulated brain regions with cluster statistics (*p*-values or *z* values or *t* scores) were also collected. In general, the studies reported either Talairach or MNI coordinates, a text file renamed to the first author containing peak coordinates, and the associated *t* score was created. Additionally, a datasheet, including the first author's name, *t* threshold for significant clusters, number of participants in the experiment, and control groups, was created. For studies that reported multiple comparisons, the results of the acupuncture (ST36) and sham tests were recorded. For studies that reported *p*-values or *z* values, the statistics were converted to *t* scores using the online SDM converter. If a study did not provide information about the *t* threshold or corrected *p*-value, the minimum *t* score was used as a conservative estimation. Seed-based d Mapping with Permutation of Subject Images (SDM-PSI, version 6.2.2) is used in the current work to summarize the peak coordinates of brain activities in ST36 acupuncture stimulation (family-wise error-corrected followed by threshold free cluster enhancement with 1,000 permutations), and the results are thresholded to the statistical significance level of voxel-wise $p < 0.005$ with a cluster threshold of 50 voxels. An approach was adopted by conducting full analyses after iteratively leaving one of the included studies' datasets out to test the robustness of the results. Heterogeneity analyses with I^2 statistics were carried out to examine the interstudy heterogeneity of individual clusters, and $I^2 > 30\%$ was defined as major heterogeneity.

Subgroup analysis was performed for the control procedures, such as sham acupuncture, control point acupuncture, and sensory tactile stimulation. The effects of MA and EA stimulation were also analyzed to explore the difference in brain activation under different stimulation intensities. Additional subgroup analysis was conducted in studies that reported direct comparisons between the ST36 acupuncture and control procedures to unmask the acupuncture-specified activated brain regions.

The needle retention time was meta-regressed as a variate to study the time-dependent heterogeneity of the activation in the brain during acupuncture at ST36. In the present meta-regression, if there were multiple stimulation blocks, the scanning length of the first stimulation block was regarded as the needle

retention time (min). If the study measured the brain activities for a prolonged period after one stimulation was applied and reported a series of activations with the time the activations appeared, the time (min) an activation was detected was regarded as the needle retention time. The data were extracted according to different needle retention times. For the exploratory nature of meta-regression, stringent thresholds were applied (voxel-wise $p < 0.0005$ and cluster size > 50 voxels) to decrease false-positive findings.

The included studies were placed into a non-randomized comparative design; thus, methodological index for non-randomized studies (MINORS) (23) was used to assess the methodological quality of the studies. Publication bias was assessed by graphical inspection of the asymmetry of the funnel plot for the *z* score and evaluated through Egger's test.

Mapping on Brain Network and Functional Decoding

To decipher the meta-analysis results at the network level, the identified ST36 brain activations in the meta-analysis were mapped onto large-scale functional networks based on whole-brain functional connectivity analysis (24). To further interpret the function of the identified brain regions, we used the Neurosynth database (http://www.neurosynth.org) for data-driven functional decoding. Briefly, relevant terms for which the meta-analysis map showed the largest correlations with the identified brain regions were extracted, and terms with similar functional meanings were merged and retained the largest correlation value.

RESULTS

Study Characteristics

A total of 16 studies were retrieved in the preliminary literature search. All 16 studies satisfied the eligibility criteria (4, 13, 16–22, 25–31). The detailed search processes are presented in the PRISMA flowchart in **Figure 1**. In total, 401 right-handed healthy participants consisting of 199 male and 202 female subjects were included in the current study. The characteristics of the included studies are summarized in **Table 1**. A total of two included studies were conducted in the United States, 12 studies were conducted in China, 1 study was conducted in Korea, and the remaining study was conducted in Germany. Interventions included acupuncture at ST36 with *deqi* sensation with manual manipulations or electrical stimulation, whereas the control procedures included sham acupuncture, control point acupuncture, and local anesthesia before acupuncture at ST36. All the included studies involved applying different stimulations to the same group (or partially the same group) of subjects with a multi-block design or in different sessions. A total of eleven studies conducted acupuncture at the right ST36, 3 studies conducted acupuncture at the left ST36, 1 study stimulated bilateral ST36, and 1 study performed MA at the right ST36 and EA on the left ST36. Neuroimages were acquired through a 1.5 or 3.0 Tesla MRI scanner. Analysis of Functional NeuroImages (AFNI) and statistical parametric mapping (SPM) were the dominant neuroimaging processing software among the included studies, and all results were reported in Talairach and MNI coordinate systems. Studies that reported activations from different stimulation procedures were extracted separately for subsequent subgroup analysis. Finally, baseline vs. activation results from 13 studies of verum acupuncture were used to synthesize the pooled effects of acupuncture at ST36 (4, 13, 17, 18, 22, 25–31), and baseline vs. activation results from 6 studies were pooled for the control procedure effects (4, 13, 16, 17, 22, 25).

Methodology Assessments

The potential methodological quality of the study and risk of bias were examined through the MINORS tool. Most of the studies failed to address the unbiased assessment process (blind to the evaluation of the end points, item 5), and none of the studies mentioned the sample size calculations or power estimation. Due to no current optimal standard of interventions for the neural effect of acupuncture (positive control), the included studies adopted negative control approaches, such as control point acupuncture, pressure or sensory tactile stimulation of the skin, control point acupuncture, and local anesthesia. We rated items 9 to 1 for all the studies. Hence, the overall MINORS scores ranged from 17 to 21.

Meta-Analysis

The meta-analysis shows that acupuncture at ST36 positively activates three brain clusters (**Figure 2** and **Table 2**), namely, the opercular part of right IFGr (IFG. R; Brodmann area 48; 4946 voxels; peak MNI coordinates: 48, 12, 2; peak SDM-*Z*: 5.447; $p < 0.001$; extended to right insula, Rolandic operculum, supramarginal gyrus, and STG regions), left superior temporal gyrus (STG. L; 3,095 voxels; peak MNI coordinate: −46, −6, −6; peak SDM-*Z*: 4.893; $p < 0.001$; extended to left insula, Rolandic operculum, middle temporal gyrus, and postcentral gyrus regions), and right median cingulate/paracingulate gyri (MCG. R; Brodmann area 32; 914 voxels; peak MNI coordinates: 4, 14, 44; peak SDM-*Z*: 4.570; $p < 0.001$; extended to left median cingulate/paracingulate gyri, left anterior cingulate/paracingulate gyri, and left supplementary motor area). On the other hand, control stimulation procedures positively activate brain regions similar to but smaller than those in verum acupuncture except for MCG. R (**Supplementary Table S1**), such as the right Rolandic operculum (Brodmann area 48; 1648 voxels; peak MNI coordinates: 54, −14, 14; peak SDM-*Z*: 4.719; $p < 0.001$), left postcentral gyrus (Brodmann area 43; 489 voxels; peak MNI coordinate: −58, −12, 32; peak SDM-*Z*: 4.139; $p < 0.001$), and right insula (Brodmann area 47; 55 voxels; peak MNI coordinates: 36, 22, 2; peak SDM-*Z*: 4.717; $p < 0.001$). No negative activation was identified in the verum acupuncture or control stimulations. Except for MCG.R ($I^2 = 21.607\% < 30\%$), the heterogeneity I^2 values for the remaining identified clusters were <10%, indicating no heterogeneity among the studies. The jackknife sensitivity analysis revealed that the pooled activation regions for acupuncture at ST36 were preserved, except that MCG.R failed to be identified while excluding Napadow et al.'s study (17) on EA intensity (**Supplementary Table S2**), indicating that the activation of these areas might be associated with electric stimulation or

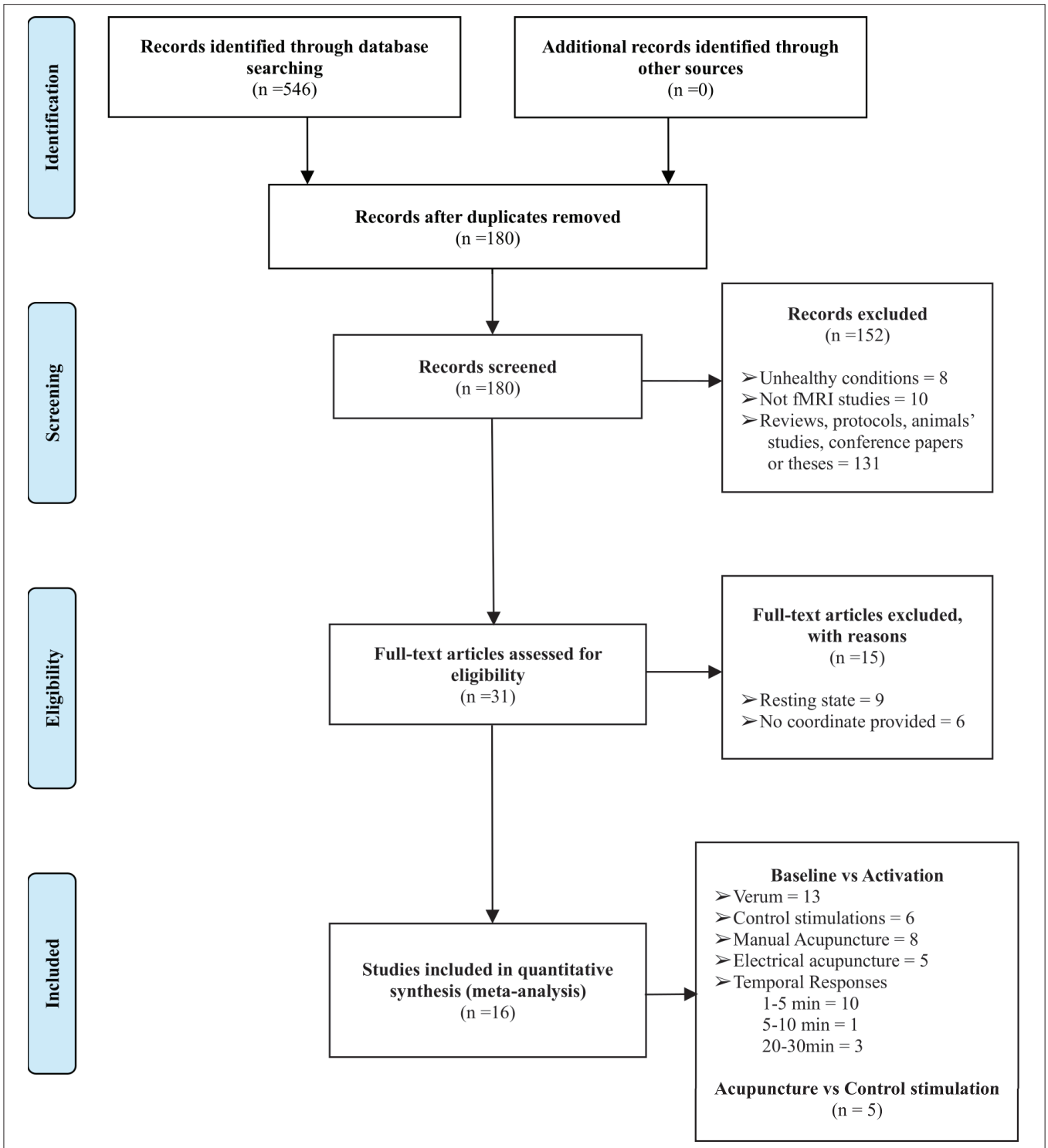

FIGURE 1 | The PRISMA flow diagram of the detailed search and literature selection processes. fMRI, functional magnetic resonance imaging.

stimulus strength. Left- and right-side stimulation could be confounding to the analysis, and we performed additional sensitivity analysis on the main outcomes with x-axis flipped results from left ST36 stimulation studies to reduce false-negative errors from the meta-analysis. Similar outcomes were shown, indicating robustly activated regions during acupuncture at ST36 (**Supplementary Table S3** and **Supplementary Figure S1**). The funnel plots of the identified clusters in ST36 acupuncture were roughly symmetric, and Egger's test did not detect significant publication biases ($p < 0.05$).

TABLE 1 | The characteristics of the included studies.

Study–author (Publication–year)	Conducted region	Ethic	Stimulation	Activation type	Block design	MRI scanner	TR/TE/Flipping–Angle/Slices–Thickness/Gap–/FOV/Matrix–size	Acupuncture protocol	Control	Processing software	Coordinate system	Study participants	Age (Years)	Sex (M/F)	Handiness	MINORS scores
Hui et al. (22)	America	Asian−1 Hispanic−2 White−12	MA, Sensory control	Baseline-activation	Multiple Stimulation Blocks	1.5-T Siemens Sonata	4000 ms/30 ms/90°/3.0 mm/0.6 mm/200×200 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:−0.22 mm **Insertion–depth**:−2–3 cm **Manipulation**:–rotate–needle–in−1 HZ–for−2 min	Tap–on–right–ST36–acupoint–with–monofilament	AFNI	Talairach	15	29.8 ± 7.5	8/7	Right	19
Napadow et al. (17)	America	Caucasian−10 Hispanic−1 African=-1 American−1 Asian−1	MA, EA, Sensory control	Baseline-activation	Multiple Stimulation Blocks	3.0-T Siemens Allegra	4000 ms/30 ms/90°/3.0 mm/0.6 mm/200×200 mm/64×64	**Location**: MA–left–ST36 EA–right–ST36 **Needle–diameter**:−0.22 mm **Insertion–depth**:−1–1.5c **Manipulation**: MA–rotate–needle–in−1 HZ–for−1 min EA−0.7–3.6 mA–biphasic–rectangular–pulses–for−1 min (1 ms–for−2 HZ, −0.2 ms–for−100 HZ)	Tap–on–left–ST36–acupoint–with–monofilament	AFNI	Talairach	13	21–42	6/7	Right	19
Li et al. (19)	China	NA	MA, Sham	Stimulus-stimulus	Single Stimulation Block	1.5-T Siemens	3000 ms/50 ms/90°/6.0 mm/1.2 mm/ 220×220 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:−0.30 mm **Insertion–depth**:–NA **Manipulation**:–rotate–needle–in−1 HZ–for−3 min	CP−1–located–on–lower–right–leg–below–the–knee CP−2–located–on–the–top–of–the–right–foot	SPM	Talairach	54	23.7 ± 3.6	31/24	Right	18

(Continued)

TABLE 1 | Continued

Study–author (Publication–year)	Conducted region	Ethic	Stimulation	Activation type	Block design	MRI scanner	TR/TE/Flipping–Angle/Slices–Thickness/Gap–/FOV/Matrix–size	Acupuncture protocol	Control	Processing software	Coordinate system	Study participants	Age (Years)	Sex (M/F)	Handiness	MINORS scores
Bai et al. (16)	China	NA	MA, Sham	Baseline-activation	Multiple Stimulation Blocks	3.0-T GE Signa–Lx	1500 ms/30 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:–0.20 mm **Insertion–depth**:—2–3 cm **Manipulation**:–rotate–needle–in—1 HZ–for—1 min	2–3 cm–lateral–to–right–ST36	SPM	Talairach	26	21.4 ± 1.8	13/13	Right	18
Jiang et al. (25)	China	NA	EA	Baseline-activation	Single Stimulation Block	1.5-T Marconi	3000 ms/40 ms/90°/NA/NA/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:–0.25 mm **Insertion–depth**:—3 cm **Manipulation**:—3-8V—5 HZ–continuous–EA–pulse–for—5 min	-	SPM	Talairach	16	18–28	10/6	Right	19
Jiang et al. (26)	China	NA	MA	Baseline-activation	Single Stimulation Block	1.5-T Marconi	3000 ms/40 ms/90°/NA/NA/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:—0.25 mm **Insertion–depth**:—3 cm **Manipulation**:–reinforcing–or–reducing–techniques with—3–8V—5 HZ–continuous–EA–pulse–for—5 min	-	SPM	Talairach	32	23.8 ± 4.3	18/14	Right	19

(Continued)

TABLE 1 | Continued

Study–author (Publication–year)	Conducted region	Ethic	Stimulation	Activation type	Block design	MRI scanner	TR/TE/Flipping–Angle/Slices–Thickness/Gap–/FOV/Matrix–size	Acupuncture protocol	Control	Processing software	Coordinate system	Study participants	Age (Years)	Sex (M/F)	Handiness	MINORS scores
Jiang et al. (27)	China	NA	EA, Sham	Baseline-activation	Single Stimulation Block	1.5-T Marconi	3000 ms/40 ms/90°/NA/NA/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:–0.25 mm **Insertion–depth**:–3 cm **Manipulation**:–3–8V–5 HZ–continuous–EA–pulse–for–5 min	2–3 cm–horizontally–lateral–to–right–ST36	SPM	Talairach	13	NA	7/6	NA	19
Bai et al. (4)	China	NA	MA, Sham	Baseline-activation	Single Stimulation Block	3.0-T GE Signa–Lx	1500 ms/30 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:–0.20 mm **Insertion–depth**:–2-3 cm **Manipulation**:–rotate–needle–in–1 HZ–for–1.5 min	2-3 cm–apart–from–right–ST36	SPM	Talairach	16	22.5 ± 1.8	8/7	Right	18
Cho et al. (20)	Korea	NA	MA, Pressure Control	Stimulus-stimulus	Multiple Stimulation Blocks	3.0-T Philips Achieva–Best	3000 ms/35 ms/90°/4.0 mm/0.0 mm/230×230 mm/64×64	**Location**:–left–ST36 **Needle–diameter**:–0.25 mm **Insertion–depth**:–1.5–2 cm **Manipulation**:–rotate–needle–in–2 HZ–for–0.5 min	Pressure–on–right–ST36–with–cotton–tip	SPM	Talairach	10	55–65	5/5	Right	19
Liu et al. (21)	China	Asian–18	MA, Sham	Stimulus-stimulus	Single Stimulation Block	3.0-T GE Signa–Lx	1500 ms/30 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:–0.22 mm **Insertion–depth**:–2–3 cm **Manipulation**:–rotate–needle–in–2 HZ–for–1.5 min	2–3 cm–horizontally–lateral–to–right–ST36	SPM	Talairach	18	24.2 ± 2.9	9/9	Right	19

(Continued)

TABLE 1 | Continued

Study–author (Publication–year)	Conducted region	Ethic	Stimulation	Activation type	Block design	MRI scanner	TR/TE/Flipping–Angle/Slices–Thickness/Gap–/FOV/Matrix–size	Acupuncture protocol	Control	Processing software	Coordinate system	Study participants	Age (Years)	Sex (M/F)	Handiness	MINORS scores
Hu et al. (28)	China	NA	MA	Baseline-activation	Multiple Stimulation Blocks	1.5-T GE Signa–HDxt	3000 ms/50 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–left–ST36 **Needle–diameter**:−0.3 mm **Insertion–depth**:–NA **Manipulation**:–thrust–and–rotate–needle–in−1 HZ–for−0.5 min	-	SPM	Talairach	20	25–29	0/20	Right	18
Sun et al. (29)	China	NA	MA	Baseline-activation	Multiple Stimulation Blocks	3.0-T Siemens Allegra	2000 ms/30 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:−0.3 mm **Insertion–depth**:−2–3 cm **Manipulation**:–rotate–needle–in−1 HZ–for−1 min	-	SPM	Talairach	50	23.3±2.1	25/25	Right	19
Jin et al. (18)	China	NA	MA, local anesthesia	Baseline-activation Stimulus-stimulus	Multiple Stimulation Blocks	3.0-T Siemens	2000 ms/30 ms/90°/5.0 mm/0.0 mm/240×240 mm/64×64	**Location**:–right–ST36 **Needle–diameter**:−0.25 mm **Insertion–depth**:−2 cm **Manipulation**:–rotate–needle–in−1 HZ–for−1–min	Subcutaneous –(2 cm–depth)–injection–of lidocaine −2ml–(5ml:0.1g)–before–acupuncture–on–right–ST36	SPM	Talairach	40	22–25	20/20	Right	17

(Continued)

TABLE 1 | Continued

Study–author (Publication–year)	Conducted region	Ethic	Stimulation	Activation type	Block design	MRI scanner	TR/TE/Flipping–Angle/Slices–Thickness/Gap–/FOV/Matrix–size	Acupuncture protocol	Control	Processing software	Coordinate system	Study participants	Age (Years)	Sex (M/F)	Handiness	MINORS scores
Li et al. (30)	China	NA	MA	Baseline-activation	Multiple Stimulation Blocks	1.5-T Siemens Symphony	4000 ms/30 ms/90°/NA/NA/192×192 mm/64×64	**Location**:–bilateral–ST36 **Needle–diameter**:−0.25 mm **Insertion–depth**:−1.5–2.0 cm **Manipulation**:−2 HZ−2mA–for−3 min	-	-	Talairach	40	21–32	20/20	RIght	19
Nierhaus et al. (13)	German	NA	MA, CP	Baseline-activation, Stimulus-stimulus	Single Stimulation Block	3.0-T Siemens Verio	2000 ms/30 ms/90°/4.0 mm/5.0 mm/NA/NA	**Location**:–right–ST36 **Needle–diameter**:−0.2 mm **Insertion–depth**:−1–2 cm **Manipulation**:–rotate–needle–in−1–1.5 HZ and–lift-thrusting−0.3–0.5 cm–in–depth–random–stimulation for−13–21s–within−6 min	CP–located–in–L5–dermatome between–Gallbladder–and–Bladder–meridian–skin–area–lateral–to–right–ST36	SPM	Talairach	22	22–32	11/11	Right	21
Wei et al. (31)	China	NA	MA, ultrasound stimulation	Baseline-activation	Multiple Stimulation Blocks	3.0-T Siemens Trio–Tim	3000 ms/30 ms/90°/3.0 mm/0.6 mm/200×200 mm/64×64	**Location**:–left–ST36 **Needle–diameter**:−0.32 mm **Insertion–depth**:−2–3 cm **Manipulation**:–rotate–needle–in−2 HZ–for−1–min	824k HZ–and−1.75w–ultrasound–stimulation–on–left–ST36	SPM AFNI	MNI	16	21–30	8/8	Right	19

MA, manual acupuncture; EA, electric acupuncture; CP, control point; NA, not available.

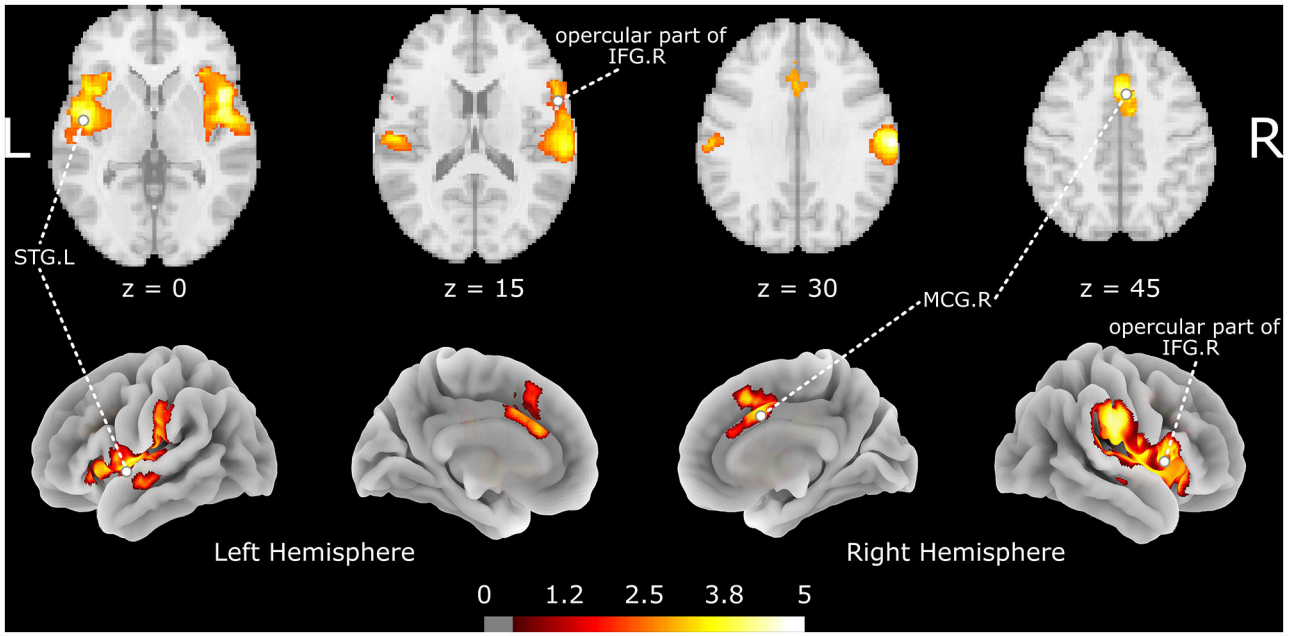

FIGURE 2 | The brain regions activated by acupuncture at ST36. The color map indicates the SDM-*Z* values with a cutoff level of 0.5; STG, superior temporal gyrus; IFG, inferior frontal gyrus; MCG, median cingulate/paracingulate gyri; L/R indicates the left or right hemisphere.

TABLE 2 | The brain regions activated by acupuncture at ST36.

Anatomical region	MNI Coordinate	SDM-*Z*	*P* value	Voxels	Cluster breakdown
Right inferior frontal gyrus, opercular part (BA 48)	48, 12, 2	5.447	< 0.001	4946	Right insula (BA 48), Right rolandic operculum (BA 48), Right supramarginal gyrus (BA 48), Right superior temporal gyrus (BA 48), Right insula (BA 47), Right superior temporal gyrus (BA 22)
Left superior temporal gyrus	−46, −6, −6	4.893	< 0.001	3095	Left insula (BA 48), Left superior temporal gyrus (BA 48), Left rolandic operculum (BA 48), Left superior temporal gyrus (BA 22), Left middle temporal gyrus (BA 22), Left postcentral gyrus (BA 48)
Right median cingulate / paracingulate gyri (BA 32)	4, 14, 44	4.570	< 0.001	914	Right median cingulate / paracingulate gyri (BA 24), Left median cingulate / paracingulate gyri (BA 24), Left anterior cingulate / paracingulate gyri (BA 24), Right median cingulate / paracingulate gyri (BA 32), Left supplementary motor area (BA 32), Left supplementary motor area (BA 8)

MNI, Montreal Neurological Institute; SDM, Seed-based d mapping; BA, Brodmann Area.

Subgroup Analysis

As shown in the meta-analysis, EA might be a potential source of heterogeneity. A total of two subgroup analyses were conducted among 8 studies that adopted manual manipulation techniques (13, 16–18, 22, 28, 29, 31) and 5 studies that performed EA (17, 25–27, 30). The results (**Supplementary Table S4**) showed that manual manipulation techniques positively activated the right supramarginal gyrus (Brodmann area 2; 158 voxels; peak MNI coordinates: 66, −22, 32; peak SDM-*Z*: 5.841; $p < 0.001$) and opercular part of right IFG (Brodmann area 48; 113 voxels; peak MNI coordinates: 48, 12, 2; peak SDM-*Z*: 4.586; $p = 0.003$). Interestingly, EA positively activates wider areas

TABLE 3 | The brain region related to needle retention time.

Anatomical region	MNI Coordinate	SDM-*Z*	*P* value	Voxels	Cluster breakdown
Left olfactory cortex (BA 11)	−4, 24, −12	3.790	< 0.0005	163	Left gyrus rectus (BA 11), Left olfactory cortex (BA 25), Left superior frontal gyrus, medial orbital (BA 11), Corpus callosum, Left olfactory cortex (BA 11), Right superior frontal gyrus, medial orbital (BA 11)

MNI, Montreal Neurological Institute; SDM, Seed-based d mapping; BA, Brodmann Area.

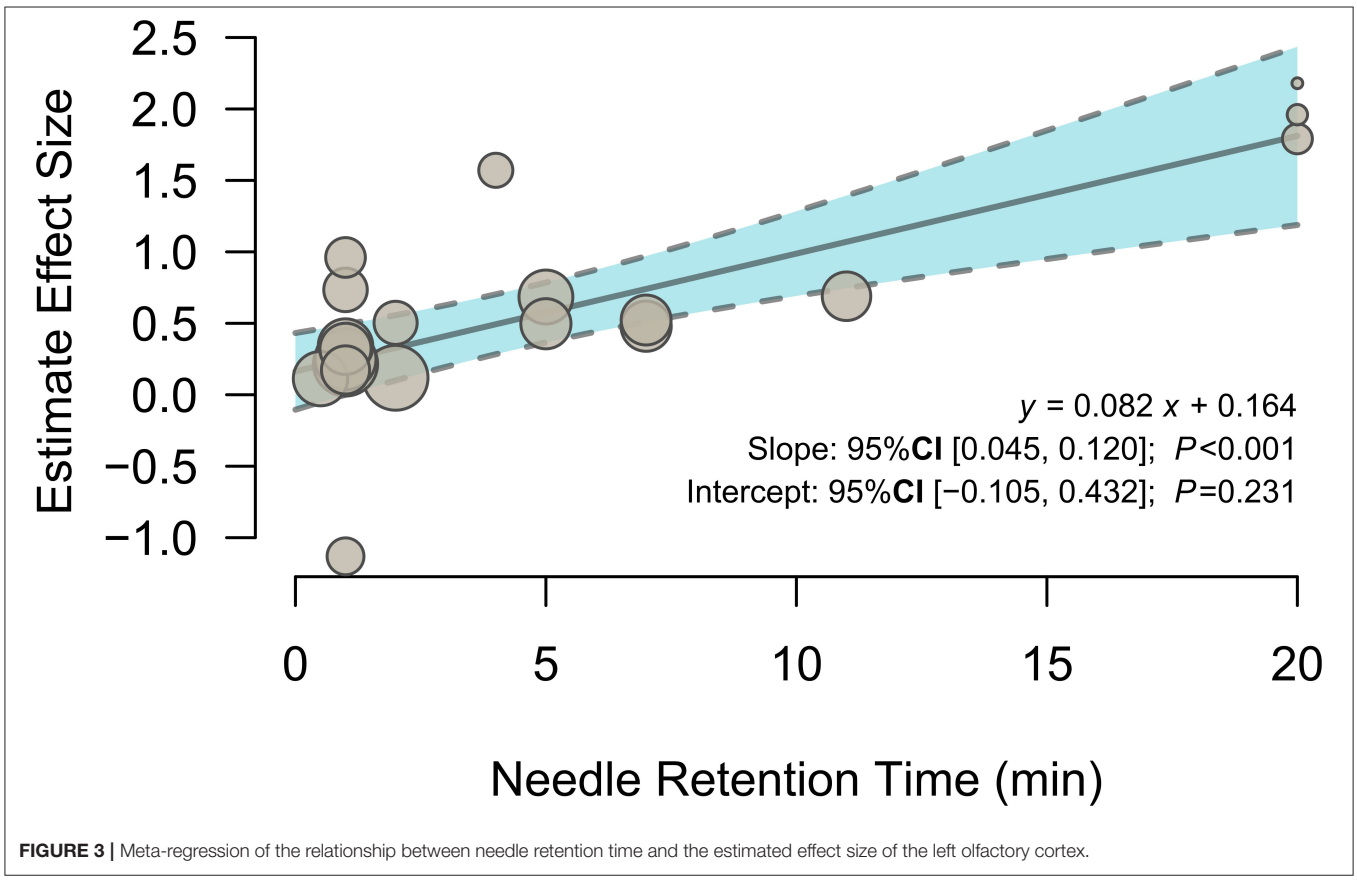

FIGURE 3 | Meta-regression of the relationship between needle retention time and the estimated effect size of the left olfactory cortex.

(**Supplementary Table S5**), such as the left superior frontal gyrus, medial orbital (Brodmann area 11; 2679 voxels; peak MNI coordinates: −6, 42, −8; peak SDM-*Z*: 4.003; $p < 0.001$), STG. R (Brodmann area 42; 2,095 voxels; peak MNI coordinates: 60, −22, 16; peak SDM-*Z*: 4.391; $p < 0.001$), STG. L (1,167 voxels; peak MNI coordinates: −46, −4, 0; peak SDM-*Z*: 4.197; $p < 0.001$), and left anterior thalamic projections (819 voxels; peak MNI coordinates: −12, 14, 6; peak SDM-*Z*: 4.323; $p < 0.001$). The subgroup analysis results of the manual manipulation techniques and EA indicated that electric stimulation could be the major source of heterogeneity in the pooled results.

A total of five of the included studies reported group-level comparisons of verum acupuncture and control stimulations (13, 18–21); hence, an additional subgroup analysis was conducted to address another interest of the present study to identify the specified brain activations of acupuncture. Compared to control stimulations, a small area located in the right supramarginal gyrus (Brodmann area 42; 86 voxels; peak MNI coordinates: 62, −24, 18; peak SDM-*Z*: 4.714; $p < 0.001$) was activated specifically following acupuncture on ST36 (**Supplementary Table S6**).

Meta-Regression Analysis

To investigate the potential effects of needle retention time, a meta-regression analysis was conducted with the mixed-effects model. The meta-regression results (**Figure 3** and **Table 3**) showed that activation in the left olfactory cortex (Brodmann area 42; 163 voxels; peak MNI coordinates: −4, 24, −12; peak SDM-*Z*: 3.790; $p < 0.0005$) was positively associated with needle retention time [effect size: 0.083 95% CI (0.045, 0.120), $p < 0.001$].

TABLE 4 | Brain network mapping of the brain regions activated by acupuncture at ST36.

Network	Overlap voxels	/	Total network voxels	Percentage (%)
Anterior salience network	966	/	4727	20.44
Auditory network	1226	/	1542	79.51
Basal ganglia network	0	/	1610	0
Dorsal DMN	12	/	7953	0.15
Higher visual network	0	/	2547	0
Language network	113	/	3850	2.94
Left ECN	0	/	4716	0
Posterior salience network	606	/	3155	19.21
Precuneus network	0	/	2635	0
Primary visual network	0	/	1120	0
Right ECN	0	/	6995	0
Sensorimotor network	0	/	5024	0
Ventral DMN	0	/	5325	0
Visuospatial network	129	/	5479	2.36
Total overlap / Total activated voxels	3052	/	8955	34.08

DMN, default mode network; ECN, executive control network.

Large-Scale Brain Network Mapping and Functional Decoding

The activated brain regions following acupuncture on ST36 were mapped on the large-scale functional network atlas, showing that the majority of voxels mapped to the auditory network, anterior salience network, and posterior salience network, and some small regions were mapped to the visuospatial network, language network, and dorsal default-mode network (DMN). To further decipher the functional effects of ST36 acupuncture, a neurosynth decoding analysis was performed. As shown in **Table 4**, which depicts the functional profiles, acupuncture on ST36 was associated with SII stimulation, such as pain, touch, tactile, and electrical stimulation; sound and language processing, such as auditory sensory and speech; and mood regulation (**Figure 4**). The full list of the decoding results is recorded in **Supplementary Table S7**.

DISCUSSION

The introduction of fMRI technology is advantageous to acupuncture research in that neural-therapeutic mechanisms of the (de)activation of brain regions under acupuncture intervention can be accessed on an image-referencing basis. Studies have shown that acupuncture of ST36 induces multiple activations of relevant brain regions, including the frontal lobe, temporal lobe, postcentral and cingulate gyri, insula, hypothalamus, hippocampus, and other limbic systems (32, 33), but the results were based on relatively small sample size and heterogeneous. The present work is a meta-analysis summarizing task-based fMRI studies of ST36 acupuncture in healthy individuals. The pooled results showed the opercular part of IFG. R, STG. L, and MCG. R regions were positively activated following ST36 acupuncturing, and no negative activations were detected. Functional network mappings of the identified clusters revealed that the activated areas were located in the auditory network, anterior salience network, and posterior salience network. Further functional decoding implied that our findings may help to elucidate the neural targets of acupuncture at ST36 for pain, speech, and mood disorder management.

Stomach 36 has been an important acupoint for improving gastrointestinal function and enhancing physical fitness since ancient China. ST36 is located in the tibialis anterior muscle four fingers beneath the lower patella margin and one finger aside from the anterior border of the tibia and is thought to strengthen the spleen and stomach, relax the meridians, activate collaterals, and strengthen the body in Chinese medicine theory. ST36 acupuncture is popular for analgesia, cognitive function and cerebral circulation improvement, and gastrointestinal disease regulation in modern practices. Studies on cerebral infarction patients and animal models have reported that acupuncture at ST36 improves brain metabolites and memory function and promotes motor function, indicating neural and cognitive recovery promoting the effects of acupuncture (34, 35). Moreover, acupuncture at ST36 has neuroprotective effects in hydrocephalus infantile rats, exhibiting anti-inflammatory and neuroprotective effects *via* inhibition of reactive astrogliosis (36).

In the present study, we mainly focused on temporal brain activities following an acupuncture session. We found that acupuncture at ST36 positively activates the opercular part of IFG. R, STG. L, and MCG. R, which is consistent with the conclusions of another meta-analysis that reported brain activations following acupuncture at ST36 with *deqi* sensation in subjects with varying background health situations (15). The clusters of the opercular part of IFG. R and STG. L were stable in jackknife analysis, indicating the robust activation of these regions during ST36 acupuncturing. The IFG and STG regions, involved in the classic Wernicke–Lichtheim–Geschwind language processing model (37), are the important components of the auditory network that are in line with the results in large-scale network mapping and functional decoding analysis. Part of the human ability to comprehend syntax and syntactic processing, as well as overall language comprehension seems to be located in the IFG (38). The STG is primarily responsible for processing sound and is also involved in processing the emotional meaning derived from facial expressions (39). The auditory network, consisting of the IFG, STG, and adjacent insula, plays an important role in language and interaction with the environment (40). However, there are limited reports on the relationships between acupuncture at ST36 and the auditory network, and the clinical applications of acupuncture in language disorders should be explored.

The activated regions also extend to bilateral insular areas that involve pain processing (41). Interestingly, it has been reported that the insular/opercular area is one of the strongest activated regions in thermal stimulation and electrostimulation and positively responds to stimulation intensity during electrostimulation (42, 43). The brain area associated with somatic nociception and central neuroendocrine system regulation is inhibited after acupuncture at ST36 (44).

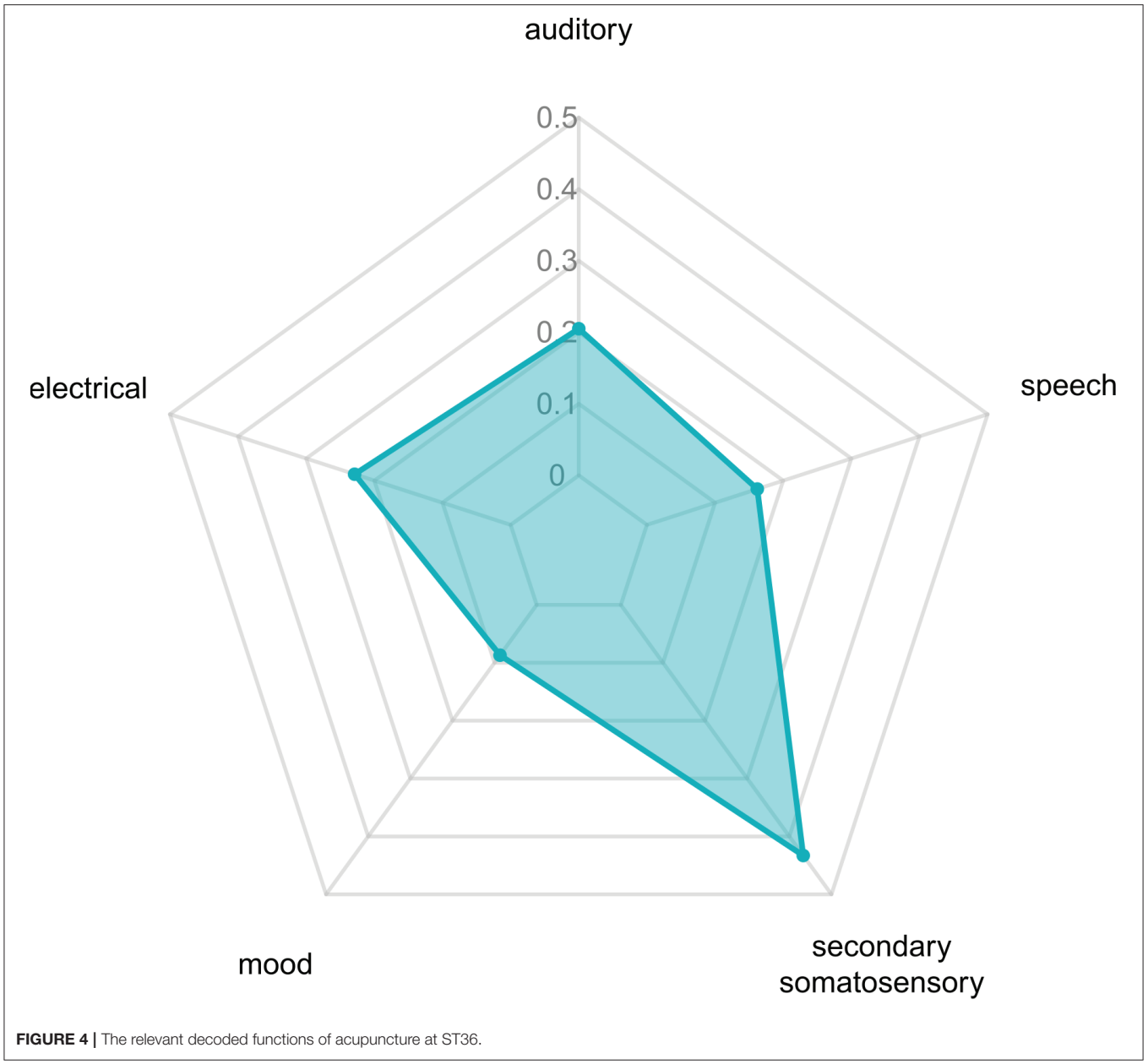

FIGURE 4 | The relevant decoded functions of acupuncture at ST36.

Multiple limbic system regions, mid-inferior occipital gyrus, precentral gyrus, and postcentral gyrus with altered long-term simultaneous activities after ST36 acupuncture associated with sensation and pain, are found in the studies (45, 46), which implies that the modes of action to the central nervous system for acupuncture analgesia may be time-dependent. Further research is needed to elucidate the short- and long-term mechanisms of acupuncture.

The MCG together with the parahippocampal gyrus are the important components of the limbic lobe with the functional of emotion processing and short- or long-term memory conversion (47). However, the cluster in the MCG was unrobust in jackknife analysis after the removal of the results from the study of Napadow *et al.* (17), which introduced EA stimulation at ST36. Although we did not identify significant heterogeneity among clusters, EA treatment could be a potential source of heterogeneity. Subgroup analyses for MA and EA stimulation were performed separately. The results revealed that the extent of activation in brain regions after EA stimulation was much greater than that after MA stimulation, indicating that different neural mechanisms may underlie EA and MA during acupuncture. A study showed that electrical stimulation at other acupoints generated different activation patterns (48), indicating that acupoint-specific activations may exist. However, Jin *et al.* (18) blocked the local sensation with lidocaine infiltration subcutaneously in healthy subjects before MA, resulting in

an attenuation of the activated regions without anesthesia, indicating that cutaneous sensation (*deqi* feelings) may be the major aspect of stimulation that generates brain activation. The effects of ST36 on gastrointestinal diseases have been frequently reported (49, 50). One of the included studies showed that the oscillated secretion of gastric-related peripheral humoral factors is accompanied by hypothalamus activation in healthy subjects during EA stimulation (27). However, the pooled results and the subgroup analysis results did not show hypothalamus activity alteration, which may be due to complex gut–brain regulations that remained unclear. Additionally, subgroup analysis of control procedures revealed activation patterns similar to those following verum acupuncture. As the subgroup analysis results could not be directly compared, whether most of the acupuncture effect comes from electrical (or cutaneous) stimulations is still unknown.

We screened five studies reporting the intragroup comparison results of acupuncture vs. control for subgroup analysis to explore the ST36-specific activation of brain regions during acupuncture. The results showed that the activation of a small area located on the right supramarginal gyrus is specific to ST36 acupuncture. However, the findings conflict with the result that the regions that are specific to ST36 acupuncturing partially overlapped with the control stimulation pooled results. Moreover, based on the relationship between the group activations and the baseline, four activation modes can be observed in intragroup comparisons of task-based fMRI studies, namely, hyperactivations (treatment > control in task > baseline), hypo-activations (treatment < control in task > baseline), failures of deactivation (treatment < control in task < baseline), and hyperactivation (treatment > control in task < baseline) (51, 52), but the studies included in the subgroup analysis provide no information on the accurate activation mode, and we simply regarded the results as hyperactivation and failures of deactivation in the subgroup analysis. Thus, the result should be interpreted with caution.

Acupuncture treatment sessions generally take 5 to 40 min; hence, the relationship between needle retention time and brain activity is another important interest in the present work. Positive brain activation was found in the left olfactory cortex that positively correlated with needle retention time. Research has linked the association between acupuncture and olfactory regions. A canine model study has shown the left olfactory peduncle activation after postanesthesia acupuncture at BL60 (*Kunlun*) (13). Acupuncture at Li4 (*Hegu*) and Li20 (*Yingxiang*), as well as other acupoints, showed to improve olfactory sensitivity in healthy subjects (53) and postinfectious smell loss patients (54). Although olfactory dysfunction is one of the initial symptoms that appear years before motor symptoms and cognitive decline in several neurodegenerative diseases (55, 56), studies have tested the activation effects of acupuncture at ST36 to the left olfactory cortex on Alzheimer's animal models (57, 58), and clinical evidence on ST36 acupuncture effects in the olfactory cortex is still lacking. Our findings indicated that prolonged needle retention time during acupuncture at ST36 may strengthen the activation of the left olfactory cortex in healthy subjects, and thorough probe investigations into the clinical implications of this exploratory result may be required.

The mapping of acupuncture ST36-activated brain regions to a large-scale functional network atlas shows that most voxels map to auditory networks, the anterior salience network, and the posterior salience network, as well as the visuospatial network, language network, and dorsal DMN. The functional decoding results suggested that the activated regions were involved in pain, SII, electrical stimulation, auditory sensory and speech, and mood regulation. A study reported consistent results that acupuncture at ST36 produced the activation in the somatosensory area, insula, and the median cingulate cortex but deactivation in DMN areas (59). You *et al*. (60) reported alterations in DMN hub configurations following acupuncture at ST36. A meta-analysis of acupuncture for low back pain revealed that the brain regions involved in acupuncture were located in the salience network, DMN, pain matrix, and descending pain modulatory system (61), demonstrating the analgesic effect of acupuncture. The DMN is associated with several advanced cognitive functions; the salience network mediates the switching between the DMN and the central executive network, and those three networks are theoretically the core "triple networks" in cognition. The modulator interactions between the "triple networks" following acupuncture at ST36 need further investigation.

Notably, no SI area activation was observed in our pooled results, which may be inconsistent with some previous acupuncture fMRI results. Activations in SI have been reported in the included acupuncture studies (13, 22). However, another included study demonstrated decreased activities in the SI and SII, which might be due to ST36 inhibited or modulated pain sensory for analgesic effects (21). A recent study showed the activations in SI and SII, insula, and thalamus region during sponge scrubbing, whereas the SI region did show activation during real acupuncture at Li4 (Hegu) (62). Another study reported evidence of functional diversity within SI that higher SI activation was found in the anticipation phase (a visual cue to inform participants that pain would be delivered) and lower activation in pain stimulation, indicating the differences in attentional and sensory pain processing (63). In our results, SII activation was observed and agreed with the frequently reported results, indicating that acupuncture may involve complex sensory processing. Nonetheless, the somatosensory and analgesic mechanism for acupuncture at ST36 remains to be further researched.

The present study had the following limitations. First, the number of included studies and the total number of involved participants were relatively small. Second, the present meta-analysis did not study the effects of *deqi* sensations which are believed to be a key factor in the therapeutic effect of acupuncture. Although the acupuncture sensation scale (64), the Massachusetts General Hospital acupuncture sensation scale (65), and the Southampton needle sensation questionnaire (66) were introduced and validated, inconsistencies in the evaluation of *deqi* sensations were found across the included studies, and it was difficult to precisely define the intensities of *deqi* sensations in the present meta-analysis. Universal tools for quantifying the *deqi* phenomenon may be of value in further

research. Third, there is a relatively large publication year span of the included studies. Techniques and software have been substantially updated, which may introduce inestimable heterogeneity to the results. Forth, despite in most experimental paradigms, the needles were inserted into the skin before the scan and stayed in place throughout the scan session, the effects of the needle penetrating the skin were ignored. The needle retention time for the meta-regression was only considered as one stimulation period or plus the following non-resting state period but not the full length of the session. Specific experimental paradigms and analysis workflow considering for the nature of the acupuncture therapeutic effects may be needed in further studies. Fifth, the included studies tested different stimulations on the same subjects, and the design inevitably faces the concerns of selection bias and incomplete washout periods. A randomized controlled design with a larger sample size should be adopted in future research. Sixth, the MINORS scores of the included studies were below the recommended cutoff for comparison studies, suggesting methodological defects in the studies. However, considering the specialized designs, developing a new assessment tool for comprehensive methodological evaluation of task-based fMRI studies may be a solution. Finally, this study examined acupuncture-specific brain activation. Because of the relatively small sample size of included studies and unclarified mode of activation in the two-sample comparisons, the results need to be interpreted with caution. Nonetheless, acupuncture-specific brain activity is an important topic that warrants rigorous clinical studies and experimental validations.

CONCLUSION

Acupuncture at ST36 in healthy individuals mainly activates three clusters located in the opercular part of IFG.R, STG.L, and MCG.R. EA stimulation may expand the activated brain regions. The needle retention time during an acupuncture session may enhance the activation of the left olfactory cortex. Our findings facilitate an understanding of the mechanisms of acupuncture treatment and provide neurological evidence for the clinical implications of acupuncture in analgesia, language processing, and mood disorders.

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

HH, XY, and XH performed data analyses and wrote the main manuscript. SK, YR, and YW were involved in the search and selection of eligible articles. WL, LW, and JZ extracted the data. JZ and HL were responsible for image preparation. SQ and WZ designed the research study. All authors reviewed and approved the manuscript.

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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.2022.930753/full#supplementary-material

Supplementary Figure S1 | The brain regions activated by acupuncture at ST36 with flipped results from left ST36 stimulation studies. The color map indicates the SDM-*Z* values with a cutoff level of 0.5; L/R indicate the left or right hemisphere.

Supplementary Table S1 | The brain regions activated by control stimulation. MNI, Montreal Neurological Institute. SDM, seed-based *d* mapping; BA, Brodmann area.

Supplementary Table S2 | The jackknife sensitivity analysis of the activated regions for ST36 acupuncture. BA, Brodmann area.

Supplementary Table S3 | The brain regions activated by acupuncture at ST36 with flipped results from left ST36 stimulation studies. MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping; BA, Brodmann area.

Supplementary Table S4 | The brain regions activated by manual acupuncture at ST36. MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping; BA, Brodmann area.

Supplementary Table S5 | The brain regions activated by electrical acupuncture at ST36. MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping; BA, Brodmann area.

Supplementary Table S6 | The brain region activated is specific to verum acupuncture at ST36. MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping; BA, Brodmann area.

Supplementary Table S7 | Functional decoding of activated brain regions following acupuncture at ST36.

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Efficacy and safety of acupuncture combined with auricular acupressure for smoking cessation: A study protocol of a multicentre, randomized, controlled clinical trial

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Background: Nicotine dependence is an addictive behavioral disease facilitated by habitually smoking cigarettes. In many countries, acupuncture and auricular acupressure have attracted growing attention as complementary or alternative treatments for smoking cessation; however, there is a lack of rigorous randomized, controlled studies evaluating the combination of these two interventions specifically for smoking cessation. The aim of this study is to evaluate the efficacy and safety of using acupuncture combined with auricular acupressure (A&AA) to increase the rates of smoking cessation and ultimately reduce the rates of relapse.

Methods: This is a multicentre, prospective, parallel, randomized, controlled trial. A total of 360 patients with severe nicotine dependence will be randomized into test (A&AA) or control (nicotine replacement therapy, NRT) groups. The test group will be treated with A&AA twice weekly, while the control group will use an NRT patch daily. All treatments will be administered for 8 weeks, with a follow-up period of 4 months. The primary outcome will be the smoking abstinence rate at week 24, with a combined safety assessment. The secondary outcomes will be smoking cessation rates at other timepoints, saliva cortisone test results, and scores on the Fagerstrom Test for Nicotine Dependence, the Autonomy over Tobacco Scale, the Hamilton Anxiety Rating Scale, the Self-rating Anxiety Scale, and the Pittsburgh Sleep Quality Index. The cost of treatment will also be used to evaluate the economic effects of different smoking cessation interventions. Statistical analysis on the data collected from both the intention-to-treat (all randomly assigned patients) and per-protocol (patients who complete the trial without any protocol deviations) patients, will be performed using the statistical software package, IBM SPSS 27.0.

Discussion: This study will provide rigorous clinical evidence evaluating the efficacy and safety of using A&AA as a smoking cessation therapy.

Trial registration: Chinese Clinical Trial Registry (Registration number: ChiCTR1900028371).

KEYWORDS

acupuncture combined with auricular acupressure (A&AA), smoking cessation, nicotine dependence, acupuncture therapy, auricular acupressure therapy

Background

Nicotine dependence has been classified as a mental and behavioral disorder by the 2010 International Classification of Diseases codes issued by the World Health Organization. According to research published in the fields of tobacco economics and control, tobacco kills approximately six million people, costs the world's economies more than one trillion dollars annually, and remains one of the major causes of premature death (1). China has the highest rates of cigarette addiction worldwide, especially among male smokers. In China, more than one million people lose their lives each year from smoking-related diseases (2). Diseases and mortality associated with smoking pose a serious threat to public health. The high smoking rate and the difficulty in controlling this addiction suggests that key policymakers should devote significant resources to this issue. In fact, health authorities in many countries have strongly recommended that doctors intervene to help patients quit smoking.

The main methods for achieving smoking cessation are nicotine replacement therapy (NRT), antidepressant medications, and psychological counseling, with various studies confirming that these methods improve the success rate of smoking cessation to varying degrees (3, 4). Unfortunately, these therapies also have potential side effects, including chest tightness, insomnia, dry mouth, skin allergies, and gastrointestinal reactions (5–12), which can reduce patient compliance and most importantly, the efficacy of smoking cessation.

Since 2015, complementary and alternative medicine for substance use disorders has increasingly gained attention, and acupuncture may be a hotspot in this field (13). Various types of acupuncture, such as hand acupuncture, ear acupuncture, laser acupuncture, have gained attention in many countries as therapeutic interventions for smoking cessation (14). In a smoking cessation trial in Norway (15), the experimental group received an acupuncture intervention at the "Shenmen," "Mouth," and "Liver" acupoints of the ear, as well as at the acupuncture points, Kongzui (LU 6) and Lieque (LU 7), leading to significant changes in the taste of cigarettes and the desire to smoke, compared with the control group. A multicentre, randomized trial of 300 patients in China (16) also showed that the effects of acupuncture on smoking cessation were not inferior to NRT. Available evidence supports the acupuncture therapy have very wide popularization and application prospects in smoking cessation, while it is also suggested that single type acupuncture therapy is relatively insufficient in the long term of the abstinence rate, and the evidence is insufficient in the efficacy of combined acupuncture therapy (17–19). Thus, we carry out this RCT to observe the effect of combined acupuncture therapy on smoking cessation.

This multicentre, randomized, controlled clinical trial, which is based on a previous study of acupuncture for smoking cessation, will be the first to evaluate whether the combination of a short-term but strong stimulation, elicited by acupuncture and the long-term, milder stimulation elicited by auricular acupressure, will lead to better smoking cessation outcomes. Additionally, we hope to determine whether this treatment (A&AA) has better smoking cessation outcomes and is safer than NRT. We also hope to evaluate the benefits of A&AA from the perspective of health economics, in order to develop effective and affordable smoking cessation plans.

Methods

Study design

For this study, a multicentre, prospective, randomized controlled trial will be conducted to compare the effects of A&AA with those of NRT, on smoking cessation. A total of 360 patients with severe nicotine dependence, who are willing to voluntarily quit smoking, will be randomly divided into a treatment group (A&AA) or a control group (NRT). The First Affiliated Hospital of Guangzhou University of Chinese Medicine, the Hong Kong Pok Oi Hospital, and the Shenzhen Chinese Medicine Hospital will be responsible for patient recruitment, screening, interventions, and the follow-up of 280, 30, and 50 patients, respectively. All outcomes will be assessed at The First Affiliated Hospital of Guangzhou University of Chinese Medicine. Management of the randomization

Abbreviations: A&AA, acupuncture combined with auricular acupressure; NRT, nicotine replacement therapy; TCM, Traditional Chinese Medicine.

sequence, blinding, and data analyses, will be carried out at the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. Ethical approval for this study was received from the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. ZYYECK [2019] 099), and this study will be conducted according to the Declaration of Helsinki, 7th revision (2013). Informed written consent will be obtained from all patients. The flow diagram for patient selection and methodology is shown in Figure 1. This protocol is reported in accordance with the Standard for Reporting Interventions in Clinical Trials of Acupuncture recommendations (STRICTA) (20).

Patients

Smokers have the intention to quit smoking and meet our following criteria will be recruited at three sites simultaneously. Posters, leaflets and WeChat advertisements will be used in the recruitment process. Formal enrollment is only considered if participants signed written informed consent.

Inclusion criteria

Patients who meet all the following criteria will be included: (1) Meet the diagnosis of ICD-10 Nicotine Dependence; (2) between 18 and 65 years of age; (3) smoking history of ≥1 year; (4) currently smokes ≥20 cigarettes per day over the past 1 year; (5) detection of cotinine in saliva; (6) a Fagerstrom Test for Nicotine Dependence (FTND) score of ≥4; (7) willingness and ability to sign a consent form, ensuring that they understand the trial and will take part in it voluntarily; and (8) an elution period of more than 1 month for all smoking cessation therapies, including acupuncture, auricular acupressure, and NRT.

Exclusion criteria

Patients will be ineligible to participate in this trial if they meet any of the following criteria: (1) severe heart, lung, brain, or blood system diseases or diabetes; (2) drug use or those diagnosed with mental illnesses; (3) history of stroke or nervous system diseases; (4) unexplained symptoms; (5) history of a coagulation disorder or anticoagulant drug history; (6) moderate or severe impairment of liver or kidney function; (7) pregnant or breast feeding; or (8) already using smoking cessation therapies, such as acupuncture, auricular acupressure, NRT, etc.

Elimination criteria

Patients will be eliminated from the trial based on the following criteria: (1) patients who are willing to participate, but fail to meet the inclusion criteria, and (2) those who fail to complete instructions or procedures with obvious implications for efficacy or safety.

Termination criteria

The trial will be terminated if the following situations occur during its course: (1) therapies exacerbate the state of the illness or lead to secondary infections; (2) external factors worsen the patients' conditions; or (3) patients are unwilling to continue the trial.

Sample size

According to a previous randomized, controlled study of acupuncture for smoking cessation (15), we expect that the success rates for smoking cessation will be on average 44% in the NRT (control) group and 60% in the A&AA (treatment) group, using the abstinence rate for smoking cessation at week 24 (24-h carbon monoxide [CO] clearance rate of <10 parts per million) as the primary outcome. Using PASS 2008 software, the sample size required for each group was estimated to be 152 cases by two independent sample rate comparison methods.

Therefore, considering an expected loss of 15% during the follow-up period, we will recruit a total of 360 (≈304/0.85) volunteers for this study. Allocation into the two groups will be assigned in a 1:1 ratio, and each group size will be set at 180.

Randomization and allocation

Eligible patients will be randomly assigned to receive A&AA or NRT *via* a central randomization system (Clinical Research and Data Center, Guangzhou University of Chinese Medicine). Random numbers will be generated using the stratified block method by a designer from the Clinical Research and Data Center, not involved in the study. Because of the obvious differences between the two types of therapies, blinding of patients and healers will not be possible; therefore, only outcome evaluators will be blinded to the treatment allocation.

Interventions

Patients with chronic diseases who are taking medication can continue to take medication as prescribed by specialist doctors during the phase of this trial.

A&AA group

Patients in this group will receive acupuncture and ear acupuncture treatment in sequence delivered by licensed

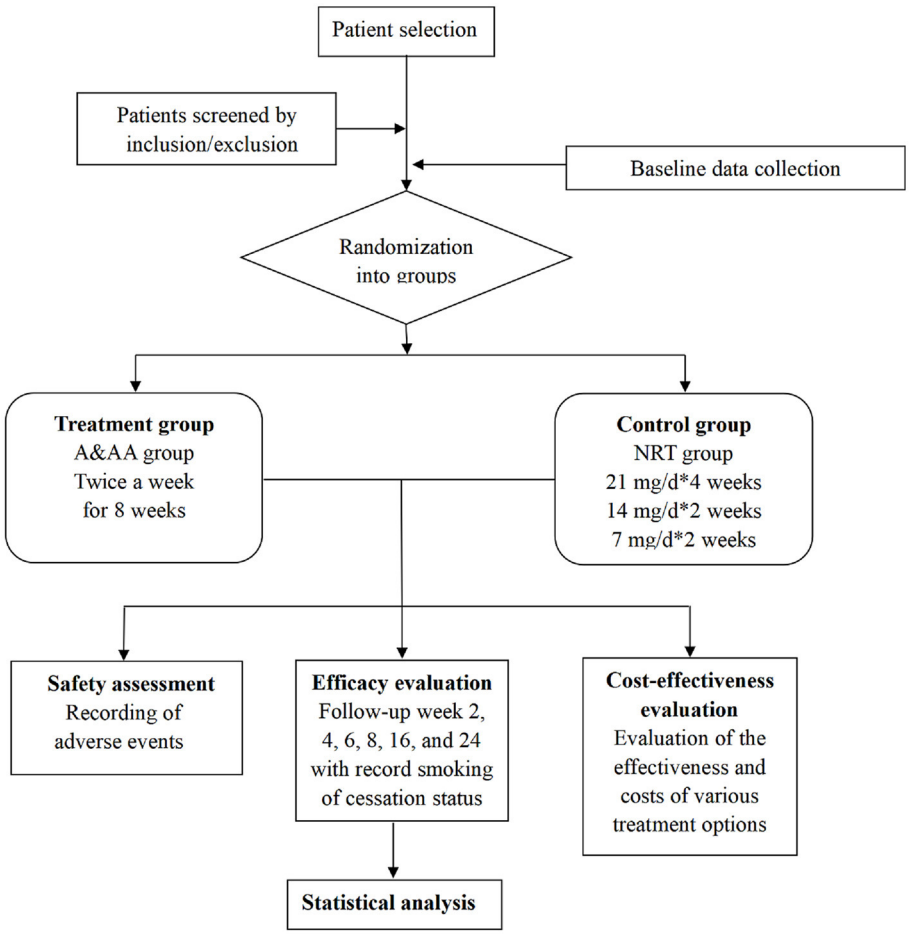


FIGURE 1
Patient selection and methodological flow.

acupuncturist with at least 5 years of therapeutic experience. Locations of all the acupoints are in line with the National Standard of the People's Republic of China's (GB/T 12346–2006) standard.

Manual acupuncture acupoint prescriptions include:Baihui (DU 20), Yintang (EX-HN3), bilateral Lieque (LU 7), and bilateral Hegu (LI 4) (Figure 2). The acupuncture procedure will be as follows: Before acupuncture, patients will be placed in a supine position to expose the acupoints. After skin disinfection, 40-mm disposable sterile needles will be inserted horizontally at Baihui (GV 20), bilateral Hegu (LI 4), and bilateral Lieque (LU 7, point to Yangxi), and a 25 mm needle will be inserted vertically at Yintang (EX-HN3). The neutral supplementation and draining method will be applied at all acupoints for 30 min after achieving the arrival of qi; the needle will be manipulated every 10 min to avoid discomfort (needle sensation as soreness or numbness).

After the acupuncture procedure, auricular compression at Shenmen (TF 4), Fei (CO 14), Wei (CO 4), Neifenmi (CO 18), Pizhixia (AT 4), and Jiaogan (AH 6) (Figure 3) will be applied. The acupuncture procedure will be as follows: after routine disinfection of the auricle and ear circumference, a patch of vaccaria seeds will be stuck to the auricular acupoints mentioned above on one ear (contralateral to the ear on which this technique was performed 3-day earlier). In addition, patients will be instructed to press each auricular acupuncture point for 60 s, 3–5 times per day.

The A&AA interventions will be performed simultaneously twice a week for a total treatment course of 8 weeks.

NRT group

Patients in the NRT group will receive NRT patches purchased from Novartis (approval number: N07BA01) which are composed of nicotine at three different dosages, including 21, 14, and 7 mg. After removing the protective foil, the patch will be applied to a clean, dry, intact area of skin (free from lotion, alcohol, or ointment), preferably on the trunk or otherwise on

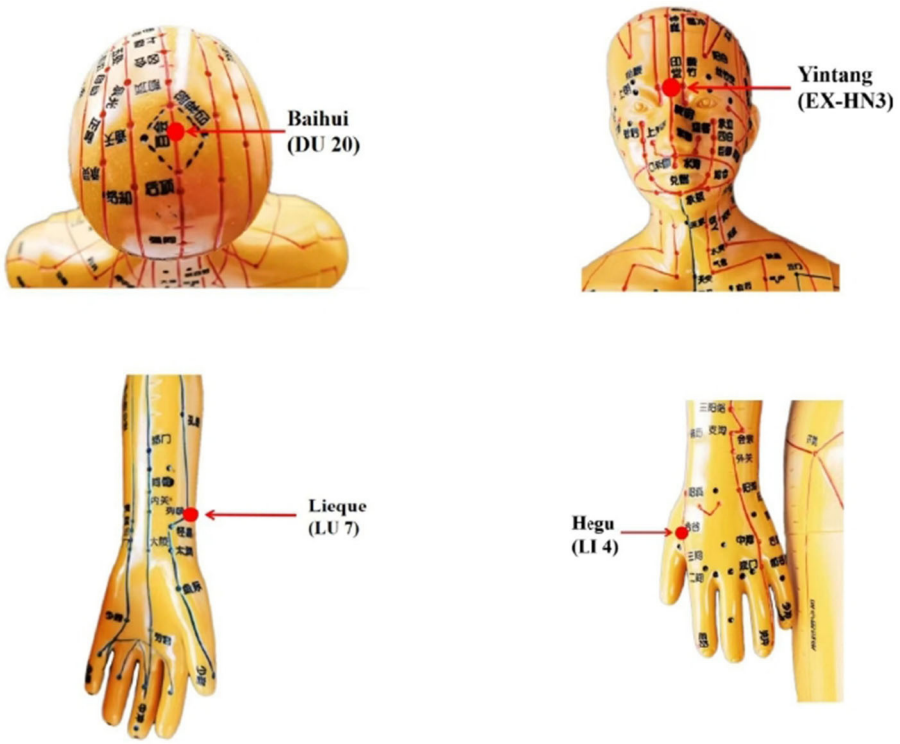


FIGURE 2
Acupuncture points.

the upper arm or hip, and pressed with the palm for 10 s. To avoid local irritation of the skin, a different site of application will be chosen each day. Patients will be asked to use one patch per day and visit the outpatient clinic twice per week. Treatment will start at 21 mg/d for 4 weeks, followed by 14 mg/d for 2 weeks, and 7 mg/d for the final 2 weeks. The total course of treatment will be 8 weeks.

Strategies to improve adherence

All the therapies and medical examination items in this trial will be provided to the patients free of charge, and patients who can complete all the visits will be reimbursed the transportation expenses. These measures will improve the patients' compliance.

Outcome measures

Primary outcome

The abstinence rate for smoking cessation at week 24 (number of people who quit smoking/total number of people) will be considered the primary outcome. Patients with a 24-h CO clearance rate of $<$10/1,000,000 at the 24th week of therapy, will be considered to have successfully quit smoking.

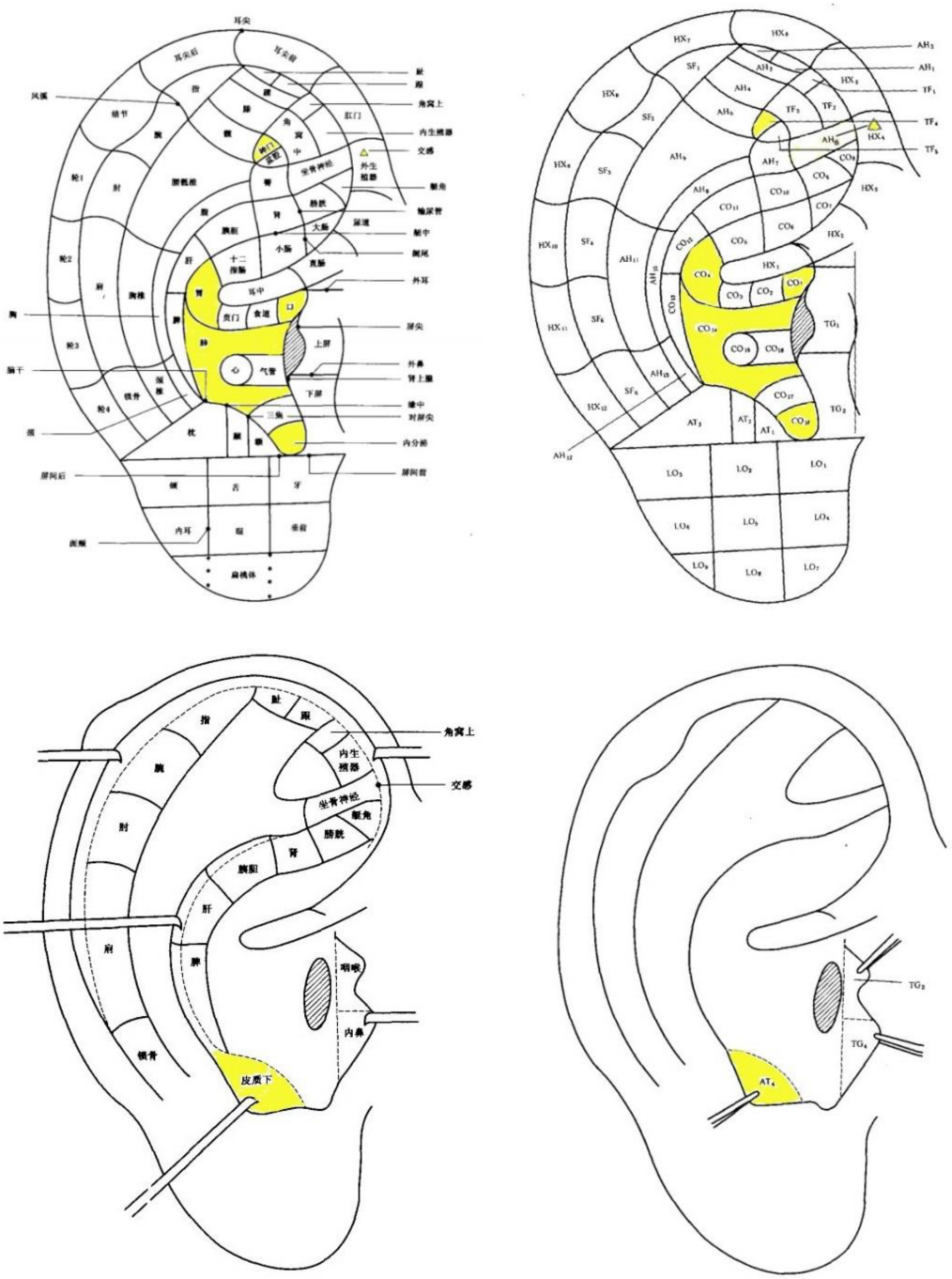
Secondary outcomes

The secondary outcomes will be the prolonged abstinence rate, the abstinence rate at other time points, the results from a saliva cortisone test, and scores on the Fagerstrom Test for Nicotine Dependence (FTND), the Autonomy over Tobacco Scale (AUTOS), the Hamilton Anxiety Rating Scale (HAM-A), the Self-rating Anxiety Scale (SAS), and the Pittsburgh Sleep Quality Index (PSQI). Additionally, we will conduct safety assessments of and evaluate cost of treatment.

Detection time point of outcomes

Baseline will be recorded before clinical trial, safety will be conducted at the beginning and end of trial. The clinical symptoms, efficacy observation indicators, laboratory indicators and scale evaluation of the patients were examined before treatment and at the follow-up of 2, 4, 6, 8, 16 and 24 weeks after treatment.

All the above results will be timely and truthfully filled in the clinical case report form (CRF).



Shenmen (TF 4), Fei (CO 14), Wei (CO 4), Neifenmi (CO 18), Pizhixia (AT 4), and Jiaogan (AH 6).

FIGURE 3
Nomenclature and location of auricular points (21).

Assessment of adverse events

All adverse events will be reported in detail in an observation table (Table 1), including the type of event, the extent of symptoms or diseases, the date of onset, frequency, duration, the remission date, treatment measures, treatment process, results, and follow-up, for evaluation of any correlations between adverse reactions and A&AA or NRT.

Assessment of health economics

A cost-effectiveness analysis from a societal perspective will be performed. Cost information, including that regarding medical and non-medical costs, will be collected during treatment, at the end of treatment, and at week 24. The effectiveness index will be considered the primary outcome (Table 1). Cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER) will be calculated to compare the difference in the cost and clinical outcomes between the two groups. The stability of the results will be tested using sensitivity analysis by the means of bootstrapping and presented with cost-effectiveness acceptability curves (CEAC).

Data management and monitoring

The data will be monitored by the Electronic Data Capture System (EDC) of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. Dynamic monitoring of patient enrolment, data entry, and quality verification will be performed by this system in order to strengthen data accuracy and maintain data quality. Study Completed Statistical results will be public access file upload in Chinese Clinical Trial Registry. Participants' personal information will be kept confidential before, during and after the trial.

Statistical analysis

Data management and statistical analyses for this study will be carried out blingdingly by an independent third party (Clinical Research and Data Center, Guangzhou University of Chinese Medicine). The statistical tests involved in this study will include unilateral and bilateral tests with a significance level of $\alpha = 0.05$. Statistical analysis will be completed using IBM SPSS 27.0.

All Subjects who will be randomized to undergo at least one treatment comprised the Intention-To-Treat (ITT) population of the study. Subjects who will be randomized into groups and underwent at least one treatment constitute the Safety group of this study. The Per-Protocol analysis data set (PPS), which refers to the cases that comply with the study plan, with the following conditions: the primary variables are clear, no baseline variables are missing, completed all scheduled studies for the 8-week treatment period, and subjects who seriously violate the protocol will be excluded. The safety dataset will be analyzed for subjects who have received at least one treatment after randomization. General demographic, clinical characteristics, and other baseline data will be used to compare the balance between the two groups. Primary outcome measures will be analyzed using ITT population, secondary outcome measures and other outcomes will be analyzed using PPS population. The safety analysis will use the safety population.At each time point, descriptive analyses will be performed to show the two groups of different means (SD and 95% CI) and the rate of outcome change. If the data follow normal distribution, the independent sample *T*-test will be used for comparison. If not, the rank sum test is applied. In order to distinguish therapeutic effects from temporal effects, analysis will be performed using a repeated measurement design.

Safety analysis

Patients will be questioned about adverse events at each visit, and all adverse events will be recorded and assessed by investigators to identify any causal relationships with the treatment. Blood tests, urinalysis, and electrocardiographic examinations will be performed before and after treatment. Furthermore, Blood lipids, kidney and liver function tests will be re-examined at weeks 16 and 24, and all abnormal changes from the baseline laboratory tests will be evaluated by investigators. Patients will have to report any adverse events that occur at any time to the study team.

Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at baseline and at follow-up visits for each treatment group. All details about adverse events, such as timing, severity, treatment, and causality to the intervention, will be recorded in CRF tables and descriptive statisticswill be performed. Chi-square test or Fisher's exact probability will be used to compare the incidence of adverse events between the two groups, and rank sum test will be used to compare the severity of adverse events.

Handling of missing data

In the event of a nonresponse after follow-up, the subjects will be informed by our researchers and be asked to provide the missing data. Some loss to follow-up is expected over the 24 weeks. The proportion of patients with missing data for each outcome will be summarized in each group and at each timepoint. If there is <5% of data missing for a specified primary or secondary outcome, we will perform a complete case analysis without imputing the missing values. If there is more than 5%

TABLE 1 Description of the study schedule.

Task	Screening	Observation period				Follow-up period		Unplanned follow-up
	Visit 0 Week 0	Visit 1 Week 2	Visit 2 Week 4	Visit 3 Week 6	Visit 4 Week 8	Visit 5 Week 16	Visit 6 Week 24	
Medical history collection	√	–	–	–	–	–	–	–
Signing informed consent	√	–	–	–	–	–	–	–
Inclusion criteria	√	–	–	–	–	–	–	–
Exclusion criteria	√	–	–	–	–	–	–	–
Basic information	√	–	–	–	–	–	–	–
Vital signs	√	√	√	√	√	√	√	√※
Blood and urine tests	√	–	–	–	√	–	√	
Liver and kidney function	√	–	–	–	√	–	√	
Respiratory carbon monoxide determination	√	√	√	√	√	√	√	
Coagulation	√	–	–	–	√	–	√	
Blood lipids + HCY	√	–	–	–	√	–	√	
Saliva cotinine test	√	–	–	–	–	√	√	
ECG	√	–	–	–	–	–	√	
FTND	√	√	√	√	√	√	√	
AUTOS	√	√	√	√	√	√	√	
HAM-A	√	√	√	√	√	√	√	
SAS	√	√	√	√	√	√	√	
PSQI Scale	√	√	√	√	√	√	√	
Adverse event record	–	√※	√※	√※	√※	√※	√※	
Combined medication records	√※	√※	√※	√※	√※	√※	√※	
Termination test evaluation	–	√※	√※	√※	√※	√※	√※	

AUTOS, Autonomy over Tobacco Scale; ECG, electrocardiogram; FTND, Fagerstrom Test for Nicotine Dependence; HAM-A, Hamilton Anxiety Rating Scale; SAS, Self-rating Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index.
"√※" is recorded when necessary.

of data missing, we will perform fewer tests. We will continue to analyse all the cases without imputing missing values if the complete case dataset is indicated by fewer tests to be a random sample. If the complete case dataset is not indicated to be a random sample by Little's test, we will then report the point estimates and their 95% confidence intervals by applying the worst- and best-case scenario imputations for the missing values. Multiple imputations will not be performed if the worst- and best-case analyses allow for the same conclusion. Otherwise, multiple imputations will create 10 imputed datasets under the assumption of data missing at random. The results of the trial will be a pooled intervention effect and 95% confidence interval of the analyses of each data set after multiple imputations.

Quality control

To control quality in multi-centers, we have developed some strategies: firstly, elaborate clinical documents, such as investigator's brochure, case report form, acupuncture operation guideline, are prepared in electronic and paper versions for all the researchers; secondly, pre-trial training is required for all researchers which contains the introduction to the entire study execution, demonstration of standardized acupuncture practice procedures, procedures for follow-up and implementation of the questionnaire, etc.; thirdly, CRFs from various centers will be extracted and checked against data from original medical records; finally, on-site monitor will put into effect regularly by specified managers to find out and fix up the practical issue in the process of trial in time.

Discussion

At present, most RCTs on acupuncture for smoking cessation usually use blank controls or fake acupuncture for comparison (22). These studies cannot directly and objectively show the effect of acupuncture on smoking cessation. In 2015, the clinical guideline for Smoking cessation in China (23) recommended three drug therapies: NRT, bupropion, and varenicline. To objectively prove if A&AA can aid successful

quitting of smoking, it is necessary to compare it with the drug treatments described in the clinical guidelines. In Jang et al.'s clinical study on smoking cessation, the control group received only NRT and counseling, and the trial group received Traditional Chinese Medicine (TCM). The study found that the effect of smoking cessation was improved using TCM, but the increase of TCM treatment cost had no statistical significance on whether TCM could improve the success rate of smoking cessation (24). Our study design is different in that we compared A&AA and NRT to verify if acupuncture is superior to NRT for smoking cessation. Acupuncture may have greater safety, fewer side effects, while being cost-effective. In China, hospitals at all levels set up acupuncture or TCM clinics, and people who want to quit smoking can easily find A&AA intervention. However, psychological counseling and smoking cessation medicine are not widely available, and it is difficult for people to avail these services.

This study will investigate the effectiveness, safety, and economic benefits of the use of A&AA for smoking cessation. This protocol is designed to be a prospective, parallel, multicentre, large-scale, randomized controlled clinical trial. In this trial, Nicotine patches will be provided to the control group as a form of NRT, since all licensed forms of NRT (gum, transdermal patch, nasal spray, inhalator, and sublingual tablets/lozenges) have been reported to help people increase their chances of successfully stopping smoking and to reduce nicotine withdrawal symptoms.

The treatment group will receive A&AA treatment. We designed acupoint combination of acupuncture and ear acupuncture based on traditional acupuncture theory and previous literature studies (22, 25–28). Baihui and Yintang can connect the Du meridian to regulate the consciousness and calm the mind which are reported to reduce dependence, relieve anxiety for addicts (29). Lieque, a acupoint of lung meridian connected with Conception Vessel, can diffuse and regular the lung qi as well as nourish yin-fluid to relieve pharyngeal discomfort in smokers (30). Acupuncture at Hegu can regulate qi movement of spleen and stomach to relieve the discomfort caused by smoking cessation (31). Auricular acupuncture was incorporated into our treatment strategy with the aim of working with manual acupuncture to produce a longer treatment effect for patients to achieve a longer and more stable abstinence rate. Likewise, auricular acupoints play a role in tranquilizing the mind and regulating the Qi of lung and stomach. And it is reported that the continuous stimulation of auricular acupoints will produce the release of neurotransmitters and the change of endocrine that conducive to smoking cessation (32–34).

The limitations of this trial must be acknowledged. First, due to the long experimental and follow-up periods, a high dropout rate may occur, especially in the treatment group. Because of busy professional lives, job mobility, or the lack of acupuncture knowledge, patients may lack the motivation to complete a 24-week course. To reduce this dropout rate, the researchers will have to fully explain the process during the initial stage and will maintain positive contact with volunteers. Second, because this is an unblinded design, there is the possibility of bias due to the expectations or biases of the participants or research staff. To minimize this potential source of bias, researchers will provide public education about acupuncture for smoking cessation, including the principles of acupuncture, and will share stories of successful cases. Last but not least, we must acknowledge that this design lacks a professional psychologist to educated patients, although an educational video has been recorded and all operators have been trained.

So far, the research program has been recruiting patients for 10 months at three centers and patients have already been incorporated into the study. Moreover, 67 patients have decreased their smoking. This preliminary data suggest that A&AA treatment may be promising. This study will provide more evidence to support the use of acupuncture therapy for cessation syndrome, which has been a major concern in recent years.

Conclusion

In summary, we will apply appropriate clinical trial methods to create a scientific design based on the previous randomized controlled trials on acupuncture use for smoking cessation. We will report the results of this clinical trial in accordance with the international norms of the Consolidated Standards for Reporting of Trials 2010 (CONSORT, 2010). We anticipate that the results of this trial will provide rigorous scientific and clinical evidence to inform smoking cessation programs in severely tobacco-dependent individuals.

Author contributions

Conception and design: JZ. Administrative support: MC and YG. Provision of study materials or patients: GL, MC, and YG. Collection and assembly of data: YL, ZC, and GC. Data analysis and interpretation: XW. Manuscript writing and final approval of manuscript: All authors.

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needles, NRT patches, etc.), instruments, and pay labor fees, etc.

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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.

The handling editor CT declared a shared parent affiliation with the authors JZ, YL, XW, GC, ZC, YG, and GL at the time of review.

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Effectiveness and safety of acupuncture for post-stroke spasticity: A systematic review and meta-analysis

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Objective: This systematic review and meta-analysis aimed to comprehensively evaluate the effectiveness and safety of acupuncture for post-stroke spasticity.

Methods: Nine electronic databases were searched from their inception to 6 June 2022, to identify randomized-controlled trials (RCTs) that investigated the effectiveness and safety of acupuncture for post-stroke spasticity. Two reviewers independently screened the studies, extracted the data, assessed the risk of bias. The reporting quality of interventions in controlled trials of acupuncture was evaluated using Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). The RevMan 5.4 and R 4.2.0 software were used for statistical analysis.

Results: A total of 88 eligible studies were included, involving 6,431 individuals. The pooled data demonstrated that acupuncture combined with conventional rehabilitation (CR) was superior to CR in reducing the Modified Ashworth Scale (MAS) score (standardized mean difference [SMD] = −0.73; 95% CI = −0.83 to −0.63; I^2 = 65%; low certainty of evidence). The favorable results were also observed in comparisons of acupuncture vs. CR (SMD = −0.22, 95% CI = −0.36 to −0.07; I^2 = 49%; moderate certainty of evidence). Subgroup analysis showed that acupuncture treatment with a frequency of once or twice a day was more effective than CR. In addition, the antispasmodic effect of acupuncture treatment increased with more sessions. Four studies explicitly reported slight acupuncture-related adverse events.

Conclusion: Acupuncture could be recommended as adjuvant therapy for spasticity after stroke. However, due to the high risk of bias and heterogeneity of the included studies, the effectiveness of acupuncture for post-stroke spasticity remains to be confirmed.

KEYWORDS

acupuncture, spasticity, stroke, systematic review, meta-analysis

Introduction

Spasticity is one of the most common complications after stroke with a prevalence of 30–80% (1). As a motor dysfunction after the central nervous system lesions, spasticity is characterized by a velocity-dependent increase in tonic stretch reflex with exaggerated tendon jerks (2). Spasticity often results in several clinical symptoms, including joint contractures, deformities, swelling, and pain, which severely limits the motor functions of patients with stroke (3). Moreover, the presence of spasticity may interfere with self-care ability of patients, reduce their quality of life and lead to depressive symptoms (4). More importantly, spasticity brings a heavy financial burden to families and society. According to statistics, approximately 50% family members have to reduce work hours or even stop working to take care of patients with spasticity after stroke (5). The direct cost for patients with spasticity is US$84,195 during the 1st year after stroke, which were four times higher than those without spasticity (6).

Currently, there are quite a few therapeutic strategies (e.g., physiotherapy, oral spasmolytics, injections of botulinum toxin) to treat post-stroke spasticity, while the therapeutic effect of spasticity is unsatisfactory. In terms of physiotherapy, the limited effect and long-term treatment course may lead to poor compliance (7). The effect of oral spasmolytics is not long-lasting, and prolonged use of these drugs might cause multiple side effects, such as hepatotoxicity and muscle weakness (8). Repetitive injections of botulinum toxin may result in the formation of neutralizing antibodies and attenuate the treatment efficacy (9). Therefore, there is a need for an effective and safe therapy for post-stroke spasticity.

Acupuncture, as a pragmatic and safe traditional Chinese medicine (TCM) treatment (10), has been used for the rehabilitation of patients with post-stroke spasticity (11). Several SRs have explored the effectiveness of acupuncture for spasticity in stroke survivors. Notwithstanding, they showed inconsistent results (12–19). With the emergence of new randomized-controlled trials (RCTs) in recent years, we plan to conduct this SR and meta-analysis to update the evidence of the effectiveness and safety of acupuncture for post-stroke spasticity.

Methods

The protocol of this SR has been registered on PROSPERO https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=129779 (registration ID: CRD42019129779) and published in advance (20). We conducted this study strictly in compliance with A Measurement Tool to Assess Systematic Reviews (AMSTAR 2.0) (21) and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analysis 2020 (PRISMA) statement (22). The completed PRISMA checklist is shown in Supplementary File 1.

Literature search

We performed a literature search in the following databases from their inception to 6 June 2022: PubMed, Embase, the Cochrane Library, Web of Science, Epistemonikos Database, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wangfang Database. Comprehensive search strategies applied to the above databases were developed by a professional library staff (DLZ), which used logical operators to link subject terms and free words together. The detailed search strategies of all databases are shown in Supplementary File 2. We also searched the Chinese Clinical Trial Registry and ClinicalTrials.gov to identify possible eligible trials. Potential articles were hand-searched from gray literature, reference lists of included studies, and relevant SRs. In addition, we also consulted the experts in this field.

Inclusion criteria

Types of studies

We included RCTs published in English or Chinese that evaluated the effectiveness and safety of acupuncture for post-stroke spasticity. The included studies should specify the randomization method in detail.

Types of participants

Patients with post-stroke spasticity were included. The stroke was diagnosed according to the acknowledged diagnostic criteria and confirmed by magnetic resonance imaging or computed tomography. The spasticity was defined as Brunnstrom stage II–V, the Modified Ashworth Scale (MAS) graded I–IV, or Composite Spasticity Scale (CSS)/Clinical Spasticity Index (CSI) >0 (23). There were no restrictions on age, gender, race, duration of stroke, type of stroke, and position of spasticity.

Types of interventions

The experimental group received acupuncture as a monotherapy or adjunctive therapy. We included manual acupuncture, electroacupuncture, body needling, abdominal acupuncture, scalp acupuncture, and eye acupuncture in accordance with definition of acupuncture [1].

1 Available online at: https://www.news-medical.net/health/What-is-Acupuncture.aspx.

Types of comparisons

Patients in the control group were treated with conventional rehabilitation (CR), sham acupuncture, or Western medicine (WM). CR mainly included general supportive care, kinesiotherapy, occupational therapy, and physical factor therapy. Sham acupuncture was designed using the method of "shallow needling to non-acupoints" (24).

Types of outcome measures

The primary outcome was the MAS score of affected limbs. The secondary outcomes included effective rate (ER) that refer to the reduction of MAS by more than one grade, Fugl–Myer Assessment (FMA), Barthel Index (BI), CSS, CSI, integral electromyography (iEMG), root mean square (RMS), a ratio of maximum H-reflex to maximum M response (H_{max}/M_{max} ratio), co-contraction rate (CCR), and acupuncture related adverse events.

Exclusion criteria

Studies were excluded if (1) they were quasi-RCT, crossover RCT, and cluster RCT; (2) patients had no clear diagnostic criteria or suffered from spasticity due to other reasons, such as traumatic brain injury, tumor, or poisoning; (3) studies explored the effect of different types of acupuncture; (4) other types of acupuncture (e.g., warm-needle moxibustion, acupoint injection, floating acupuncture, cutaneous needle, dry needling, and plum-blossom needle) were used as treatment for spasticity; (5) acupuncture combined with other TCM therapy (e.g., Chinese herb, massage, moxibustion, scraping, cupping, and bloodletting) to alleviate spasticity; and (6) data were unavailable by extensive searching.

Study selection

The retrieved records were imported into Endnote (X9). After removing duplicates, two researchers (WJT and JS) independently reviewed the titles and abstracts to eliminate irrelevant records, and then read the rest records in full text to identify eligible studies. Disagreements were settled through team discussion or consultation with the third reviewer (JL).

Data extraction

Two reviewers (CX and YXL) independently extracted data from the included studies using a predesigned extraction form. The following information was extracted: (1) the general characteristics of included studies, (2) demographic data of patients at study level, (3) characteristics of interventions and comparators, and (4) outcome measures. After extraction, two reviewers crosschecked to ensure accuracy. For multiarm RCTs, we extracted the eligible comparisons or extracted the comparison with inferior effect size. When the study reported indicators of spasticity more than one position, the recommended formula was used to merge the mean and standard deviation of multiple positions (25, 26). During this process, any ambiguities were resolved by the third author (RJJ).

Evaluation of reporting quality of interventions in controlled trials of acupuncture

We used Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) to appraise the reporting quality of interventions in controlled trials of acupuncture (27). The STRICTA consists of six items, including acupuncture rationale, details of needling, treatment regimen, co-interventions, practitioner background, and control or comparator interventions. Each study was assessed by two independent reviewers (CZJ and YYZ) using STRICTA. Discrepancies were resolved by the third reviewer (YF).

Assessment of risk of bias

The risk of bias was evaluated using the revised Cochrane risk-of-bias tool for randomized trials (ROB 2.0) (28). This tool contains five domains, namely, randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as "low risk of bias," "some concerns," or "high risk of bias." Two trained reviewers (CZJ and YYZ) pre-assessed the five included studies with ROB 2.0. Then, the intraclass correlation coefficient (ICC) statistic was calculated to evaluate the inter-rater agreement. If consistency reached at least 80%, formal evaluations were performed. Any disagreements were arbitrated by discussion or consensus with a third reviewer (YF).

Statistical analysis

The ICC was calculated using Statistical Package for Social Sciences 25.0 to test consistency between reviewers. According to the ICC, the consistency was defined as poor 0.0–0.2, fair 0.21–0.4, moderate 0.41–0.6, good 0.61–0.8, and very good 0.81–1.00 (29). The Review Manager software (RevMan, version 5.4) and R software (version 4.2.0) were used for data synthesis. Mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) was measured for continuous variables, and relative risk (RR) with 95% CI was calculated for dichotomous data. We defined *p*

< 0.05 as a statistically significant difference. If MAS was presented as rank variable, we transformed it into continuous data. Chi-square test and I^2 statistic were conducted to assess the heterogeneity among studies. When $I^2 \leq 50\%$, $p > 0.1$, we used fixed-effect model to pool data; otherwise, the random-effect model was used.

Subgroup analysis

We conducted subgroup analysis based on the following factors: (1) position of spasticity (upper limbs, lower limbs); (2) frequency of treatment (once a day, twice a day, once every other day); (3) total sessions of treatment (10–30, 30–60, >60 sessions); (4) needle stimulation (manual acupuncture, electroacupuncture); and (5) follow-up time (1 month after treatment, 3 months after treatment).

Sensitivity analysis

Sensitivity analysis was carried out to verify the robustness of the result by removing study one by one. Furthermore, we pooled data from the studies with unclear blinding of outcome assessors and explicit blinding of outcome assessors separately. We also explored the impact of risk of bias on the pooled estimate.

Publication bias

If the number of included trials over 10, funnel plots and *Egger*'s test were applied to detect publication bias.

Grading of recommendations assessment, development, and evaluation

We assessed the certainty of evidence by using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (30) and summarized the evidence profile using the GRADE profiler (version 3.6) software. Each outcome was evaluated from five considerations: limitations, inconsistency, indirectness, imprecision, and publication bias. Then, the certainty of evidence was rated in four grades, namely, high quality, moderate quality, low quality, or very low quality.

Results

Search results

A total of 25,096 records were identified, of which 7,523 duplicates were removed. By screening titles and abstracts, 17,076 irrelevant articles were eliminated. Among the remaining 497 articles, 88 studies (31–118) fulfilled the eligible criteria and were eventually included. The reasons for excluding the studies are listed in Supplementary File 3 (Supplementary Table S1). A detailed screening process is presented in Figure 1.

Studies characteristics

The characteristics of the included studies are presented in Supplementary File 3 (Supplementary Table S2). A total of 88 studies involving 6,431 patients were identified (3,347 in the intervention group and 3,084 in the control group). The average age of the patients ranged from 50 to 78. A total of 38 studies (31, 47, 48, 52, 55, 56, 59, 60, 62, 63, 66, 67, 69, 71–76, 79, 80, 82, 83, 88–90, 92–94, 99–101, 104, 107, 110, 112–114) included patients who suffered from stroke for the first time. The duration of stroke ranged from 2 weeks to 1 year. In addition, 19 studies (35, 40, 41, 44, 45, 47, 51, 52, 61, 65, 67, 68, 70, 77, 85, 100, 108, 109, 116) recruited patients with cerebral ischemia and 1 study (84) focused on cerebral hemorrhage; the rest studies included patients with ischemic stroke and hemorrhagic stroke. A total of 41 studies (33, 36, 38, 39, 41–43, 45, 49, 53–57, 59, 61, 65–67, 70–73, 78, 80, 82, 87, 88, 90, 96, 97, 100–102, 104–106, 108, 110, 116) observed spasticity of upper limbs, 25 studies (31, 32, 44, 47, 51, 62–64, 68, 77, 79, 81, 83, 84, 86, 89, 91, 93, 94, 98, 99, 107, 111–113) focused on lower limbs, and 22 studies (34, 35, 37, 40, 46, 48, 50, 52, 58, 60, 69, 74–76, 85, 95, 103, 109, 114, 115, 117, 118) reported both upper and lower limbs. The included studies involved the comparisons of acupuncture plus CR vs. CR, acupuncture vs. CR, acupuncture vs. WM and verum acupuncture vs. sham acupuncture.

Acupuncture protocols in included trials

A total of 61 studies (33, 35, 38, 39, 41–43, 45–48, 50, 52, 55–60, 63, 64, 66–73, 75, 78, 79, 81–90, 92, 94–96, 99, 100, 102, 103, 105–110, 112, 114–117) used manual acupuncture, and 27 studies (31, 32, 34, 36, 37, 40, 44, 49, 51, 53, 54, 61, 62, 65, 74, 76, 77, 80, 91, 93, 97, 98, 101, 104, 111, 113, 118) used electroacupuncture. All included studies described the choice of acupoints. As shown in Figure 2, the most frequent acupoints on upper limbs were *Hegu* (LI 4), *Jianyu* (LI 15), *Quchi* (LI 11), *Waiguan* (SJ 5), and *Shousanli* (LI 10). And *Zusanli* (ST 36), *Yanglinquan* (GB 34), *Sanyinjiao* (SP 6), *Taichong* (LR 3), and *Xuehai* (SP 10) in the lower limbs (see Figure 3). The retention time for the body acupuncture varied from 15 to 40 min. As for scalp acupuncture, the parietal median line (MS 5), parietal anterior temporal oblique line (MS 6), and parietal posterior temporal oblique line (MS 7) were commonly used. The retention time for scalp acupuncture ranged from 15 min to 6 h. Treatment frequency was once a day (31–37, 39–41, 44,

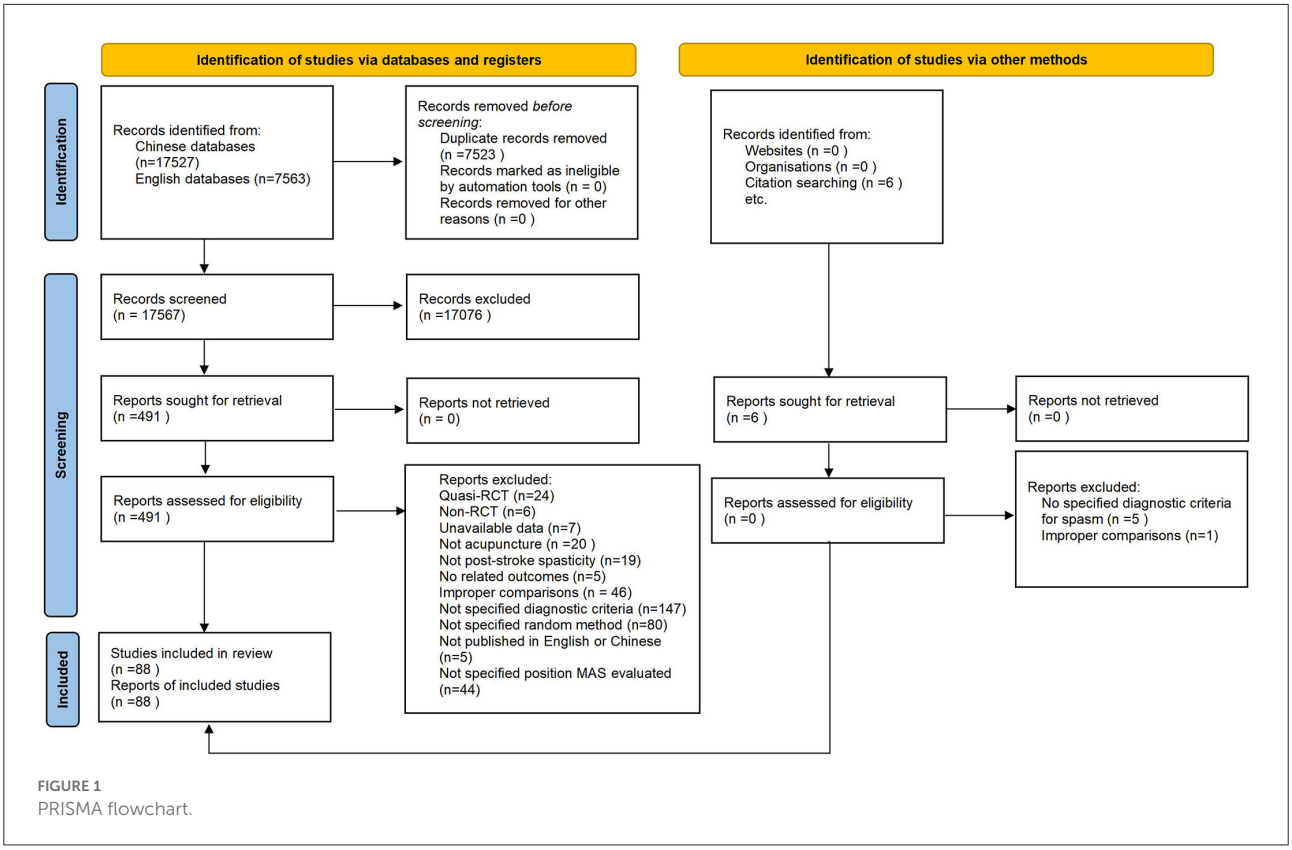

FIGURE 1
PRISMA flowchart.

45, 47–60, 63–67, 69–81, 83–110, 112–114, 116–118) twice a day (42, 43, 61, 62, 82, 111), and once every other day (38, 68, 115). Treatment period ranged from 2 weeks (52, 109) to 6 months (68, 70). The treatment positions were mostly located on affected limbs. Only one study (54) selected acupoints on the unaffected limb (opposing acupuncture). A total of 13 studies (31, 44, 50, 55, 73, 75, 81, 85, 87, 95, 109, 111, 115) used individualized acupoint protocol according to syndrome differentiation. The remaining studies applied fixed acupoint protocol. A total of 54 studies (31, 32, 34, 35, 37, 38, 40–45, 48, 49, 52, 54, 58, 59, 61–63, 66, 67, 71, 75, 78–80, 83–86, 88, 90, 92–98, 101–103, 105–109, 111, 113–116) emphasized *De qi*, which was a unique needling sensation and was essential for clinical efficacy (119).

STRICTA checklist for the included studies

The STRICTA checklist is shown in Supplementary File 3 (Supplementary Table S3). Almost all studies reported the style of acupuncture, needle stimulation, acupoint selection, needle retention time, frequency, and total sessions of treatment. More than half of the studies described unilateral or bilateral of acupoints, depth of insertion, *De qi*, and thickness of acupuncture. A total of 23 studies (41, 49, 53–55, 59, 60, 66–71, 75, 79, 83, 86, 87, 89, 92, 94, 95, 100) specified the rationale of acupoint protocol and 12 studies (36, 41, 53, 55, 60, 62, 69, 71, 74, 76, 79, 87) mentioned the number of needle insertions. Except for eight studies (45, 50, 55, 58, 106, 108, 114, 116), the remaining studies described the control in detail, but none of the studies elucidated the rationale of control group. A total of 80 studies (31–44, 46–49, 51–54, 56, 57, 59–105, 107, 109–113, 115, 117, 118) reported details of co-interventions. All included studies did not specify the setting and context of treatment. Among the included studies, merely eight studies (49, 54, 68, 70, 84, 102, 113, 118) provided information about the certification of acupuncturists.

Risk of bias assessment

The ICC value between the two reviewers for ROB 2.0 assessment was 0.917, which indicates very good agreement. The summary of risk of bias is presented in Figure 4, and the graph of risk of bias is provided in Supplementary File 3 (Supplementary Figure S1). Due to no blinding of outcome assessors, deviations from intended interventions, and missing outcome data, the overall risk of bias of 66 studies (31, 34, 35, 37, 39–46, 48–53, 55, 57–59, 61–65, 67–70, 73–79, 81, 83, 85, 86,

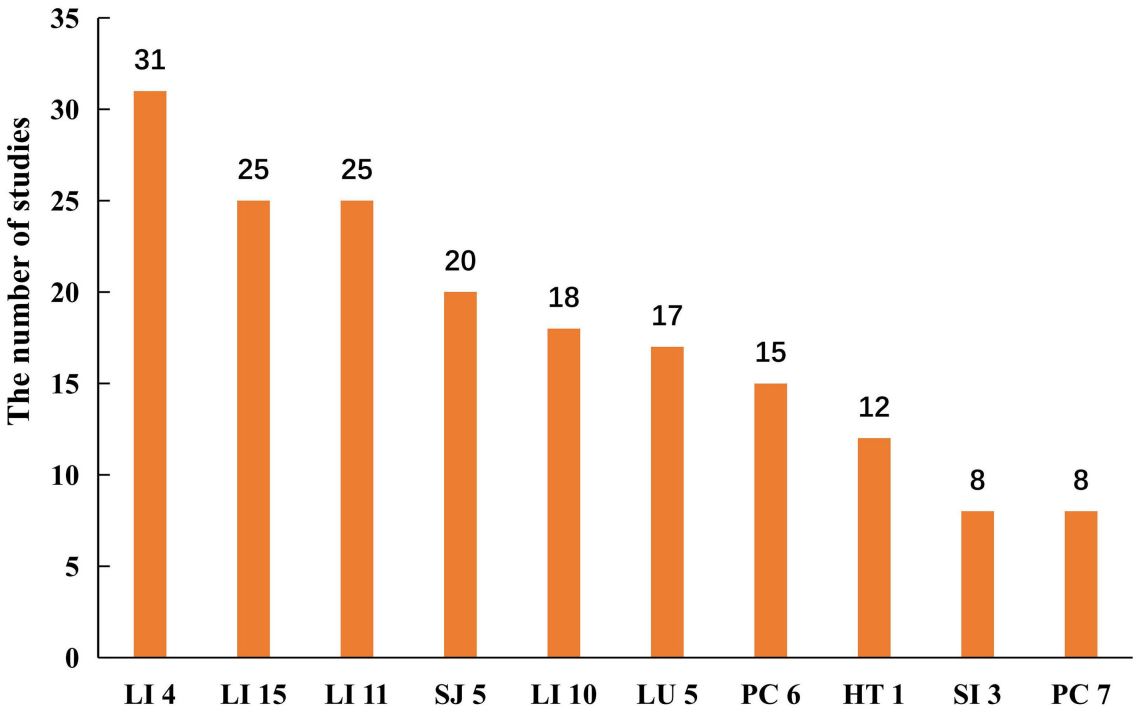

FIGURE 2
Acupoints selection on upper limbs.

89, 91–94, 96, 97, 99, 101–103, 105–112, 114–118) was evaluated as "high risk of bias," and because of selective reporting results (no protocol), 22 studies (32, 33, 36, 38, 47, 54, 56, 60, 66, 71, 72, 80, 82, 84, 87, 88, 90, 95, 98, 100, 104, 113) were categorized as "some concerns."

Primary outcome

Acupuncture plus CR vs. CR

A total of 70 trials (35–37, 40, 42–51, 53–60, 62, 63, 65, 67–71, 73–77, 79–89, 91, 93–100, 102–106, 108–112, 114–118) with 4,921 participants used the MAS score to evaluate the therapeutic effect of acupuncture for post-stroke spasticity. The results of meta-analysis revealed that acupuncture plus CR was superior to the CR in decreasing MAS score (SMD = −0.73; 95% CI = −0.83 to −0.63; $p < 0.00001$; $I^2 = 65\%$) (Figure 5). The funnel plot and *Egger*'s test ($p = 0.005$) indicated that potential publication bias might exist (Figure 6).

Acupuncture vs. CR

A total of 10 trials (33, 35, 41, 48, 56, 57, 73, 78, 96, 112) with 728 participants compared the effects of acupuncture with CR. The pooled data showed that acupuncture had a better effect than CR in ameliorating spasticity in patients with stroke (SMD = −0.22, 95% CI = −0.36 to −0.07; $p = 0.004$; $I^2 = 49\%$) (Figure 7). Funnel plot and *Egger*'s test ($p = 0.486$) showed no obvious publication bias (Figure 8).

Descriptive Analysis

Two trials (88, 90) reported that acupuncture was more effective than sham acupuncture in relieving spasticity. There was (92, 101) no significant difference between acupuncture and WM in reducing MAS score.

Subgroup analysis

The results of subgroup analysis (acupuncture plus CR vs. CR) are summarized in Table 1. With regard to sessions of acupuncture treatment, we found that acupuncture treatments of 10–30 sessions (SMD = −0.65, 95% CI −0.76 to −0.55), 30–60 sessions (SMD = −0.79, 95% CI −1.06 to −0.52), and >60 sessions (SMD = −0.97, 95% CI −1.25 to −0.69) were superior to CR in improving post-stroke spasticity. As for acupuncture frequency, acupuncture combined with CR with once a day (SMD = −0.75, 95% CI −0.86 to −0.64) or twice a day (SMD = −0.55, 95% CI −0.85 to −0.25) reduced more MAS score than CR. However, once every other day showed no significant difference in reducing MAS score compared

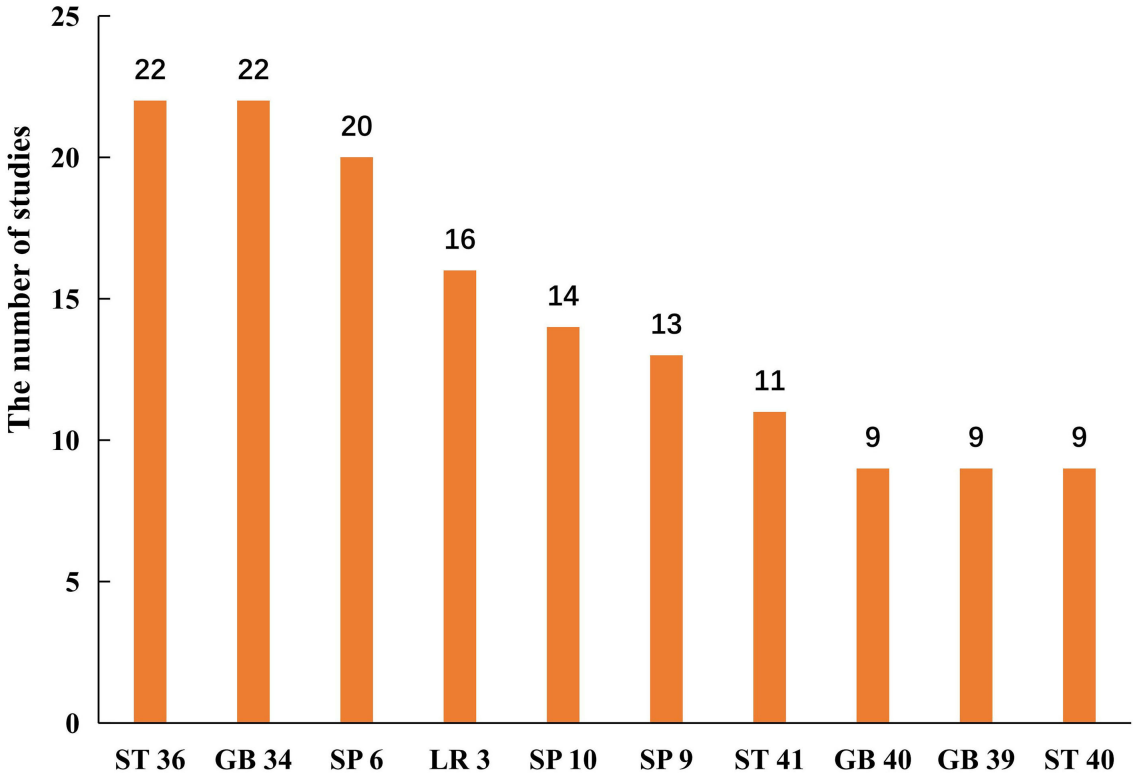

FIGURE 3
Acupoints selection on lower limbs.

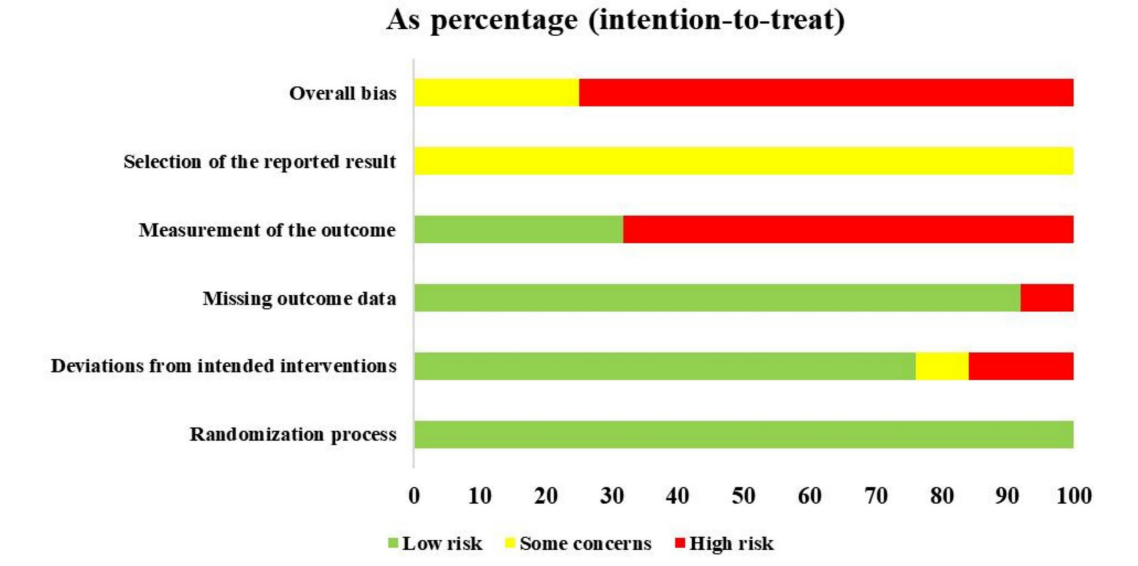

FIGURE 4
Risk of bias summary.

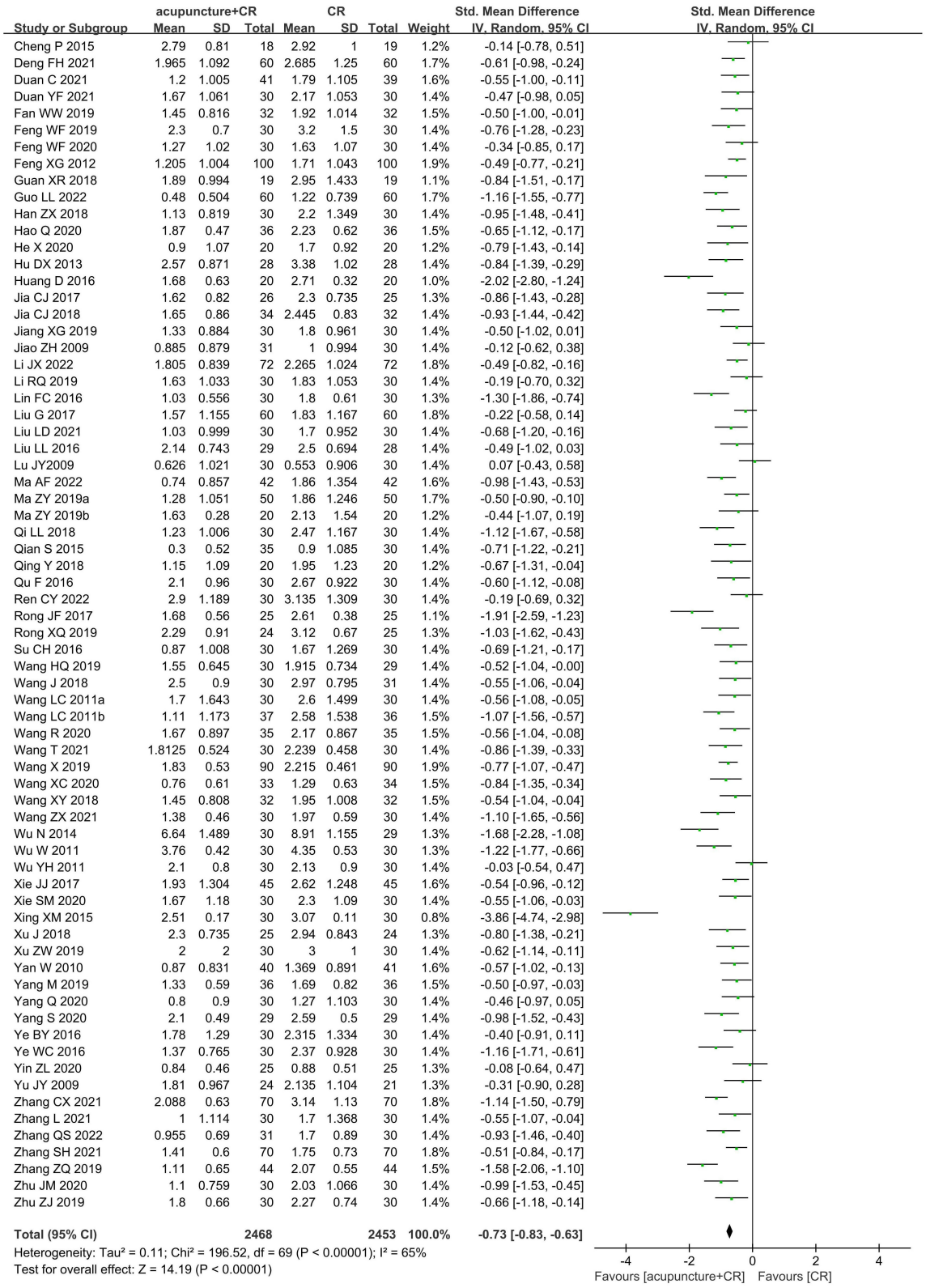

FIGURE 5
The forest plot of MAS score in comparison of acupuncture plus CR vs. CR.

with the CR (SMD = −0.56, 95% CI −1.31 to 0.18). Manual acupuncture (SMD = −0.74, 95% CI −0.84 to −0.64) and electroacupuncture (SMD = −0.71, 95% CI −0.96 to −0.46) combined with CR decreased greater MAS score than CR. For different positions of spasticity, acupuncture plus CR was better than CR in improving spasticity of both upper limbs (SMD = −0.74, 95% CI −0.87 to −0.61]) and lower limbs (SMD = −0.76, 95% CI −0.94 to −0.58). One study (54) reported that acupuncture treatment had long-term effect (3 months) in ameliorating spasticity.

Sensitivity analysis

As for primary outcome in the comparison of acupuncture plus CR vs. CR, we used three methods to verify the robustness of the result. By excluding studies one by one, we found that the pooled effect size of MAS score was stable (Figure 9). By synthesizing the data from studies with unclear and explicit blinding of outcome evaluators respectively, the results demonstrated that acupuncture plus CR was superior to CR in relieving post-stroke spasticity (Figure 10). Moreover, the result was stable *via* merging studies with "some concerns" and "high risk of bias" separately (Figure 11).

Regarding the MAS score in the comparison of acupuncture vs. CR, as shown in Figure 12, the result altered when excluding Wu NA 2014 (48). As shown in Figure 13, we pooled data from studies with blinding of outcome assessors and the result changed.

Secondary outcomes

The pooled data of secondary outcomes are shown in Table 2. Meta-analysis showed that patients receiving acupuncture plus CR achieved better improvements on FMA and BI than those receiving CR alone. In addition, relevant

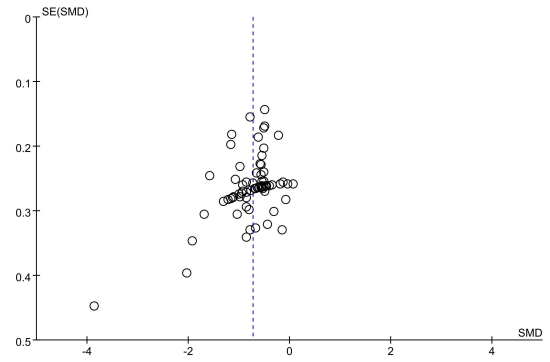

FIGURE 6
The funnel plot of MAS score in comparison of acupuncture plus CR vs. CR.

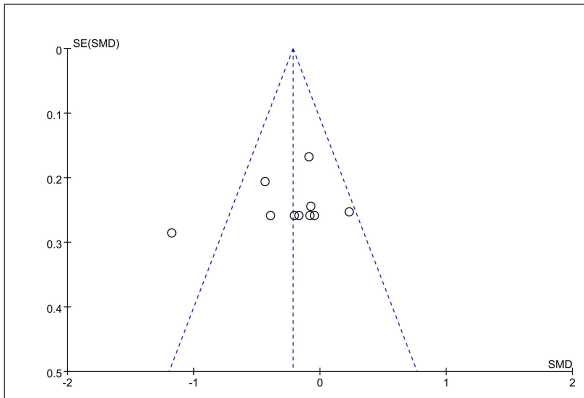

FIGURE 8
The funnel plot of MAS score in comparison of acupuncture vs. CR.

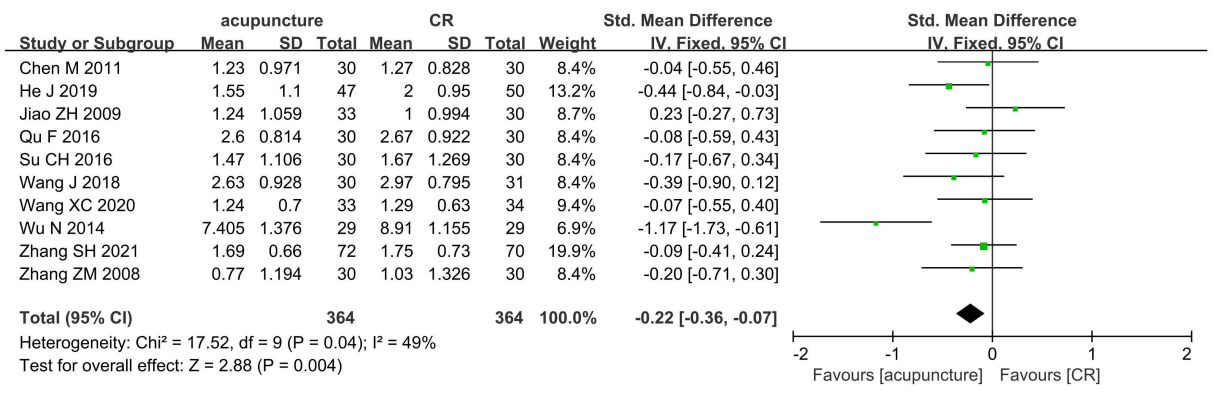

FIGURE 7
The forest plot of MAS score in comparison of acupuncture vs. CR.

TABLE 1 Subgroup analyses of MAS score.

Subgroups	No. of studies	MAS Effect size (95% Cl)	*P*-value	I^2
Positions of spasticity				
Upper limbs	50	−0.74[−0.87, −0.61]	<0.00001	72%
Lower limbs	39	−0.76[−0.94, −0.58]	<0.00001	81%
Frequency of treatment				
Once a day	62	−0.75[−0.86, −0.64]	<0.00001	66%
Twice a day	5	−0.55[−0.85, −0.25]	<0.001	46%
Once every other day	2	−0.56[−1.31, 0.18]	0.14	76%
Total sessions of treatment, session				
10–30	42	−0.65[−0.76, −0.55]	<0.00001	44%
30–60	17	−0.79[−1.06, −0.52]	<0.00001	82%
≥60	10	−0.97[−1.25, −0.69]	<0.00001	66%
Needle stimulation				
Manual acupuncture	49	−0.74[−0.84, −0.64]	<0.00001	50%
Electroacupuncture	21	−0.71[−0.96, −0.46]	<0.00001	79%
Follow-up time				
Immediately	70	−0.73[−0.83, −0.63]	<0.00001	65%
1 month after-treatment	2	−1.28[−1.98, −0.57]	<0.001	79%
3 months after-treatment	1	−1.17[−1.72, −0.62]	<0.00001	/

MAS, Modified Ashworth Scale; 95% CI: 95% confidence interval.

indicators of surface electromyogram such as CCR and H_{max}/M_{max} indicated that acupuncture plus CR was effective in relieving the post-stroke spasticity in patients. We also found that acupuncture was better than CR in improving BI and the upper limbs of FMA and ER.

Adverse events

A total of 12 studies (33, 48, 60, 69, 75, 87, 88, 92, 94, 95, 106, 117) reported no treatment-related adverse events occurred, whereas, four studies (52, 54, 78, 118) explicitly reported adverse events, such as punctate hemorrhage (118), subcutaneous hematoma (52), subcutaneous ecchymosis (54), and needle syncope (52, 78).

Certainty of evidence

The ER of upper limbs and MAS score in comparison of acupuncture vs. CR was rated as "moderate" certainty of evidence, while the rest outcomes were considered as "low" or "very low". The certainty of evidence was downgraded primarily because of the high risk of bias of the included studies and inconsistency of results. A summary of findings table from the GRADE profiler is provided in Supplementary File 3 (Supplementary Figures S2, S3).

Discussion

This SR and meta-analysis showed that acupuncture as an adjuvant therapy could effectively reduce MAS score, CCR, and H_{max}/M_{max}, and improve FMA and BI. Subgroup analysis demonstrated that once or twice a day acupuncture treatment and a greater total sessions of acupuncture treatment might be associated with better antispasmodic effects. Notably, 66 studies were evaluated as "high risk of bias," 22 studies were categorized as "some concerns," and publication bias might exist. Therefore, the above results should be treated with caution.

Our result showed that acupuncture exerted a better effect than CR in relieving post-stroke spasticity, which was consistent with the previous findings (13, 15, 16). As is known, the minimum clinically important difference (MCID) refers to the smallest change in the outcome measurements, which is considered to be clinically meaningful for patients (120). Chen et al. (120) reported the MCID of MAS with moderate clinical significance and high clinical significance were 0.48 and 0.76, respectively. The effect size of MAS (acupuncture plus CR vs. CR) in our study was 0.73, which indicated that acupuncture combined with CR had a moderate clinical effect to attenuate post-stroke spasticity.

The results of subgroup analysis demonstrated that acupuncture treatment one or two times a day was better than CR in alleviating spasticity after stroke, whereas acupuncture treatment once every other day showed no significant difference.

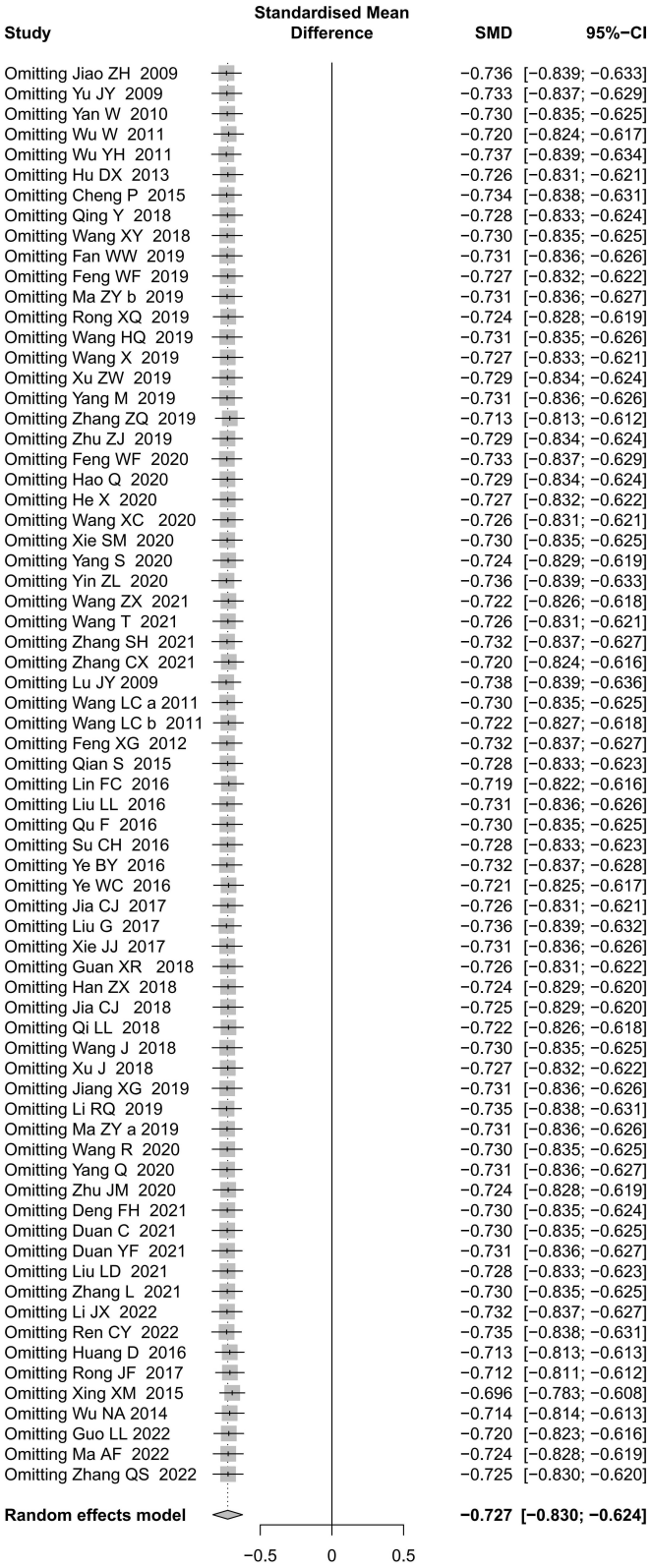

FIGURE 9
Sensitivity analysis by excluding studies one by one for MAS score (acupuncture plus CR vs. CR).

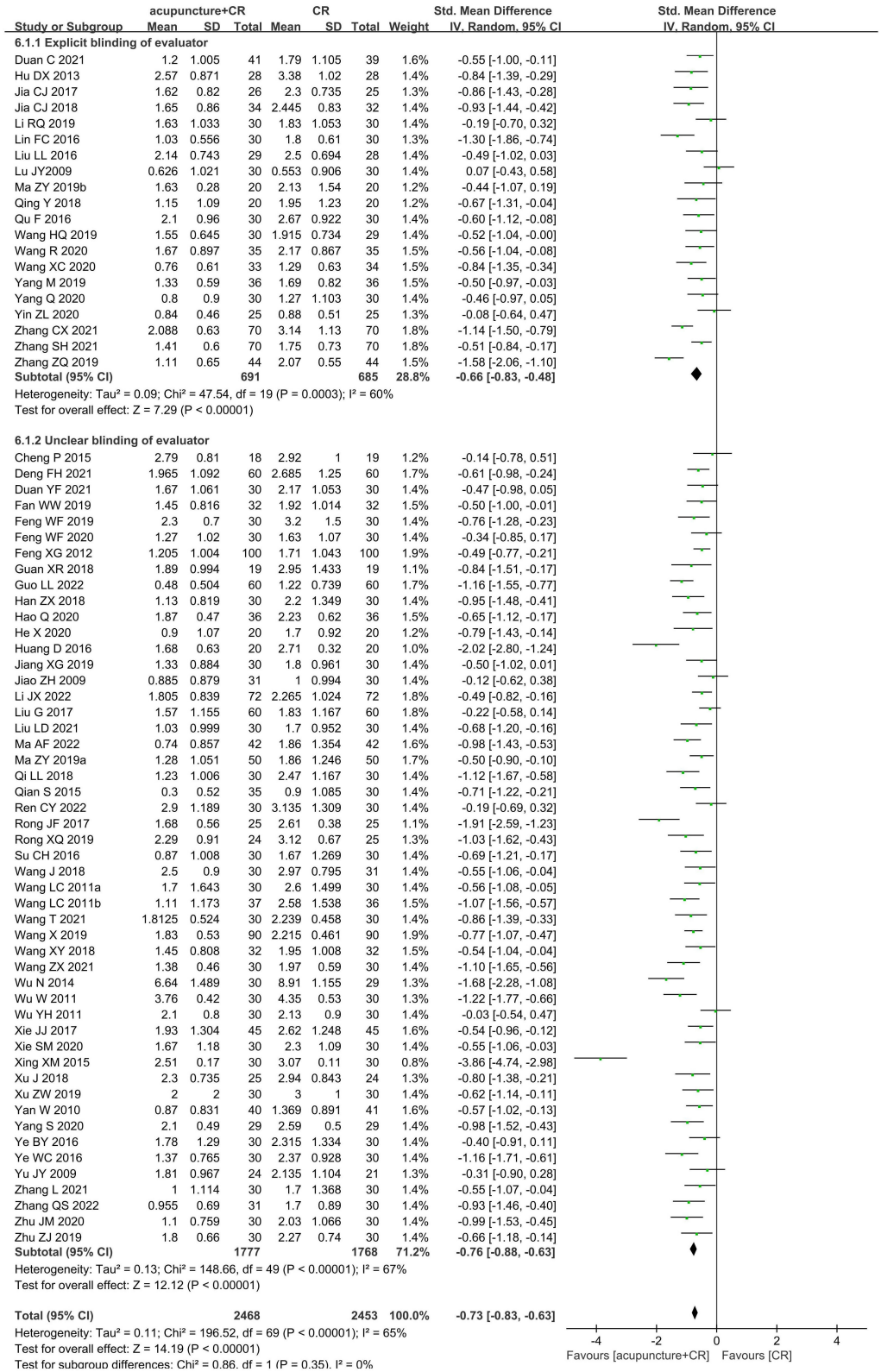

FIGURE 10
Sensitivity analysis based on blinding of outcome assessor (acupuncture plus CR vs. CR).

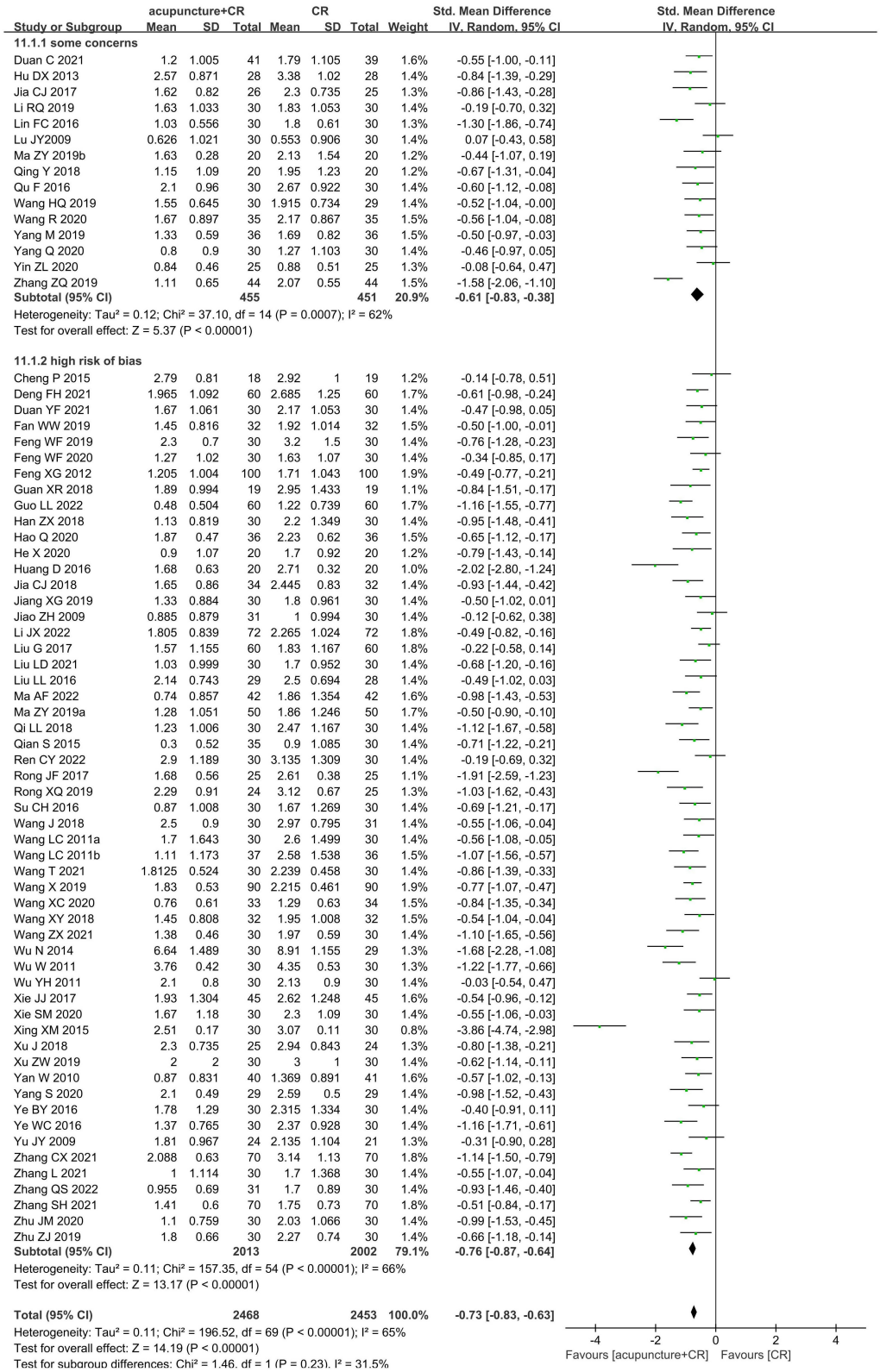

FIGURE 11
Sensitivity analysis by separately merging "high risk of bias" and "some concerns" studies (acupuncture plus CR vs. CR).

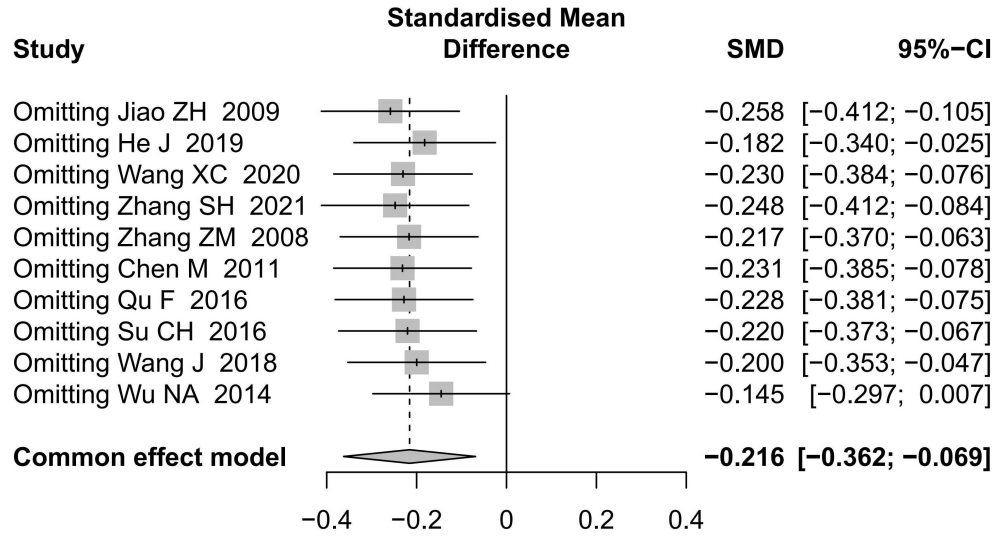

FIGURE 12
Sensitivity analysis by excluding studies one by one for MAS score (acupuncture vs. CR).

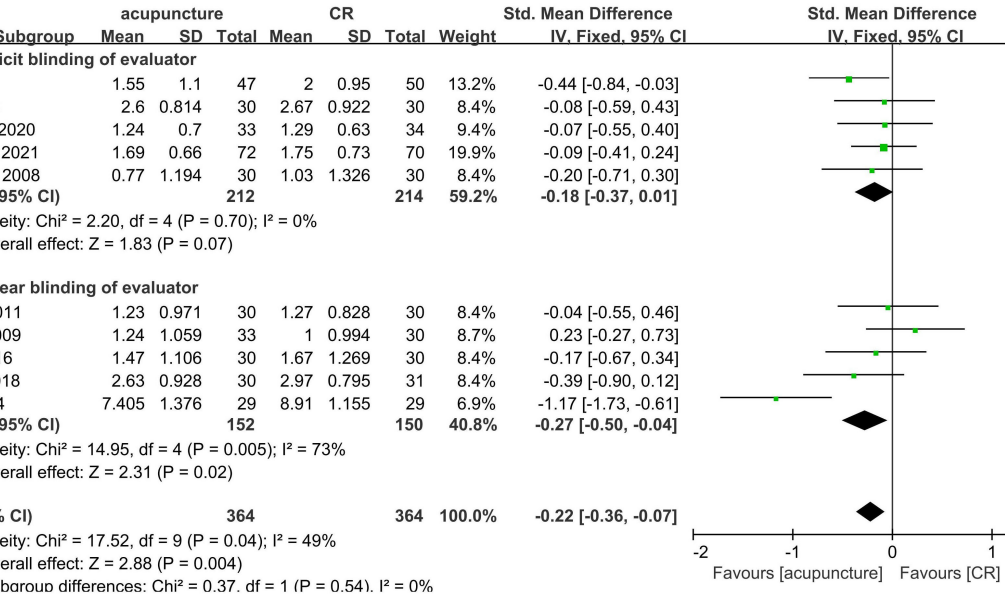

FIGURE 13
Sensitivity analysis based on blinding of outcome assessor (acupuncture vs. CR).

The possible explanation was that, as the prolongation of treatment interval, the effector substance gradually attenuated and the therapeutic effect was unsustainable (121). Besides, our result suggested that more sessions of acupuncture treatment might yield greater effect to relieve spasticity. This result might be attributed to the cumulative effect of acupuncture. Notwithstanding, considering apparent heterogeneity and high risk of bias, rigorous clinical trials are required to explore the optimal protocol of acupuncture treatment for spasticity in the future.

As the spasticity worsens, movement function and daily activities of patients would be unavoidably affected. Our results showed that acupuncture plus CR enhanced motor function and activities of daily living in patients with spasticity following stroke. The MCID of FMA of upper limbs and lower limbs were 4.48 and 3.31, separately, the MCID of

TABLE 2 Meta-analysis of secondary outcomes.

Outcomes	No. of studies	Effect size (95% CI)	*P*-value	I^2
Acupuncture plus CR vs. CR				
ER-U	18	RR 1.31[1.15, 1.50]	<0.0001	78%
ER-L	10	RR 1.15[1.01, 1.32]	<0.05	67%
FMA-U	36	MD 5.56[4.42, 6.71]	<0.00001	89%
FMA-L	23	MD 3.68[2.72, 4.65]	<0.00001	86%
BI	50	MD 8.61[6.76, 10.45]	<0.00001	90%
iEMG	6	SMD 1.49[−0.05, 3.02]	0.06	97%
CCR	3	SMD −2.42[−4.69, −0.15]	<0.05	97%
RMS	5	SMD 0.02[−1.31, 1.35]	0.97	97%
CSS	3	MD −0.15[−1.47, 1.16]	0.82	77%
CSI	10	MD −1.59[−2.17, −1.01]	<0.00001	92%
H_{max}/M_{max}	3	SMD −0.75[−1.01, −0.49]	<0.00001	9%
Acupuncture vs. CR				
ER-U	5	RR 1.08[0.97, 1.21]	0.16	0%
CSI	3	MD −0.97[−2.23, 0.3]	0.13	79%
FMA-U	9	MD 2.87[0.46, 5.28]	<0.05	84%
FMA-L	4	MD 0.14[−0.92, 1.19]	0.8	0%
BI	9	MD 4.27[0.67, 7.88]	<0.05	69%

No. of studies, number of studies; MD, mean difference; SMD, standardized mean difference; RR, relative risk; CR, conventional rehabilitation; 95% CI: 95% confidence interval; ER-U, effective rate of upper limb; ER-L, effective rate of lower limb; FMA-U: Fugl–Myer Assessment of upper limb; FMA-L, Fugl–Myer Assessment of lower limb; BI, Barthel Index; iEMG, integral electromyography; CCR, co-contraction rate; RMS: root mean square; CSS, composite spasticity scale; CSI, clinical spasticity index; H_{max}/M_{max}: ratio of maximum H reflex to maximum M response.

BI was 1.85 (122, 123). The effect size of FMA of upper limbs and lower limbs (acupuncture plus CR vs. CR) were 5.56 and 3.68, respectively, and the effect size of BI was 8.61 in our study, which demonstrated that the effects of acupuncture plus CR in improving FMA and BI were clinically meaningful.

Several problems existed in the RCTs of acupuncture for post-stroke spasticity, for example, no blinding of patients and outcome assessors, without objective outcome measures, lack of follow-up, and absence of detailed acupuncture protocol. Such problems hinder us from comprehensively and objectively evaluating the authentic efficacy of acupuncture for post-stroke spasticity. Hence, sham acupuncture should be set as comparison. Additionally, it is crucial to assess spasticity with objective indicators to obtain objective data. Future studies should also focus on the long-term effect of acupuncture for spasticity after stroke. To improve the reporting quality, researchers should report studies in accordance with the Consolidated Standards of Reporting Trials (124) and STRICTA (27).

This is the latest SR and meta-analysis that comprehensively evaluated the effectiveness and safety of acupuncture for post-stroke spasticity. The protocol of this SR and meta-analysis was registered in advance. This SR and meta-analysis was conducted strictly in accordance with AMSTAR 2.0 and reported complying with PRISMA 2020. However, some limitations should also be acknowledged. First, we used MAS score as the primary outcome measure, which is a subjective assessment scale, unclear blinding of outcome assessors and explicit blinding of outcome assessors separately, measurement bias was inevitable. Second, the published language of included RCTs in this SR and meta-analysis was limited to Chinese or English, hence, language bias might exist. Third, the overall risk of bias of the included studies was evaluated as "high risk of bias" and "some concerns."

Conclusion

Acupuncture could be recommended as adjuvant therapy for spasticity after stroke. However, due to the high risk of bias and heterogeneity of the included studies, the effectiveness of acupuncture for post-stroke spasticity remains to be confirmed.

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/s.

Author contributions

RJ, JL, and YF designed the study. DZ designed the search strategy. WT and JS selected the studies. CXu and YL extracted the data. CJ and YZ assessed the risk of bias and reporting quality. XL, HZ, and CXi analyzed the data. CXu, CJ, and YZ wrote and drafted the manuscript. All authors approved the manuscript.

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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.2022.942597/full#supplementary-material

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Case Report: Acupuncture is an effective treatment for olfactory dysfunction in the post COVID-19 condition

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Olfactory dysfunction in the post COVID-19 condition reported worldwide are refractory for some patients. For this reason, appropriate treatment is desired. In this article, we describe two cases of olfactory dysfunction in the post COVID-19 condition that was improved by traditional acupuncture treatment. By using the Yingxiang point (LI20), which is said to improve the sense of smell since ancient times, acupuncture treatment was performed 1–2 times a week in two patients about 6 and 7 months after the diagnosis of COVID-19. Acupuncture needles with a body length of 30 mm and a body diameter of 0.16 mm were inserted about 10 mm deep into the skin. We stimulated LI20 of the right and left sides until the patients felt the de qi sensation (acupuncture resonance), and left needles in the points for about 15 min. Immediately after the acupuncture treatment, the symptoms of olfactory dysfunction were alleviated, and the improvement in olfactory dysfunction lasted for 2–4 days. As the number of acupuncture treatments increased, the time until the flareup of olfactory dysfunction was prolonged, and the symptoms tended to decrease. In our experience, the acupuncture treatment was effective in a short period for treating residual olfactory dysfunction of the post COVID-19 condition, suggesting that acupuncture may serve as an adjunct to modern medical treatment, and it may also be a new option for patients who are resistant to Western medical treatment or unable to continue treatment because of side effects. In conclusion, acupuncture may be a new option for patients who are resistant to modern medical treatment or who are unable to continue treatment because of side effects.

KEYWORDS

COVID-19, post COVID-19 condition, acupuncture, olfactory dysfunction, Yingxiang point (LI20)

Introduction

Coronavirus disease (COVID-19) infections have been reported worldwide (1–6), and the World Health Organization defined the post COVID-19 condition as "symptoms that persist for more than 2 months after onset and cannot be explained by other diagnoses." Although the characteristic olfactory disturbance due to COVID-19 (7) improves early over time in most cases, some patients remain symptomatic, which has a significant impact on their quality of life. In Japan, Miyazato et al. (5) reported that 16.1% of patients continued to have olfactory dysfunction at 2 months, 9.7% at 4 months, 7.7% at 6 months, and 1.1% at 12 months (6). In other geographically different countries, such as Italy, a study reported that 13.3% of patients still had olfactory dysfunction after about 110 days (8). Therefore, olfactory dysfunction after COVID-19 infection is a common disorder worldwide that is intractable in some patients.

Olfactory deficits are not only associated with reduced quality of life (e.g., loss of flavor in food and daily life), but also with life-threatening situations, such as food spoilage, gas leaks, and smoke from fires. The treatment of olfactory dysfunction depends on the cause, but known treatments include steroids, nasal spray, surgical treatment, and olfactory training (9–11), and other than these treatments, there are few effective treatments, and treatment options are limited (12, 13). Systemic steroids may promote the recovery of olfactory dysfunction in the post COVID-19 condition (14), but may not be continued because of resistance to these treatment or strong side effects. Efforts to alleviate and treat the post COVID-19 condition are eagerly awaited by many patients around the world.

The effects of acupuncture are being scientifically elucidated. It has been reported that skin stimulation is transmitted to the brain, activates the central nervous system (15, 16), and is involved in anti-inflammatory and immunomodulatory mechanisms (17, 18). We experienced two cases of improvement of olfactory dysfunction in the post COVID-19 condition after traditional acupuncture treatment. The Yingxiang point (LI20), a meridian point that has been said to improve the sense of smell since ancient times (19), was used, and it has been used to treat various nasal symptoms and facial paralysis. Because acupuncture treatment involving LI20 has been reported to improve olfactory dysfunction after the common cold (12, 20, 21), we performed acupuncture at the LI20 for olfactory dysfunction in the post COVID-19 condition. As far as we know, there is no case report of acupuncture treatment at LI20 reducing olfactory dysfunction in the post COVID-19 condition. These two cases we experienced may offer new options for olfactory dysfunction in the post COVID-19 condition; therefore, we report their treatment progress herein.

Case descriptions

Ethics statement

The patients provided written informed consent to participate in this case report and for the publication of any potentially identifiable images or data.

Case 1

Clinical history

A 53-year-old woman was diagnosed with COVID-19 in May 2021 and was admitted to another hospital for 14 days. After discharge from the hospital, she still had some symptoms (malaise, olfactory dysfunction, taste dysfunction, midway awakening, decreased concentration, cough, shortness of breath on physical movement, insomnia, hair loss, etc.). Therefore, she was referred to our department in June 2021.

Table 1 shows the data of case 1 at the initial examination and at discharge. After the initial examination, treatment with Kampo prescription (Kamikihito) was started. There was a slight reduction in cough and general malaise, but there was no significant improvement. Hence, the patient was admitted to the hospital in October 2021. The level of olfactory dysfunction at admission was a numeric rating scale (NRS) score of 10 at the time of COVID-19 diagnosis, which persisted for approximately 5 months.

A subsequent venous olfactory test (alinamin test) result was unresponsive. An alinamin test is a test method that reflects olfactory mucosal disorders, in which prosultiamine is injected into a vein in 20 seconds (22). The time from the start of injection until the smell is perceived and the time until the smell disappears is measured. In cases of non-response to the alinamin test, a severe olfactory dysfunction involving the olfactory mucosa is suggested.

Acupuncture treatment

Acupuncture treatment was performed in October 2021 (about 5 months after the diagnosis of COVID-19). In the first session, the Shenmen point (HT7) was selected as the meridian point for the systemic symptom. After the second session, meridian points for systemic symptoms were the Yinlingquan point (SP9), Tianzhu point (BL10), Jueyinshu point (BL14), Xinshu point (BL15), Taixi point (KI3), Neiguan point (PC6), Daling point (PC7), Fengchi point (GB20), Taichong point (LR3), Danzhong point (CV7), Shengzhu point (GV12), and Baihui point (GV20). The acupuncture needle used for the systemic symptoms were 30–40 mm long and 0.14–0.18 mm in diameter, and they were inserted about 10 mm deep perpendicular to the skin.

TABLE 1 Demographic and clinical characteristics of cases 1 and 2.

	Case 1		Case 2	
Age (year)	53		38	
Sex	F		M	
BMI (kg/m^2)	26.3		36.1	
Medication history	Pregabalin Mecobalamin Theophylline Omalizumab		Acetaminophen	
Medical history	Lower back pain Bronchial asthma		Tonsillectomy	
Blood test results	**First visit**	**Discharge**	**First visit**	**Discharge**
TG (mg/dl)	127	68	223	195
LDL-cholesterol (mg/dl)	130	105	192	135
HDL-cholesterol (mg/dl)	59	60	65	53
HbA1c (NGSP, %)	5.4		5.5	
FPG (mg/dl)	135	99	95	125
SBP (mmHg)	139	125	149	143
DBP (mmHg)	78	80	95	103
CRP (mg/dl)	0.05	0.04	0.15	0.07
WBC (10^3/μl)	4.2	4.8	10.8	7.3

BMI, body mass index; F, female; M, male; TG, triglyceride; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin A1c; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; WBC, white blood cell.

After the ninth session (November 16, 2021, which was performed 1 month later (approximately 6 months after the diagnosis of COVID-19), we added the LI20 of the right and left sides for olfactory dysfunction, which is located on the face, in the nasolabial sulcus, at the same level as the midpoint of the outer margin of the nasal wings (Figure 1). SP3 or LR3 were also used as meridian points for systemic symptoms. After the ninth acupuncture treatment, the acupuncture needles used for olfactory dysfunction were 30 mm long and 0.16 mm in diameter, and they were inserted about 10 mm deep into the skin. The acupuncture needles were stimulated until the de qi sensation (acupuncture resonance) was felt, and then the acupuncture needles were left in the points for 15 min. The de qi sensation is a special sensation felt by the patient and the acupuncturist during acupuncture, and it is thought that obtaining acupuncture resonance is closely related to the degree of the treatment effect (23).

Acupuncture treatment was performed twice a week during hospitalization, and was performed once a week after discharge.

Treatment response

The degree of the patient's olfactory dysfunction was evaluated with the Numeric Rating Scale (NRS). The NRS is an evaluation method that expresses subjective sensations, such as pain, stress, and daily life obstacles that the patient is aware of, as an objective numerical value to share with others. In response to the question, "If the level of olfaction before infection was 0 and the level of not smelling at all was 10, how much is it now?" patients were asked to express their current subjective symptoms on an 11-point scale from 0 to 10. The timeline of the acupuncture treatment and NRS for olfactory dysfunction and general malaise are shown in Figure 2. After the first session, the patient returned to her hospital room and became aware of the smell of coffee and slight smell of sewage. This was the first relief of olfactory dysfunction that had remained constant for about 5 months (the NRS score decreased from 10 to 6 of immediately after acupuncture treatment). Similarly, relief of general malaise was observed immediately after treatment. The reduction in both olfactory dysfunction and general malaise were maintained for 2–3 days, but then flared up to the pre-acupuncture level. After six sessions (twice a week) were given during the hospitalization period, the patient switched to outpatient treatment because she wished to continue treatment with Kampo and acupuncture. However, after a total of eight sessions including both during hospitalization and after discharge, the patient still sustained an NRS score of 9.

When LI20 was added, starting from the ninth sessions (approximately 6 months after the diagnosis of COVID-19), the NRS score was reduced to 4 immediately after the treatment, and it was maintained at 7 after 2–3 days. After discharge from the hospital, the patient was treated once a week.

No adverse reactions were observed throughout the treatment period, including outpatient treatments. Regarding

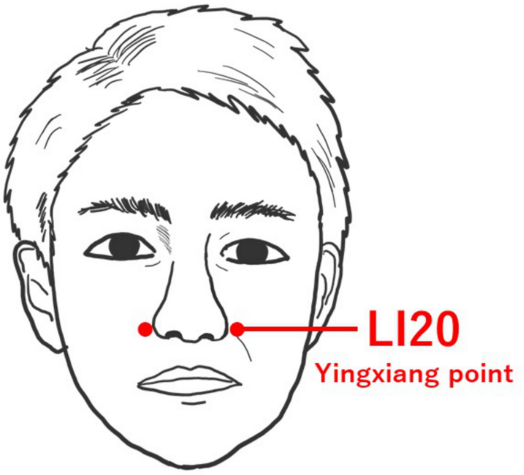

FIGURE 1
Location of LI20.

the Kampo prescription, we continued to use Kamikihito, which she had been taking since her admission.

Case 2

Clinical history

A 38-year-old man was diagnosed with COVID-19 in May 2021. He was hospitalized for 8 days until May 25, 2021 and received oxygen inhalation and other therapeutic measures, but some symptoms (malaise, olfactory dysfunction, midway awakening, decreased concentration, palpitations, fatigue after physical activity, heaviness in the head, etc.) remained after discharge, and he was referred to our department in July 2021.

Table 1 shows the information of case 2 at the initial examination and discharge. After starting Kampo prescription (Ninjin'yoeito), there was a tendency for fatigue after physical activity and olfactory dysfunction to be reduced, but the symptoms flared up again. After the symptoms continued for another 30 days, the patient was admitted to the Department of Kampo Medicine in November 2021 (about 6 months after the diagnosis of COVID-19). After admission, the patient remained unchanged for another 40 days with olfactory dysfunction (NRS score, 3) and general malaise (NRS score, 5).

Acupuncture treatment

In December 2021 (approximately 7 months after the diagnosis of COVID-19), the first acupuncture treatment was performed for systemic symptoms and olfactory dysfunction. Case 2 used LI20 from the first treatment. The acupuncture points, needles used, insertion depth, and stimulation method were the same as those in case 1. The acupuncture treatments from the second time onward were performed in the same way as the first treatment, and once a week during hospitalization. After discharge from the hospital, treatment was given twice a week to maintain the effect.

Treatment response

The subjective symptoms of olfactory dysfunction and general malaise are shown in Figure 3. After the first acupuncture treatment, the patient returned to the hospital room and became aware of the smell of alcohol in the room. The improvement of olfactory dysfunction lasted for 3–4 days, after which it flared up to the pre-treatment symptom level (NRS score, 3). After the second and third acupuncture treatments, as after the first treatment, there was a rapid reduction in symptoms (NRS score, 0). As the number of acupuncture treatments increased, the time until the flareup of olfactory dysfunction was slightly prolonged, and the level of symptoms tended to decrease.

A total of four acupuncture treatments (once a week) were given during the hospitalization period. After discharge, acupuncture treatments were continued twice a week. No adverse reactions were observed during the treatment period, including outpatient treatment. Regarding the Kampo prescription, he continued to take Ninjin'yoeito from the time of admission.

Discussion

The cases described herein suggest that acupuncture may have a positive effect on olfactory dysfunction in the post COVID-19 condition.

LI20 is located in the region of the trigeminal nerve (second branch), which transmits perception to the brain. The branches of the second branch (maxillary nerve) become mixed nerves with sympathetic and parasympathetic nerves (i.e., posterior nasal nerves) and reach the nasal cavity. Previous reports on acupuncture for allergic rhinitis suggest that it may modulate anti-inflammatory effects including neural pathways, involve the down-regulation of various cytokines (17, 18), and some reports suggest improved nasal ventilation due to sympathetic nerve dominance (24). The mechanism by which the reduction in olfactory dysfunction was achieved in this case is unknown, but previous reports showed that acupuncture may have had an effect that included anti-inflammatory effects and nerve activation. Moreover, a previous study of olfactory abnormalities after upper respiratory tract infection considered that acupuncture with LI20 may have a positive effect on the cognitive processing of odors (12). Therefore, the same possibility is considered for olfactory dysfunction in the post COVID-19 condition.

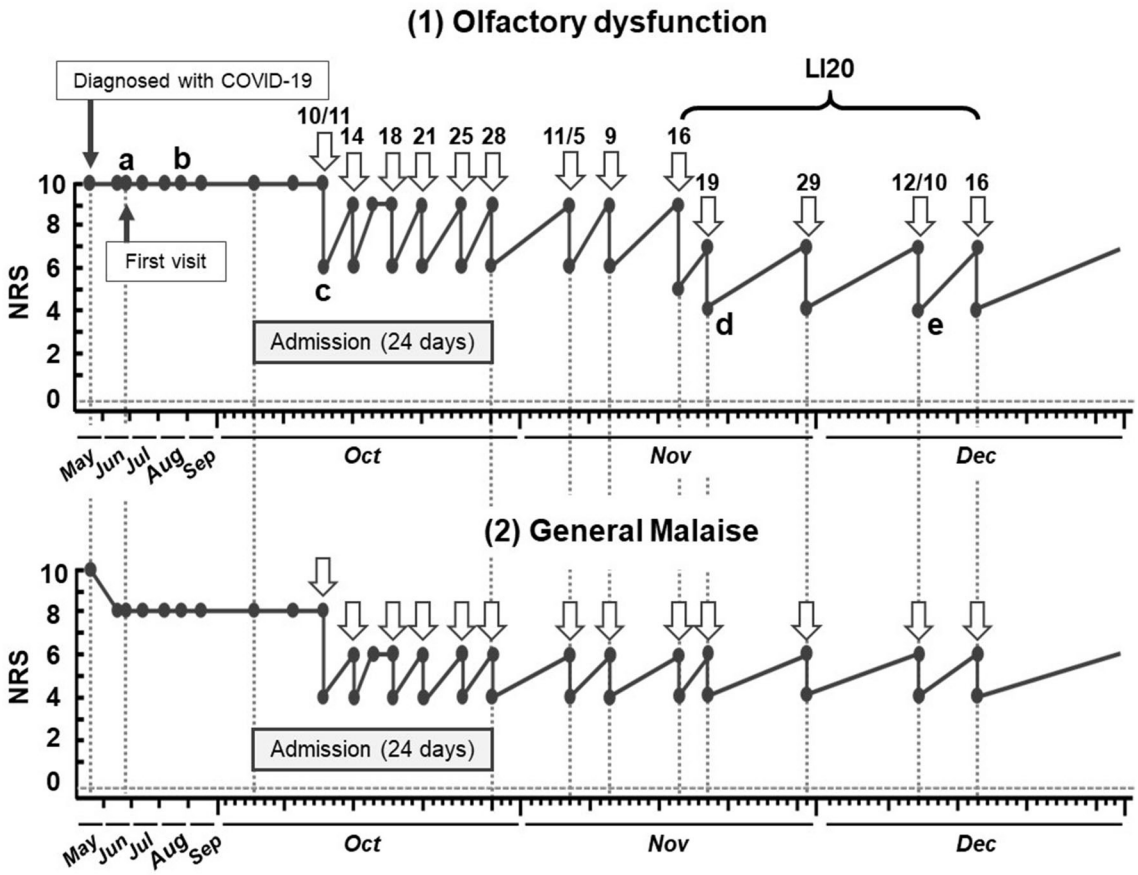

FIGURE 2
Timeline of acupuncture treatment and subjective symptoms of olfactory dysfunction and general malaise in case 1. a. Difficult to smell. b. Cannot smell chlorine bleach (for cleaning) and does not feel well. c. Recognizes slight smell of sewage and the smell of coffee. d. Can smell own stool and ginger tea. e. Can smell sewage and herbs after treatment. NRS, numeric rating scale; COVID-19, coronavirus disease.

Acupuncture treatment also alleviated malaise in our cases. This may be because of the positive effects of acupuncture stimulation of the upper and lower extremities at the Shenmen (HT7), Taibai (SP3), or Taichong (LR3) points on the visceral organs, especially the digestive system, through supraspinal reflexes (25, 26). In addition, one of acupuncture effects includes relaxation (27, 28), and the fact that both patients were aware that they did not wake up in the middle of the night after the acupuncture treatment suggests that it had a positive effect on their mind and body. On the next day after treatment, malaise flared up, and compared to the reduction of olfactory dysfunction, which lasted for about 3 days, the continuous effect was lower. This may be due to the fact that the acupuncture treatment for local stimulation was focused on only olfactory dysfunction.

In case 2, the patient's olfactory dysfunction eased to a level where he was not aware of any discomfort (NRS score, 0–1). However, in case 1, the NRS was only decreased to 7. One factor for this could be the frequency of treatment with LI20: case 2 continued to be treated twice a week, whereas case 1 was treated once a week. Some reports indicate that acupuncture treatment three times a week was more effective in analgesia than acupuncture treatment once a week (29). Therefore, it can be inferred that treatment frequency and efficacy may be related in the improvement of olfactory function as well.

Higher treatment frequency with LI20 can be considered to lead to higher treatment efficacy. An additional factor could be the difference in the level of damage to the olfactory mucosa cells.

Regarding the mechanism of olfactory deficits after COVID-19 infection of olfactory epithelial support cells, it has been suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cause damage to the nasal mucosa *via* inflammation (30). Furthermore, experiments with hamsters revealed the shedding of the olfactory epithelium, which contains olfactory receptors (receptors that receive odorants), early after infection (31). In general, the olfactory epithelium regenerates and returns to normal thickness after injury.

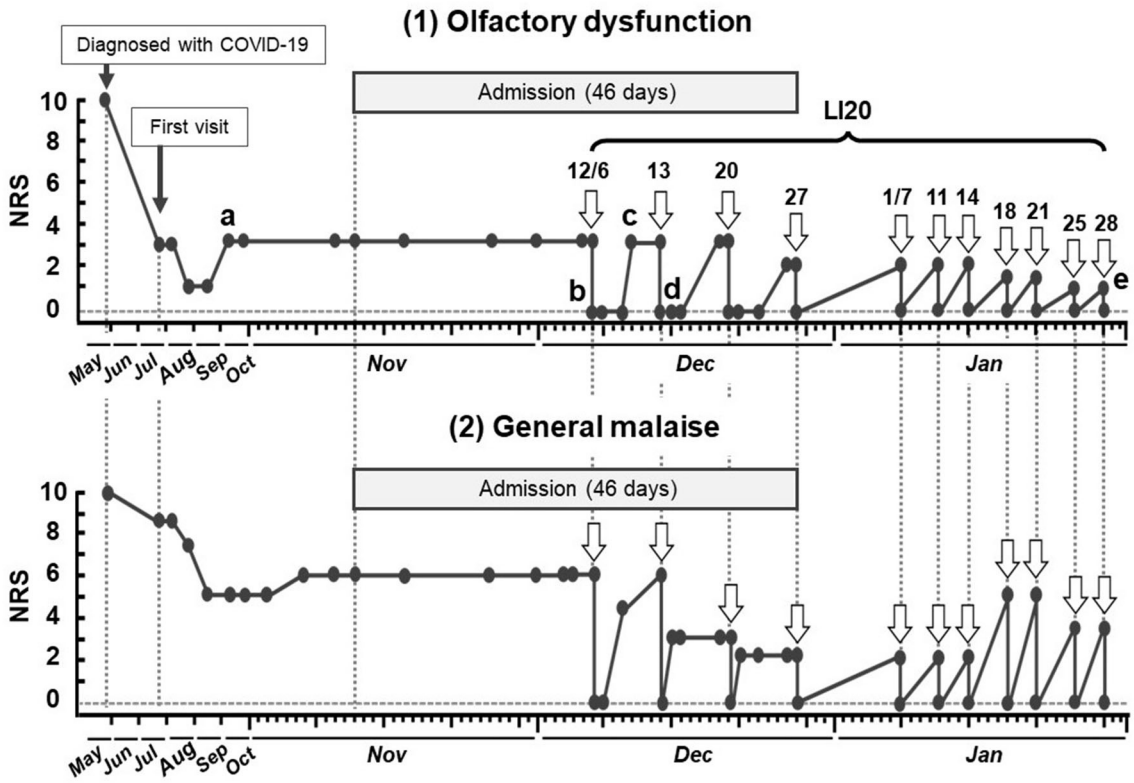

FIGURE 3
Timeline of acupuncture treatment and subjective symptoms of olfactory dysfunction and general malaise in case 2. a. Cannot recognize the smell of coffee. b. Recognizes the smell of alcohol, mayonnaise, and soy sauce in the room. c. Cannot recognize the smell of coffee. d. Can smell toothpaste. e. The smell of coffee is noticeable. NRS, numeric rating scale; COVID-19, coronavirus disease.

However, in the case of SARS-CoV-2 infection, it has been reported that the degree of injury and the speed of regeneration vary depending on the site, with most of the epithelium returning to normal thickness and some remaining damaged. Considering these SARS-CoV-2-specific symptoms, the results of the alinamin test, and NRS changes from the time of diagnosis to the first visit, we speculate that the level of damage to the olfactory mucosa in case 1 may have been stronger than that in case 2. Perhaps further symptom relief could have been obtained with high frequency acupuncture treatments with LI20.

Lastly, we will discuss the limitations of this case report. First, we have not been able to identify the type of variant that affected these patients. Based on the time when these two cases were obtained, it is expected to be the post COVID-19 condition caused by the delta variant that was spreading in Japan, but we would like to examine the effect of different variants. Second, these patients were treated with Kampo prescriptions too, so the effect of acupuncture alone could not be determined. Kampo prescription has the effect of enhancing the body's natural healing power. Kamikihito, prescribed in case 1, consists of 14 crude drugs (32) and is a Kampo prescription known to be effective in treating insomnia, anorexia, and depression (33). Ninjin'yoeito, prescribed in case 2, consists of 12 crude drugs and is used for recovery from decreased physical strength after illness or surgery and improvement of symptoms such as fatigue, anorexia (34). In our clinical practice, we have experienced the synergistic effect of acupuncture and Kampo prescription together, and in these cases, the Kampo prescription was able to regulate the digestive symptoms and correct the distortion of the biological balance, which was considered to be an important factor that enhanced the original effect of acupuncture. The third factor was weight control during the hospitalization. Obesity has been pointed out as one of the factors that prolong the post COVID-19 condition (35), and both of the patients were obese. Partly due to calorie control during hospitalization, case 1 lost 3 kg and case 2 lost 9 kg from the time of initial examination to the time of discharge. Although it is not possible to clearly conclude the effect of weight loss, this case study reduced symptoms in patients with such a high body mass index, regardless of sex or age.

Despite these limitations, our experiences show that acupuncture treatment can be an adjunct to modern

medical treatment as it is effective within a short period for treating residual olfactory dysfunction after healing from COVID-19 infection. The application of acupuncture treatment may be a new option for patients who are resistant to modern medical treatments or who are unable to continue treatment because of strong side effects.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/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

AMo and TU conducted the acupuncture treatment with support from NO and KR. AMo and AMu wrote the manuscript with support from YW, SO, KO, YH, and TN. AMu analyzed the data with support from TN. AMo and TN conceived the original idea. TN supervised the project. All authors discussed the results and contributed to the final manuscript.

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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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Early intervention with acupuncture improves the outcome of patients with Bell's palsy: A propensity score-matching analysis

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Objective: Although acupuncture is widely used as a complementary therapy in the treatment of Bell's palsy (BP) when to initiate acupuncture is still controversial. This study aims to determine the efficacy of the early intervention by acupuncture on BP.

Methods: We retrospectively gathered clinical data from the Third Affiliated Hospital of SUN-YAT SEN University between 2016 and 2021. We selected newly diagnosed patients with BP who were diagnosed by registered neurologists or acupuncturists formally. The qualified patients were divided into two groups according to whether or not initial acupuncture treatment was given within 7 days from the onset of palsy. Cohorts were balanced using 1:1 propensity score matching (PSM). Cox proportional hazards modeling and Kaplan–Meier analysis were applied to determine the differences between the two groups. The outcome included time to complete recovery of facial function, the rate of complete recovery, and the occurrence of sequelae in 24 weeks.

Results: A total of 345 patients were eligible for this study and were divided into the manual acupuncture/electroacupuncture (MA/EA) group ($n = 76$) and the EA group ($n = 125$). In the propensity score-matched cohort, the time to complete recovery was significantly shorter in the MA/EA group compared with the patients in the EA group (hazard ratio 1.505, 95% CI 1.028–2.404, $p < 0.05$). The MA/EA group had a higher rate of favorable outcomes at 12 weeks than the EA group (93.4 vs. 80.3%, $p = 0.032$), and the occurrence of sequelae at 24 weeks showed a greater reducing trend in the MA/EA group than the EA group (6.6 vs. 16.4%, $p = 0.088$).

Conclusion: Acupuncture intervention at the acute stage of BP could shorten the time to recovery and improve the outcome.

Clinical trial registration: http://www.chictr.org.cn, identifier ChiCTR 2200058060.

KEYWORDS

acupuncture, Bell's palsy, real world study, propensity score matching, retrospective study

Introduction

Bell's palsy (BP) is a common cranial mononeuropathy that accounts for 70% of peripheral facial palsies. It presents as unilateral weakness or paralysis of the face due to acute dysfunction of the peripheral facial nerve with no readily identifiable cause (1).

The described population incidence rates range from 11.5 to 40.2/100,000 (2, 3). Approximately, 30% of patients with BP have sequelae that include residual paresis, contracture, and synkinesis, which have a dramatic impact on social function, emotional expression, and psychological health (4, 5).

Previous randomized-controlled studies demonstrated the improving effect of corticosteroids on treating BP (6, 7). Moreover, it showed a greater benefit of using corticosteroids in the acute stage (8). The effect of antiviral drugs is still inconclusive (9, 10). Predictors of incomplete recovery were old age, severe facial palsy, no recovery in the first 3 months after onset, prolonged pain around the ear, pregnancy, diabetes mellitus, and hypertension. However, medications exhibit limited efficacy to promote neurological function recovery. To minimize the time to recovery and sequelae from BP, the most effective treatment has to be established, including medication and non-pharmacological therapy.

As an adjuvant therapy, acupuncture has been widely applied to neuropathy throughout East Asia for more than 4,000 years. Numerous clinical trials have shown that acupuncture could improve facial motor symptoms, release pain around the ear, and speed up recovery (11, 12). However, when to initiate the intervention by acupuncture is still controversial (13). Evidence is scarce regarding whether acupuncture in the acute stage within 7 days of palsy onset could improve the outcome of BP in long-term follow-up. Therefore, to address this gap, we aim to investigate the effect of acupuncture therapy initiating in the acute stage of BP based on relevant real-world data.

Materials and methods

Participants

In this single-center retrospective study, a total of 345 patients who underwent acupuncture secondary to BP between August 2016 and December 2021 were enrolled. The inclusion criteria were as follows: (1) patients with unilateral facial paralysis, (2) patients with neurological deficits with a House–Brackmann (H-B) grading of IV or higher during treatment, (3) patients ≥18 years of age, and (4) patients who underwent acupuncture and follow-up in the outpatient department.

The exclusion criteria were as follows: (1) facial nerve dysfunction caused by herpes zoster virus; (2) otogenic facial paralysis such as otitis media, labyrinthitis, and mastoiditis; (3) peripheral facial paralysis secondary to brainstem injury, acoustic neuroma, Guillain–Barre syndrome, or other neurological diseases; and (4) incomplete data or loss to follow-up.

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of SUN YAT-SEN University. The procedures of this study adhered to the tenets of the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry (ChiCTR 2200058060) on 28 March 2022.

Interventional procedures

All patients received standard medication management according to the latest Chinese Guidelines for BP (14). Prednisolone 30 mg was given daily orally for 7 days, and the dose was then reduced by 10 mg per day for 7 days, with a total treatment time of 21 days. In addition, acupuncture treatment based on the theory of Traditional Chinese Medicine was performed on all patients with BP. We adopted differentiated approaches according to the different timing of intervention of acupuncture. The details of acupuncture such as the chosen acupoints and needling methods are provided in the Additional File 1. The therapy was carried out by licensed acupuncturists having more than 5 years of experience.

Patients with onset of BP within 7 days received mildly manual acupuncture (MA) therapy. Sterile, stainless steel needles (length: 25 mm; diameter: 0.3 mm; Sui Xin, Suzhou Medical Appliance, Suzhou, China) were inserted into the described acupoints. After patients indicated the *Deqi* sensation (soreness, heaviness, and distension sensation), needles were left in acupoints, and manipulations of twirling, lifting, and thrusting were performed once every 10 min. The treatment was given for 30 min during each session, one time per day within 7 days after onset. After accepting MA, the patients with onset

beyond 7 days would continue to receive electroacupuncture (EA) therapy.

When palsy onset was beyond 7 days, we initiated regular EA therapy in patients. After needles were inserted into acupoints, paired alligator clips from an EA apparatus (GB6805-2, Medical Supply & Equipment Co, Ltd, Shanghai, China) were attached transversely to the needle-holders. EA stimulation lasted for 30 min with a continuous wave of 20 Hz frequency, a pulse width of 0.5 ms, and a current intensity of 0.1–2 mA depending on the individual participant's comfort level (preferably with the skin around the acupoints shivering mildly without pain). The EA was administered three times per week for 24 weeks or until complete recovery.

Follow-up

Patients were followed until recovered completely. If recovery was incomplete within 6 weeks, the next follow-up was at 12 and 24 weeks. The facial function was assessed at all visits with the H-B scale. The H-B scale is a grading system based on a six-grade score, where I is a normal function and VI is complete paralysis, for gross assessment of facial motor function and sequelae.

Data collection and outcome measures

Detailed clinical information was extracted through a retrospective review of the patient record, procedure notes, and follow-up notes. Baseline characteristics were collected, including age, gender, symptomatic presentation, previous history of BP, perinatal period, comorbidities (hypertension, diabetes mellitus, hyperlipidemia, and psychiatric disease), onset time, time from the onset to medical interventions, and H-B grading before acupuncture. We considered the primary outcome was time to complete recovery of facial function, defined as an H-B grading of I. The secondary outcome was the rate of complete recovery and the occurrence of synkinesis, facial spasm, or contracture.

Statistical analysis

We used mean and SD for normally distributed variables, or median (interquartile) for the variables not normally distributed, to summarize the participants' demographics. Statistical analyses were performed using SPSS version 26.0. Comparisons were performed using the *t*-test or Mann–Whitney test for continuous variables and chi-square test for categorical variables, as appropriate. All tests were two-sided, and an $\alpha < 0.05$ was considered significant.

Propensity score matching (PSM) was performed using SPSS version 26.0 to ensure an even distribution of possible confounders between the two groups. A 1:1 matching range by using proximity matching was performed with a caliper width of 0.01. The underlying characteristics considered in the propensity-matching process were age, gender, hypertension, diabetes mellitus, hyperlipidemia, psychiatric disease, perinatal period, history of BP, and time from the onset to medical interventions. After matching patient characteristics, the Kaplan–Meier method was used to estimate survival curves. Cox proportional hazards models were used to estimate the hazard ratio (HR) of recovery and the corresponding 95% confidence interval (CI).

Results

Demographic characteristics between two groups

The flowchart is summarized in Figure 1. A total of 345 patients with newly diagnosed BP were qualified for the study. Among the included subjects, 76 (37.8 %) patients were treated with acupuncture within 7 days after onset, and 125 patients (62.2%) received acupuncture therapy over 7 days after onset (Table 1). Significant differences between the MA/EA group and the EA group were observed. Specifically, the characteristics, namely, age, medical history, and comorbidities between the two groups are statistically significant ($p < 0.05$). Patients in the MA/EA group were more likely to seek treatment actively (80.3 vs. 65.6%, $p = 0.026$).

We ultimately used a 1:1 PSM method to select 61 patients in each group, respectively, in order to minimize the interference of confounding variables. The patients in the two groups were matched on the basis of similarities in their demographics, comorbidities, medicines used, and the time from the onset of palsy to medications, and all covariates were statistically indistinguishable between the two groups. After the matching procedure, there were no significant differences in gender, age, medical history, baseline comorbidities, and time from the onset of palsy to the start of medication management between the two groups. The median durations between the onset of palsy and the first receiving of acupuncture in the two groups were 3 and 9 days, respectively.

The effect of acupuncture within 7 days after onset of palsy

Figure 2 shows that the time to complete recovery was significantly shorter for the patients who received acupuncture within 7 days compared with the patients treated over 7 days (HR 1.505, 95% CI 1.028–2.404, $p < 0.05$). The mean time to

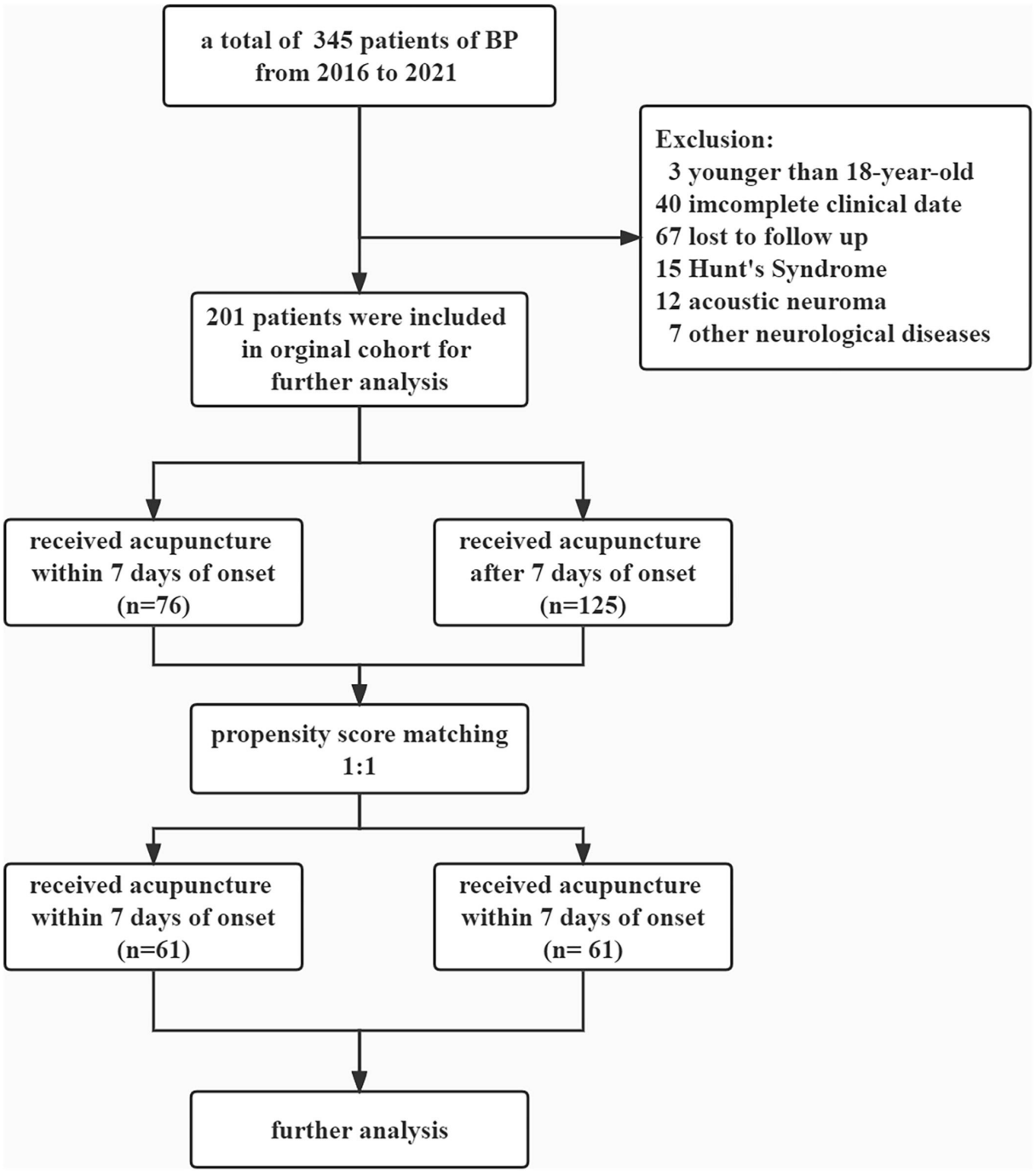

FIGURE 1
Flowchart of the included participants.

complete recovery (H-B grading of I) in the MA/EA group was shorter than in the EA group (36.62 ± 4.78 vs. 55.40 ± 6.93, $p < 0.05$).

Table 2 shows that the patients in the MA/EA group had significantly higher recovery rates at 12 weeks than the patients in the EA group ($p < 0.05$). At 12 weeks, 57 of 61 patients (93.4%) in the MA/EA group had recovered compared with 49 of 61 patients (80.3%) in the EA group.

Of the 122 patients who had 24 weeks' follow-up, sequelae were reported in 4 of 61 patients (6.6%) treated within 7 days

TABLE 1 Characteristics of patients before and after propensity score matching.

Variable	Before PSM				After PSM			
	MA/EA ($n = 76$)	EA ($n = 125$)	*P*-Value	Standardized Difference, %	MA/EA ($n = 61$)	EA ($n = 61$)	*P*-Value	Standardized Difference, %
Age	34.56 ± 12.61	39.24 ± 14.38	***0.020***	34.6	34.33 ± 11.49	35.36 ± 12.16	0.655	8.7
Gender								
Female	39 (51.3)	61 (48.8)	0.729	5.0	31 (50.8)	31 (50.8)	1.000	0
Male	37 (48.7)	64 (51.2)		5.0	30 (49.2)	30 (49.2)		0
Presentation								
Numb in Tongue	8 (10.5)	15 (12.0)	0.750	4.7	6 (9.8)	7 (11.4)	0.769	5.2
Pain around the ear	36 (47.3)	64 (51.2)	0.598	7.8	18 (29.5)	20 (32.7)	0.695	6.9
Hyperacusis	3 (3.9)	4 (3.2)	0.752	3.7	1 (1.6)	1 (1.6)	1	0
History of BP	4 (5.3)	1 (0.8)	***0.049***	26.3	1 (1.6)	1 (1.6)	1.000	0
H-B facial grading								
IV	23 (30.3)	38 (30.4)	0.944	0.2	17 (27.9)	21 (34.4)	0.733	14.1
V	49 (64.5)	79 (63.2)		2.7	42 (68.9)	38 (62.3)		13.9
VI	4 (5.3)	8 (6.4)		4.7	2 (3.3)	2 (3.3)		0
Perinatal period	1 (1.3)	6 (4.8)	0.191	0	1 (1.6)	1 (1.6)	1.000	0
Baseline comorbidity								
Diabetes mellitus	3 (3.9)	12 (9.6)	0.139	22.9	3 (4.9)	4 (6.3)	0.697	8.9
Hypertension	0 (0)	9 (7.2)	***0.017***	39.4	0 (0)	0 (0)	/	0
Hyperlipidemia	2 (2.6)	4 (3.2)	0.818	3.57	0 (0)	0 (0)	/	0
Psychiatric disease	2 (2.6)	2 (1.6)	0.612	6.9	1 (1.6)	1 (1.6)	1.000	0
Corticosteroid therapy								
Within 72 h	61 (80.3)	82 (65.6)	***0.026***	33.6	46 (75.4)	45 (73.8)	0.835	3.7

compared with 10 of 61 (16.4%) in those who did not receive acupuncture within 7 days. But these trends in the difference were not significant statistically ($p > 0.05$) (Table 3).

Acupuncture-related adverse events (AEs) occurred in 4/61(6.6%) participants in the MA/EA group and 2/61(3.3%) in the EA group ($p > 0.05$). The most commonly reported acupuncture-related AEs included subcutaneous hemorrhage, sharp pain after acupuncture, and fainting during treatment (Table 4). No significant difference was found between the two groups for the proportion of patients with AEs ($p > 0.05$ for all AEs). Neither group had severe AEs. None of the participants withdrew from the study because of AEs.

Discussion

In this PSM-based real-world study, we evaluated the efficacy of the early intervention by acupuncture therapy in patients with BP. The main findings of our study are as follows: (1) patients in the MA/EA group had a shorter time to complete recovery, and clinical outcomes at 12 weeks were more favorable in these patients than in those who did not receive acupuncture in the acute phase and (2) the effect of acupuncture in the acute phase of BP showed a trend that was better than those who did not on reducing the occurrence of sequelae. Larger sample sizes would be needed to show whether these trends in the difference between the two groups may be statistically significant.

Over the years, whether to perform acupuncture in the acute phase of BP has been hugely inconclusive and debatable (15). The focus of this issue lies in the time window of acupuncture and the method of stimulation. Some studies have revealed that an early and appropriate acupuncture therapy might shorten the time to recovery, whereas others insist that EA is not appropriate for patients with BP in the acute phase because it is inclined to aggravate edema and bioelectric conduction disorders of the facial nerve (16, 17). Based on this controversy, we adopted the stimulation of mild MA cautiously to avoid the potential hazards to patients with BP. This study provides evidence for the procedure and strategy of intervention by acupuncture in the acute phase of BP. In addition, the proportions of participants having acupuncture-related AEs in the MA/EA and EA groups were low, and the specific AEs were mild or transient. These results are similar to those reported in a previous acupuncture study (18).

A previous study by Engström M and coworkers showed that the complete recovery rates were ∼70% in patients with

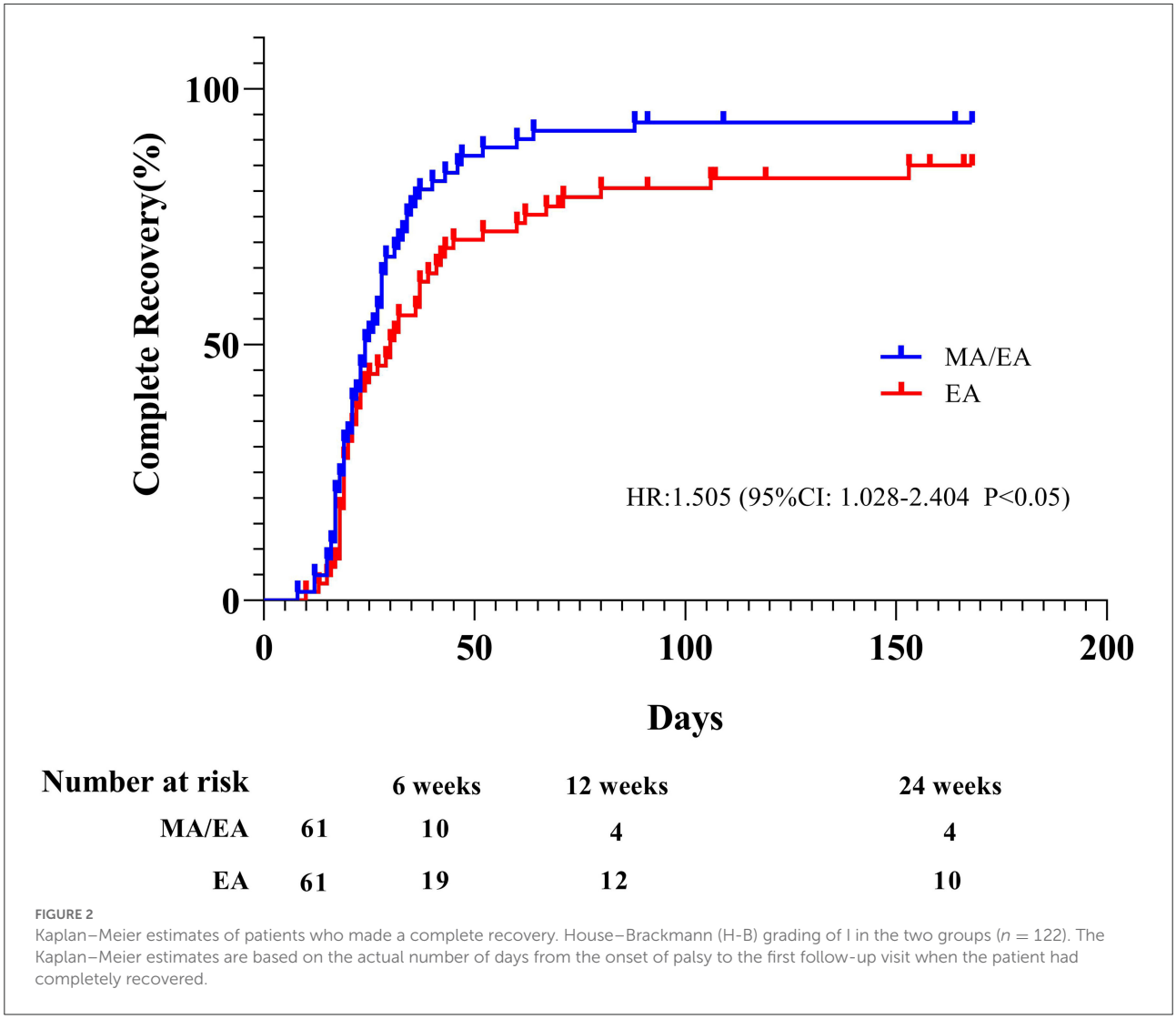

FIGURE 2
Kaplan–Meier estimates of patients who made a complete recovery. House–Brackmann (H-B) grading of I in the two groups ($n = 122$). The Kaplan–Meier estimates are based on the actual number of days from the onset of palsy to the first follow-up visit when the patient had completely recovered.

TABLE 2 Comparison of rates of complete recovery per follow-up visit between two groups.

Groups	6 weeks ($n = 61$)	12 weeks ($n = 61$)	24 weeks ($n = 61$)
MA/EA group	51 (83.6)	57 (93.4)	57 (93.4)
EA group	42 (68.9)	49 (80.3)	51 (83.6)
P-Value	0.056	***0.032***	0.088

TABLE 3 Comparison of occurrence of synkinesis between two groups.

Groups	Occurrence of synkinesis at 24 weeks ($n = 61$)
MA/EA group	4 (6.6)
EA group	10 (16.4)
P-Value	0.088

BP receiving prednisolone (6). A study found that ~70% of patients with BP recover completely within 6 months without treatment (5). In this study, our recovery rates were higher than those previously reported. The causes of the differences between this study and the previous study might be the lower recovery rates assessed by the Sunnybrook scale vs. the H-B scale. Besides, we cautiously attribute the difference as an additional benefit of acupuncture intervention plus corticosteroids probably.

Although it is reported that the Sunnybrook system assesses facial function continuously, has a wider response range, and is more reliable than the H-B scale, we used the H-B scale instead of the Sunnybrook scale as the main scale to assess facial nerve function in this study. The causes were as follows: (1) evaluation with the H-B scale is easier and quicker than that with the

TABLE 4 Adverse events related to acupuncture between two groups[a].

Adverse event	MA/EA ($n = 61$)	EA ($n = 61$)	*P*-Value
Overall	4	2	0.402
Subcutaneous hemorrhage	2	1	0.558
Sharp pain after acupuncture	1	1	/
Faint during acupuncture	1	0	0.315
infection around the site of needling	0	0	/

[a]Adverse events were counted by type rather than frequency in the same participant. Adverse events with different types occurring in a single participant were defined as independent adverse events. An adverse event with multiple occurrences in a single participant was defined as 1 adverse event.

Sunnybrook system, which is more likely to be in accordance with the current clinical situation, and (2) we focused more on endpoint evaluation, not the continuous observation of facial nerve function.

Previous findings indicate that inflammation and edema of the facial nerve are part of the pathogenesis in patients with BP (19, 20). Similar to the effect of corticosteroids on BP, the effect of acupuncture may be related to its anti-inflammatory effect. Some *in vivo* evidence suggest that acupuncture at ST 36 and ST 25 regions could produce anti-inflammatory effects by driving the vagal–adrenal axis (21). Besides, the benefit of using corticosteroids is unclear when more than 72 h have elapsed since the onset of palsy. Likewise, when beyond the time window of acupuncture, the benefit of acupuncture might decrease.

Strengths and limitations of the study

Compared with other studies on acupuncture for BP, the protocol of this study had some advantages. (1) It was easier to execute than a prospective randomized-controlled trial (RCT). An RCT study reported that it is difficult to recruit and maintain patients (11). This protocol was more conducive to protecting patients' rights and avoiding delays in treatment owing to the study design. (2) It could avoid the bias between two groups through a variety of statistical methods. Although RCT is the best way to minimize bias in ascertaining treatment effects, many studies have reported the uneven distribution of initial facial grade even if it was grouped by randomization (11, 22). (3) We took time to recover completely as primary endpoints, which was rare in the study of acupuncture for BP, whereas it was common in the study of other treatments for BP.

This study still has some limitations. First, single-center design, high rate of loss to follow-up (67/345), and small sample size are the major limitations of this study. Second, although propensity score-based matching analysis was applied in the study to reduce bias, it still has deficits such as shrinkage of the cohort's sample size and failure to eliminate unknown bias like the potential effect of antivirus treatment and unclear benefits of corticosteroid over 3 days. Third, we did not compare groups with no acupuncture or sham acupuncture. Furthermore, studies with multicenter, large samples are still needed to prove the effect of early intervention by acupuncture on BP.

Conclusion

This study revealed that acupuncture intervention at the acute stage of BP could shorten the time to recovery and improve the outcome. The findings support the use of acupuncture as a complementary therapy for BP in the acute phase.

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 human participants were reviewed and approved by Medical Ethics Committee of Third Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

L-SY and KZ: study design. B-MZ, H-GL, Q-QC, and YZ: data collection. S-ZZ and D-FZ: statistical analysis. L-SY and D-FZ: draft writing. H-ZY: draft review and modification. C-ZT: result interpretation, draft review, and editing. All authors contributed to the article and approved the submitted version.

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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.2022.943453/full#supplementary-material

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A bibliometric of research trends in acupuncture for spinal cord injury: Quantitative and qualitative analyses

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Introduction: Spinal cord injury (SCI) is a severe disease of the central nervous system with a very high disability rate that seriously affects the daily life of patients. Acupuncture is one of the rehabilitation therapies that has shown significant efficacy in treating post-SCI complications such as motor disorders, neuropathic pain, and neurogenic bladder. Current studies have focused on the effectiveness and mechanisms of acupuncture for SCI, but no studies are available to analyze the bibliometrics of publications related to this area.

Methods: Publications related to acupuncture for SCI were retrieved from the Web of Science Core Collection for quantitative and qualitative analyses. The quantitative analysis was unfolded in the following six main areas: annual publications, countries, institutions, authors, sources, and keywords. The qualitative analysis section screened out publications with high annual citation rates and categorized them according to the study content.

Results: There were 213 relevant publications, more than half of which were journal articles. The number of publications showed a fluctuating upward trend. China and the United States were hub countries for related publications and had extensive cooperation with other countries. The most relevant author was Yuanshan Zeng from Sun Yat-sen University, China. The efficacy and mechanism of acupuncture for neuropathic pain after SCI was the first research hotspot in this field, and electroacupuncture was the most widely used technique. In the past 5 years, the mechanism of acupuncture to improve the local microenvironment of SCI and promote nerve regeneration had become a new research trend. At the same time, acupuncture had been gradually applied to various complications after SCI and in veterinary medicine.

Conclusion: The findings suggest that research on acupuncture for SCI is still flourishing, and more research on electroacupuncture for promoting nerve repair and regeneration after SCI will be available in the future.

KEYWORDS

bibliometrics, acupuncture, spinal cord injury, quantitative analysis, qualitative analysis

Introduction

Spinal cord injury (SCI) is often caused by trauma, tumors, and infections, which has a high disability rate and cause enormous psychological stress and heavy economic burdens to the patient's family (1). Primary SCI is mostly improved by surgical decompression and spinal fixation, but secondary SCI due to chemical and mechanical injuries is more problematic (2). Currently, the efficacy of drug treatment for the disease is limited, and the tolerability and safety of emerging therapies such as stem cell transplantation, gene therapy, and biomaterials remain to be unequivocally proven (3, 4). Patients with SCI rely heavily on rehabilitation to promote recovery of limb function and reduce the incidence of complications in the later stages.

According to the traditional Chinese medicine theory, meridians are the channels in which the blood and qi flow, as well as the regulatory system of the body's functions (5). Acupoints are specific locations of the meridian line where qi and blood of Zang-fu organs enter and exit (6). As a rehabilitation therapy for SCI, acupuncture can free meridians and harmonize yin and yang by stimulating specific acupoints on the body's surface (7). Clinical practice has confirmed that acupuncture has significant efficacy in post-SCI complications such as motor and sensory impairment, neuropathic pain (NP), and neurogenic bladder (8–10). Fundamental studies have also shown that acupuncture can inhibit apoptosis after SCI, improve the local microenvironment, and promote nerve repair and regeneration (11, 12).

Bibliometrics is a cross-cutting science that applies mathematics and statistics to the quantitative analysis of published scientific literature to measure the impact, interrelationships, and trends of publications in a certain field (13). Currently, bibliometrics has been gradually applied in the fields of medicine, law, education, biology, sports, and other fields (14). Meanwhile, some reviews of acupuncture for SCI have emerged, such as the mechanism of acupuncture with stem cell transplantation to improve neurological function after SCI, acupuncture for SCI complications, systematic review, and meta-analysis of acupuncture and SCI neurological function, acupuncture for NP after SCI (15–18). However, many reviews of acupuncture for SCI have examined only one complication (10, 15, 19), and there are few recent studies. Up to now, there have been no bibliometric studies related to acupuncture for SCI. This study combines quantitative and qualitative analyses of the literature to explore future research directions and goals of acupuncture for SCI.

Materials and methods

All data were obtained from the Web of Science (WOS) core database, retrieved on March 13, 2022. According to the established study protocol, the search formula was Ts = [("spinal cord injury" OR "spinal cord injuries") AND ("acupuncture" OR "electroacupuncture" OR "warming needle moxibustion" OR "fire needling" OR "fire needle" OR "fire acupuncture" OR "acupuncture therapy")], spanning the period from 1979 to 2021. Two reviewers independently reviewed the titles and abstracts of the above records. Any disagreements that arose during the screening process were resolved through discussion between the two reviewers or by consulting a third reviewer if necessary. Finally, 213 publication records were screened that fit the theme of acupuncture for SCI. Extracted data included reference type, title, journal, publication date, author name and affiliation, and abstract. More details about the search strategy can be found in the first part of the Supplementary material.

Quantitative analysis of the search results was conducted using R software (version 4.1.2) and the Bibliometrix package (20). Complete details are available in Part II of the Supplementary material. Then, among the 213 records, 25 publications with an annual citation rate of no <2.5 were screened for qualitative analysis. Those papers with a high annual citation rate were divided into three groups based on their content: reviews, experimental research papers, and clinical research papers. In the next section, we would provide an in-depth analysis of the collected publication records.

Quantitative analyses

On March 13, 2022, there were 213 publications related to acupuncture for SCI in the WOS core repository. The information was then analyzed quantitatively in six areas: publications, countries, institutions, authors, journals, and keywords.

Annual publication analysis

There were 213 publications from 1979 to 2021 in nine document types, namely articles, reviews, editorial material, meeting abstracts, proceedings papers, letters, corrections, notes, and early access. Of these, journal articles were 159, accounting for 74.65% of the total literature, followed by reviews with 38 articles, as shown in Table 1. Since the late 1970s, the number of annual publications in this field has shown a fluctuating upward trend, as illustrated in Figure 1.

The total number of citations of these 213 documents was 1951, and the specific average annual article citation rate is shown in Figure 2. Since the advent of publications on acupuncture for SCI in the late 1970s, the average annual article citation rate went through three periods. Before 1997, the number of articles was limited, and the average annual article citation rate trended low and flat. The annual average article citation rate fluctuated upward from 1998 to 2012 and peaked at 9.7 in 2012. The most cited literature, also published this year,

was a review of laser acupuncture for critical illnesses such as SCI, brain injury, and heart disease, with a total of 610 citations (21). From 2013 to date, the average annual article citation rate trend had leveled off and stabilized at 1.74/year.

Analysis of countries

Among the 213 publications, the corresponding authors were distributed in 20 countries or regions, as shown in Figure 3. China has the highest number of publications, accounting for 57.90% of the total, followed by the United States (U.S.) and South Korea. Not surprisingly, the cooperation is pivoted in the U.S. and China and dispersed to other countries or regions, such as Japan, the United Kingdom, and Brazil. In addition, the closest collaboration is between U.S. and China, with 15 collaborative publications.

Table 2 shows that Switzerland, the U.S., and the United Kingdom all have an average article citation rate above 40, which is significantly better than other countries or regions. China, Korea, and Brazil are among the top publishers with low annual article citation rates, with China's average article citations being only 9.56.

TABLE 1 Central information from publications related to acupuncture for SCI.

Primary information	Results
Period	1979–2021
Documents	213
Average years from publication	8.22
Average citations per document	17.87
Average citations per year per document	1.77
Document types	9
Authors	890
Single-Authored documents	7
Multi-Authored documents	883
Authors per document	4.18
Co-Authors per document	5.69

Analysis of institutions

In terms of research institutions, Sun Yat-sen University (19.58%) had the most publications, followed by Beijing University of Traditional Chinese Medicine (8.39%) and Kyung Hee University (8.04%). Seven of the top 10 institutions are from China, while three are from South Korea. See Table 3 for more details.

Author Analysis

In the list of authors of the 213 selected publications, 890 relevant authors were listed. One of the most relevant authors is Yuanshan Zeng from Sun Yat-sen University, China, with

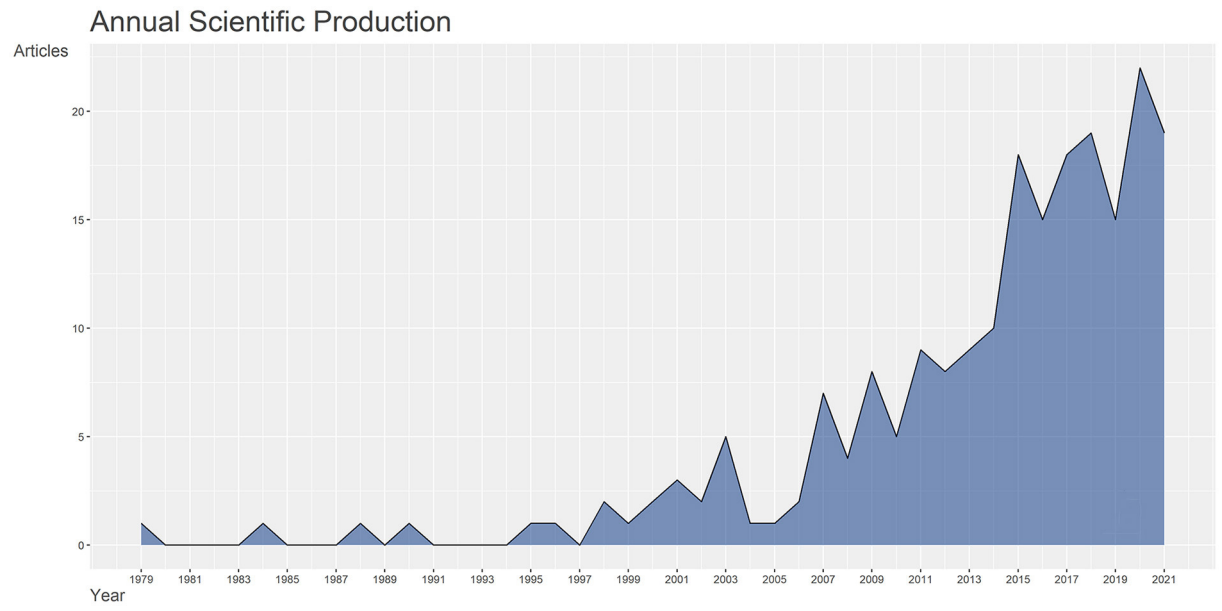

FIGURE 1
1979–2021 Annual scientific production in the field of acupuncture for SCI.

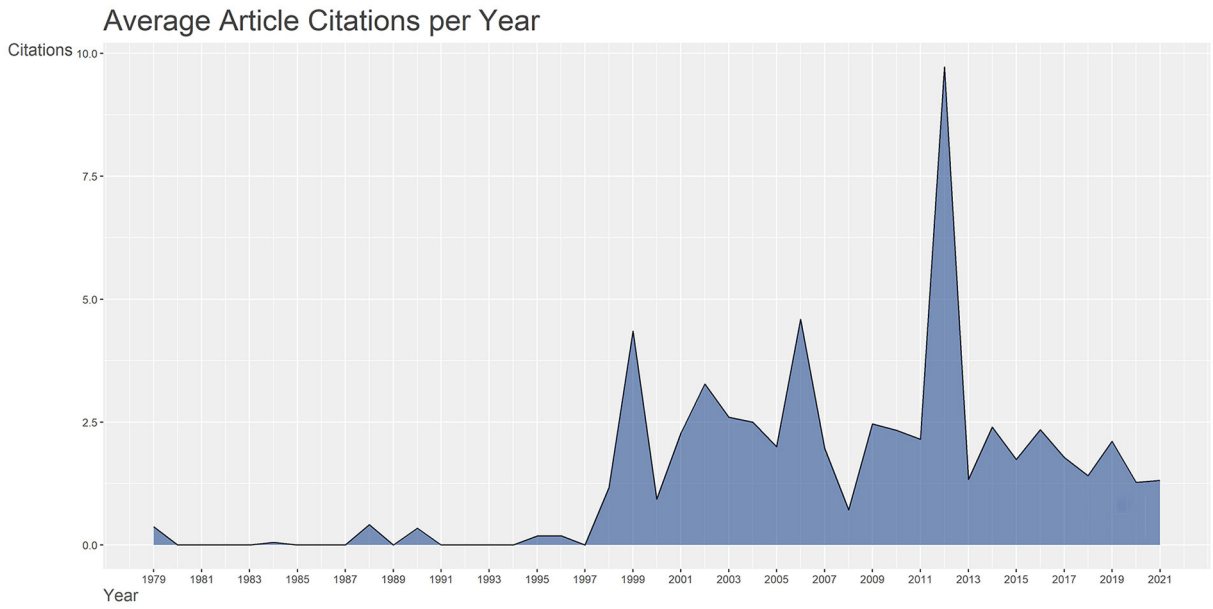

FIGURE 2
1979–2021 Average article citations per year in the field of acupuncture for SCI.

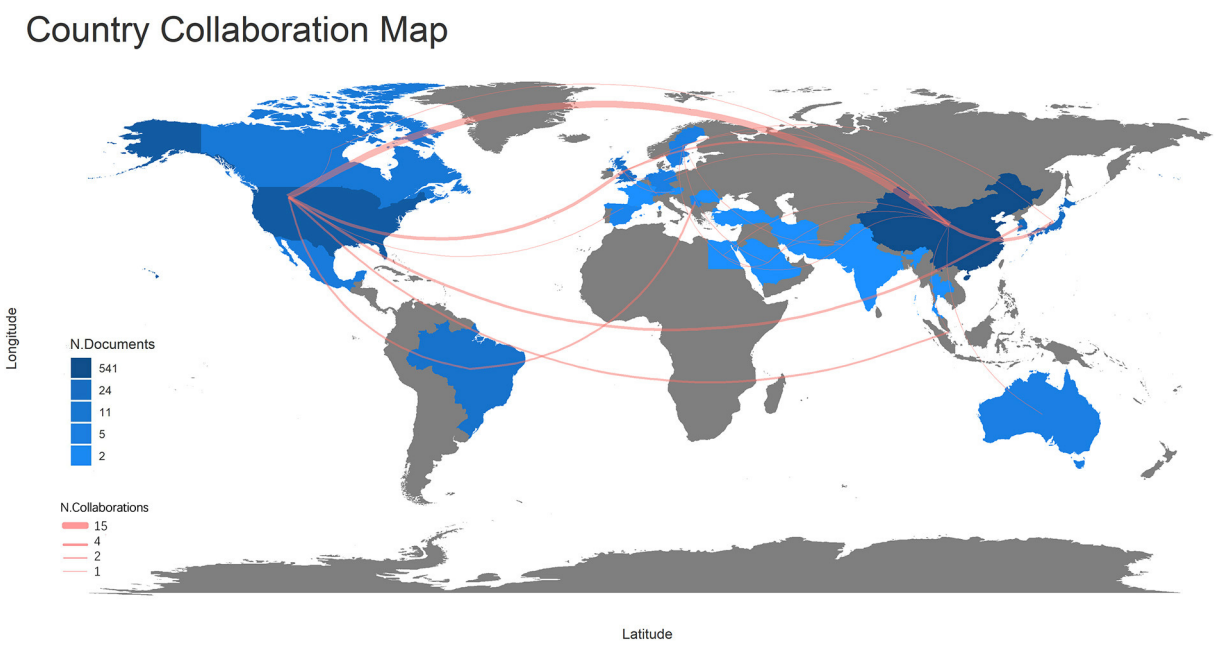

FIGURE 3
Map of national collaborations for acupuncture for SCI publications (Gray, no relevant publications in the country; blue, related publications in the country; depth of blue, number of publications; red line, connected countries have cooperation in the field, the thickness of the line: frequency of collaboration).

12 publications on acupuncture for SCI, as shown in Figure 4. Not surprisingly, in the last decade, an increasing number of fellows have become involved in the study of acupuncture for SCI.

The Author's Local Impact can be assessed using the Total Citation Index, as shown in Figure 5. Six authors were cited 610 times, all from Massachusetts General Hospital, USA. However, Yuanshan Zeng, who had the highest number of publications,

TABLE 2 Average article citations for major participating countries.

Country	Average article citations
USA	45.65
China	9.56
Korea	27.08
Japan	30.62
United Kingdom	40.00
Canada	31.20
Brazil	15.12
Switzerland	46.00
Sweden	29.33
Australia	25.00

TABLE 3 Abbreviations and publications of the major participating institutions.

Affiliations	Abbreviations	Counts
SunYat-sen University	SUNYATSENUNIV	56
Beijing University of Chinese Medicine	BEIJINGUNIVCHINESEMED	24
Kyung Hee University	KYUNGHEEUNIV	23
Shanghai Jiao Tong University	SHANGHAIJIAOTONGUNIV	17
Kunming Medical University	KUNMINGMEDUNIV	14
Capital Medical University	CAPITALMEDUNIV	13
Jilin university	JILINUNIV	13
Pusan National University	PUSANNATLUNIV	13
Seoul National University	SEOULNATLUNIV	11
Zhejiang University of Traditional Chinese Medicine	ZHEJIANGCHINESEMEDUNIV	11

ranked relatively low, in seventh place, with an overall citation index of 314.

Sources analysis

The top 20 publication sources of acupuncture for SCI were all journals, consistent with more than half of the publications being articles, as shown in Figure 6. "Neural Regeneration Research" published the most articles in this field, with 14 scholarly articles. "Evidence-Based Complementary and Alternative Medicine" ranked second with 12 publications in this field. Most periodicals are in the direction of Chinese medicine or neuroscience, with oncology, rehabilitation, and complementary medicine also covered. The research focus of these journals is critical to selecting target journals for researchers in the field of acupuncture for SCI.

Keywords analysis

Table 4 shows that "spinal cord injury," "acupuncture," and "electroacupuncture" are the three most common keywords in publications on acupuncture for SCI, representing the main scope of the study. The key words "neuropathic pain," "neurogenic bladder" and "rehabilitation" represent the superior diseases of acupuncture SCI. The use of the keywords "spinal cord injury," "acupuncture," and "electroacupuncture" has increased rapidly over the past decade, as shown in Figure 7. This trend not only indicates a growing number of articles in the field but also points to the superior technique of acupuncture for SCI, namely electroacupuncture (EA).

Figure 8 represents the author's keywords as a two-dimensional planar diagram using multiple correspondence analysis, called the concept structure diagram. Multiple correspondence analysis is an exploratory multivariate technique for the graphical and numerical analysis of multivariate categorical data. The figure divides the author keywords into two clusters, with red clusters focusing on functional recovery after SCI and blue ones on NP after SCI. The chart gives the reader a quick and general overview of the research hot spots in the field.

Qualitative analyses

From 1979 to 2021, there were 213 publications in the field of acupuncture for SCI in the WOS core database. The annual citation rate is calculated by dividing the total number of citations by the number of years since publication, and publications with high annual citation rates are usually more valuable (22). This data set was sorted according to the annual citation rate from highest to lowest, and publications with an annual citation rate more than or equal to 2.5 were included, resulting in 25 publications, accounting for 11.74% of the total. Qualitative analysis of the literature helps scholars find research directions in acupuncture for SCI that deserves further attention.

Figure 9 shows the specific classification of these 25 publications with an annual citation rate of more than 2.5. The first category is the review, which contains one Meta-analysis. The second category is experimental research papers, which are further divided into three subcategories according to specific research directions: inhibition of apoptosis, improvement of the microenvironment, and promotion of nerve regeneration. The third category is clinical research papers, including subjects of patients and animals with SCI. The details of these categories are described in Section Reviews analysis, Experimental research papers analysis, and Clinical research papers analysis. In addition, the annual citation rates, DOI numbers, and types of these papers are shown in Table 5.

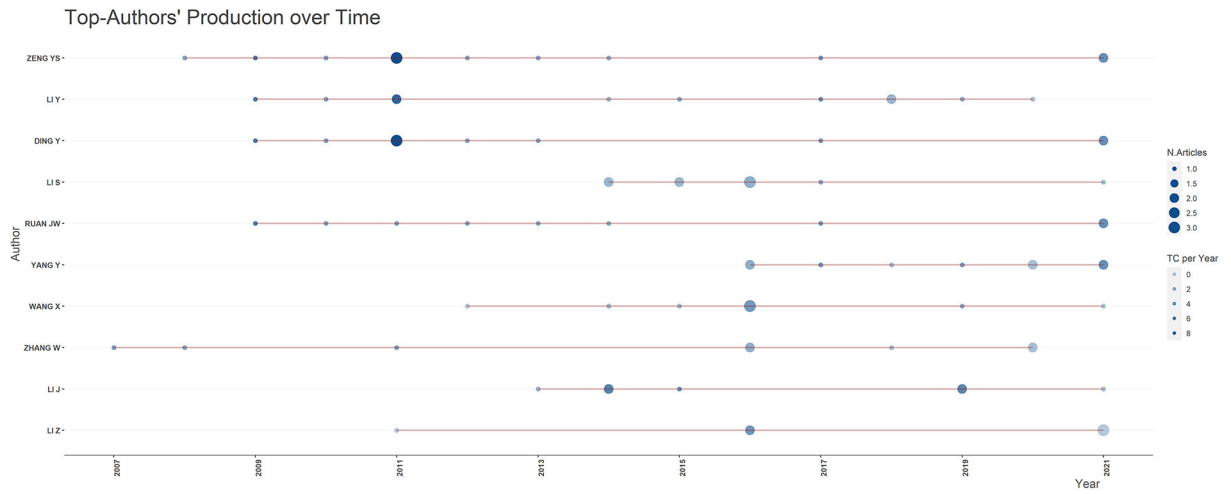

FIGURE 4
Publications of the top 10 authors in the field of acupuncture for SCI. (red line, timeline of relevant publications by this author; diameter of circle, number of publications; the shade of blue, total citation per year).

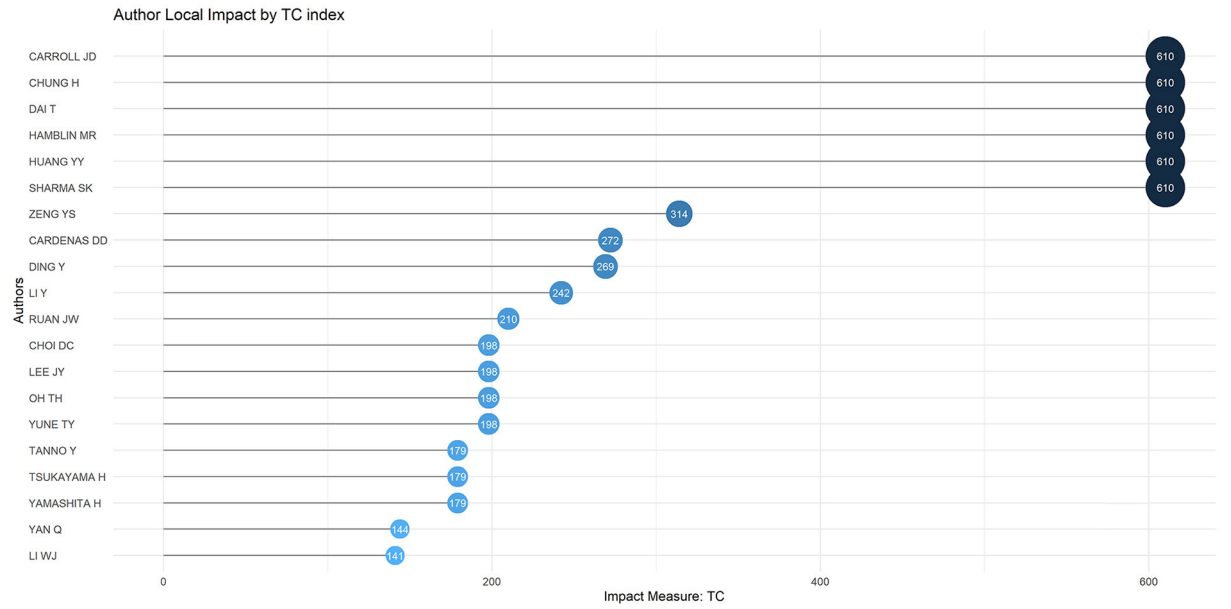

FIGURE 5
Author local impact on acupuncture for SCI.

Reviews analysis

Among the 25 high annual citation publications in acupuncture for SCI, there were seven reviews, accounting for 28% of the total. This percentage was significantly higher than the share of reviews in all publications, 17.84% for the latter. Five of these seven reviews were in the top 10, and the most cited literature in terms of annual citation rate was also a review. Therefore, the reviews are classified as the first category in this field. A chronological qualitative analysis based on these quality reviews can help people to get an overview of the research and to grasp the research trends.

Research related to acupuncture for SCI began in the late 1970s, and only in 2012 was a high annual citation rate review in this area published. The peak of review publication occurred in 2020. A 2012 review on low-level laser therapy summarized the

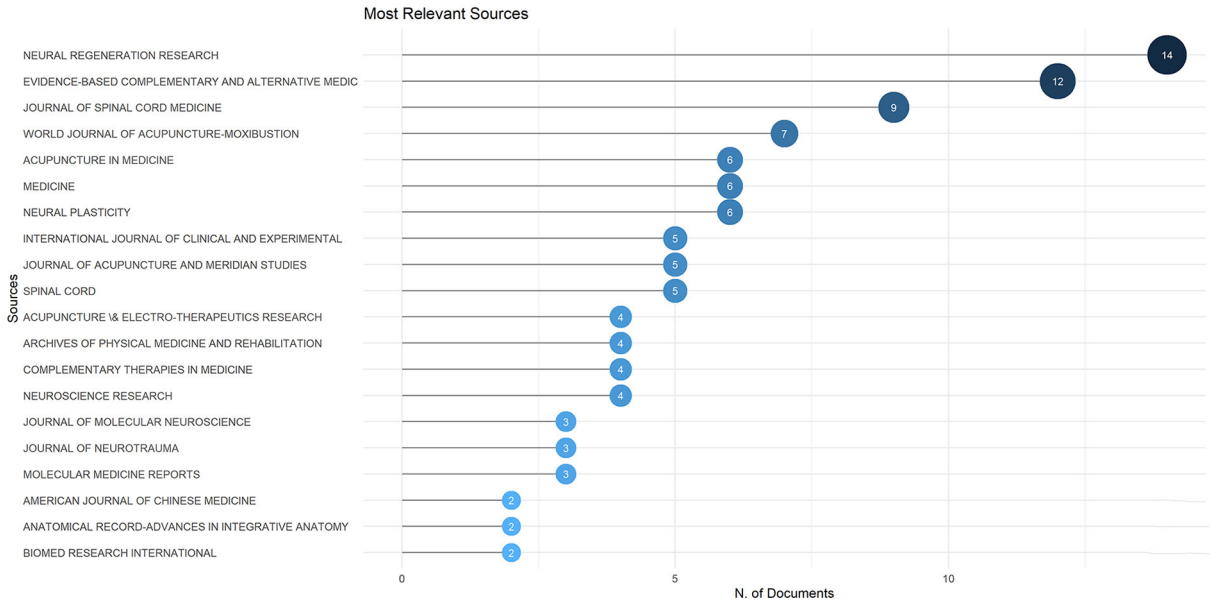

FIGURE 6
The most relevant sources in the field of acupuncture for SCI.

TABLE 4 Top 10 author keywords in the field of acupuncture for SCI.

Words	Occurrences
Spinal cord injury	76
Acupuncture	40
Electroacupuncture	40
Electro-Acupuncture	17
Neural regeneration	12
Neuropathic pain	12
Neurogenic bladder	11
Rehabilitation	11
Spinal cord	11
Spinal cord injuries	11

mechanisms of action and indications for low-level laser therapy while describing laser acupuncture stimulation in acupoints for severe diseases such as SCI and stroke (21). The review had attracted significant attention and had been cited 610 times since publication, with an annual citation rate of 55.455, four times that of the second-ranked publication in the field.

In the same year, researchers suggested that SCI had been used as a pilot for functional genomic technology and that combining basic acupuncture research with this technology could help explore the mechanisms involved (23). In 2014 Boldt et al. used a meta-analysis to summarize non-pharmacological interventions for chronic pain in patients with SCI and confirmed the effectiveness of acupuncture in pain relief (10). The high annual citation rate review in 2016 continued the hot issue of acupuncture analgesia. Sawynok concluded that all adenosine receptors modulated nociception through spinal glial cells. In addition, acupuncture could treat NP from SCI by increasing the level of endogenous adenosine (24).

With the widespread use of acupuncture techniques and the advancement of basic research in recent years, the topics of reviews on acupuncture for SCI tended to explore the relevant mechanisms and new clinical indications. In 2018, Cai and Shen investigated the anti-apoptotic mechanisms of acupuncture in neurological disorders such as SCI. The literature suggested that the anti-apoptotic effect of acupuncture was mainly characterized by elevated expression of B-cell lymphoma-2 and decreased expression of Bax and caspases, which might be related to the upregulated expression of a series of downstream signaling pathways and neurotrophic factors (25). In 2019, a study summarized the therapeutic effects and influencing factors of EA on spasticity after upper motor neuron lesions (26).

Experimental research papers analysis

This section reviewed publications with high annual citations in the category of experimental studies on acupuncture for SCI. This category had 14 publications, accounting for 56% of the high annual citation rate publications, and spanned from 2012 to 2021. These publications were further divided into inhibition of apoptosis, improvement of the microenvironment, and promotion of neural regeneration according to the research

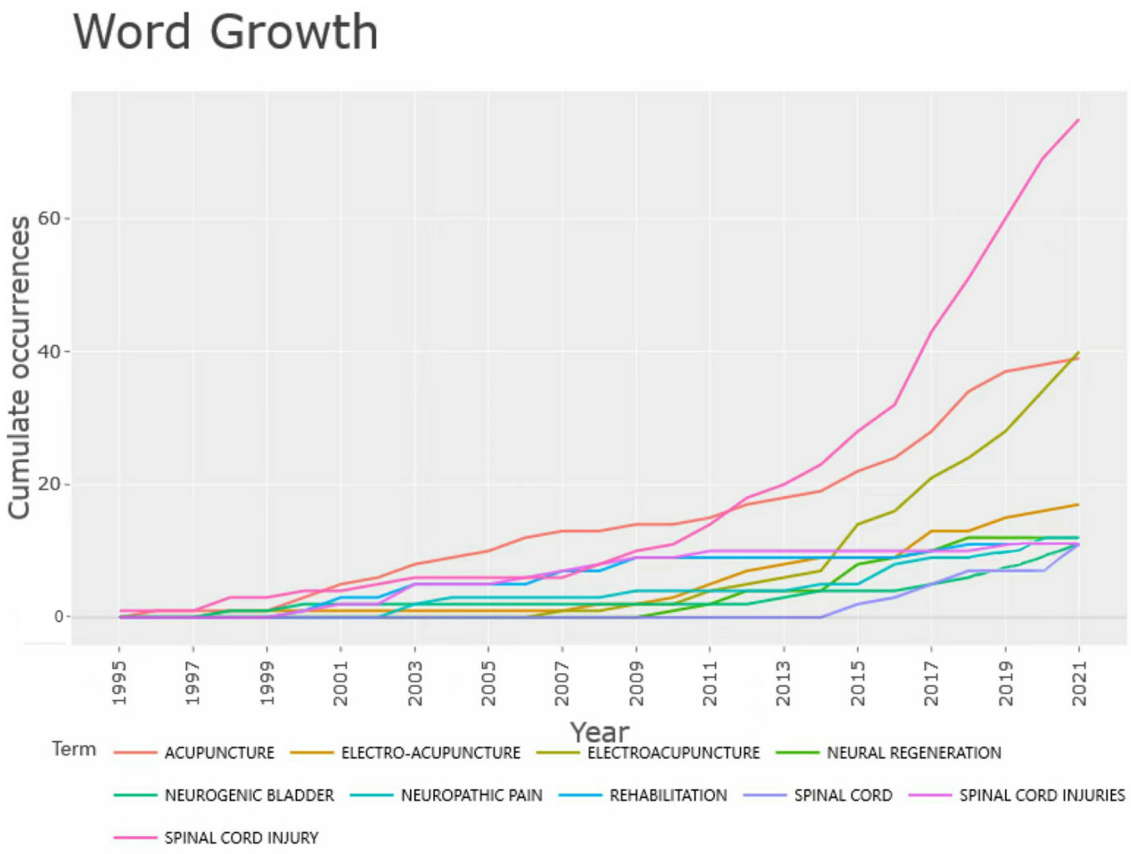

FIGURE 7
Trends (with Loess Smoothing) in the top 10 author keywords in acupuncture for SCI.

direction, with the specific mechanisms shown in Figure 10. The following is a chronological discussion of the experimental research literature in this field over the past 10 years.

Inhibition of apoptosis

In the field of acupuncture for SCI, two publications with high annual citation rates focused on the inhibition of apoptosis, both published in 2017. Apoptosis is an active, programmed process of spontaneous cell disassembly in response to environmental stimulus signals, changes in environmental conditions, or palliative damage (27). It is now believed that apoptosis of a large number of neurons, astrocytes, oligodendrocytes, and microglia in the injured spinal cord is one of the pathological mechanisms of secondary injury after SCI, and inhibition of apoptosis can effectively promote recovery of the SCI (28). Liu and Wu found that EA inhibited the SCI-induced upregulation of the apoptosis-related protein Bax and the pain-related protein Nav1.3 by regulating the expression of mir-214 to achieve analgesia and antiapoptotic effects (11). In the same year, Zhu et al. found that EA preconditioning reduced spinal cord ischemia-reperfusion injury (29).

Improvement of the microenvironment

With the in-depth basic research in the past 10 years, the research results on the mechanism of acupuncture to improve the microenvironment of SCI were fruitful. Since 2012, there had been seven high annual citation papers in this field, accounting for half of the high annual citation papers in the experimental research category. Imbalance in the local microenvironment of SCI often leads to hemorrhage or ischemia, secondary to an inflammatory response and the formation of glial scarring that accelerates and exacerbates the injury (30). The mechanisms that improve the microenvironment of SCI specifically include inhibiting inflammatory responses, lipid peroxidation, and excitatory amino acid toxicity, increasing neurotrophic factors and blood flow, and improving microcirculation in several ways (31). A chronological overview of these findings was in the following.

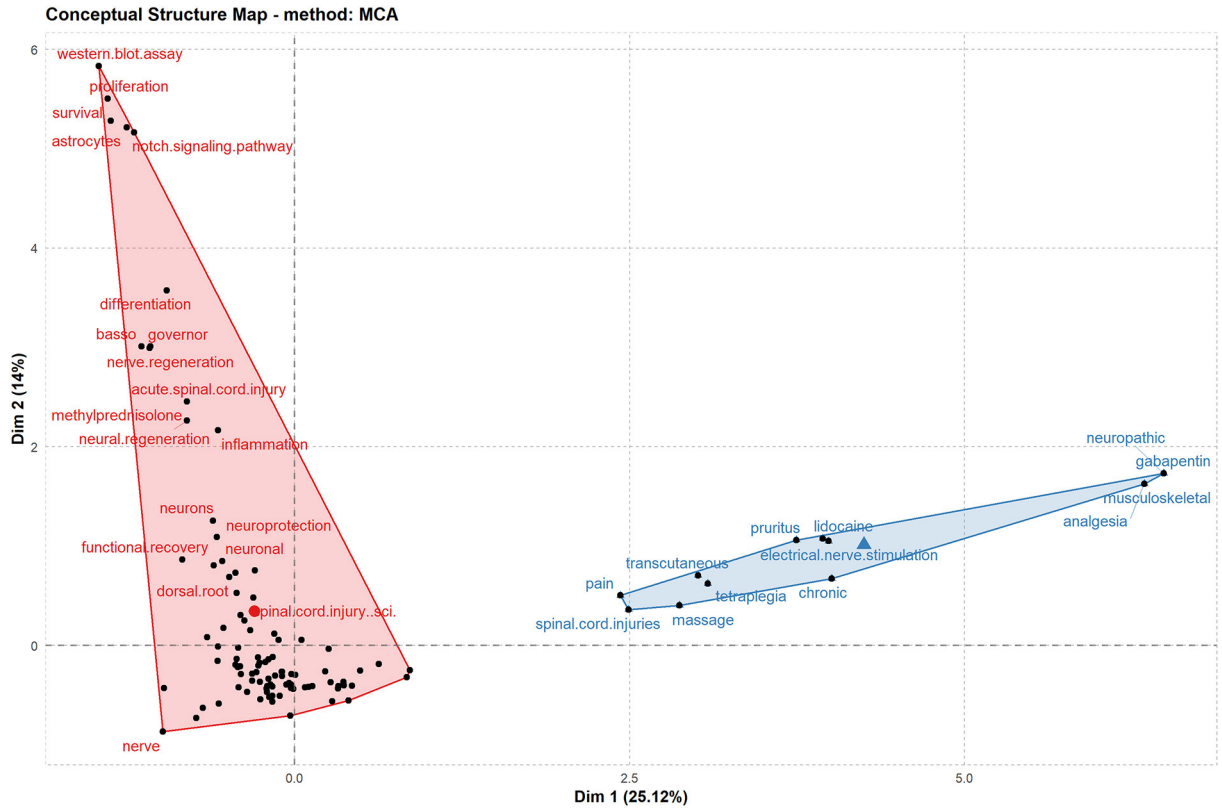

FIGURE 8
Conceptual structure map of common author keywords in acupuncture for SCI (Multilateral graphics: topic clusters, keywords in the same cluster have similarity).

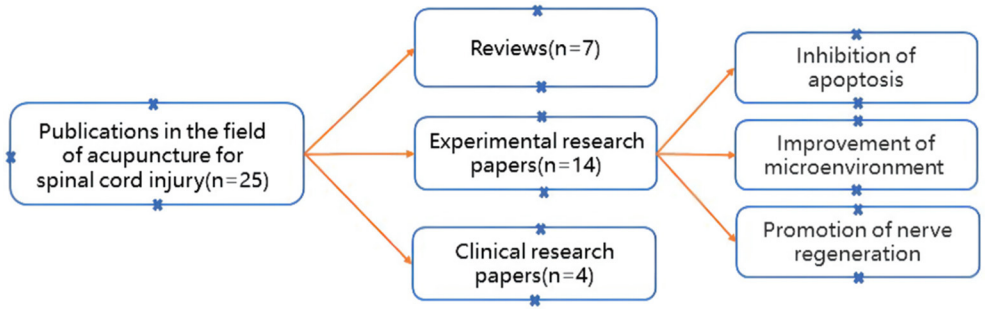

FIGURE 9
Classification of publications (annual citation rate ≥2.5) for acupuncture treatment SCI.

In 2012 Choi et al. found that the relief of NP from SCI by needling Shuigou (GV26) and Yanglingquan (GB34) might be related to the inhibition of p38MAPK and ERK activation and inflammatory mediator release (32). In 2013 Lee et al. similarly selected these two acupoints to study the mechanism of acupuncture analgesia. Acupuncture has been found to alleviate NP, such as mechanical and thermal hypersensitivity, by inhibiting the activation of Jun-N-terminal kinase in astrocytes after SCI (33). In 2014, Jiang et al. found that EA, manual acupuncture, and transcutaneous acupoint electrical stimulation all had antioxidant, anti-inflammatory, and anti-apoptotic effects (34). Macrophages are classified into M1 and M2 subtypes based on surface markers. M1-type macrophages promote immune responses by increasing phagocytosis and releasing

TABLE 5 Publications with annual citation rates more than or equal to 2.5 and their categories.

Rank	Annual citation rate	Paper	Doi	Category
1	55.455	Chung H. 2012, Ann Biomed Eng	10.1007/s10439-011-0454-7	1
2	14	Sawynok J, 2016, Neuroscience	10.1016/j.neuroscience.2015.10.031	1
3	9.625	Da Silva MD, 2015, Mol Neurobiol	10.1007/s12035-014-8790-x	2 (2)
4	8.778	Boldt I, 2014, Cochrane Database Syst Rev	10.1002/14651858.CD009177.pub2	1
5	8	Choi DC, 2012, Exp Neurol	10.1016/j.expneurol.2012.05.014	2 (2)
6	5	Hong E, 2021, J Spinal Cord Med	10.1080/10790268.2019.1665612	2 (3)
7	4.333	El-Seedi HR, 2020, Trends Food Sci Technol	10.1016/j.tifs.2020.04.026	1
8	4	Do Espirito Santo CC, 2019, Brain Behav Immun	10.1016/j.bbi.2019.01.012	2 (2)
9	3.667	Zhao J, 2017, Acupunct Med	10.1136/acupmed-2016-011107	2 (2)
10	3.6	Cai W, 2018, Am J Chin Med	10.1142/S0192415X1850026X	1
11	3.556	Jiang S, 2014, Evid -Based Complement Altern Med	10.1155/2014/431580	2 (2)
12	3.5	Geng X, 2015, Neural Regen Res	10.4103/1673-5374.153687	2 (3)
13	3.143	Glaser J, 2016, Spine	10.1097/BRS.0000000000001525	3
14	3	Estores I, 2017, J Spinal Cord Med	10.1080/10790268.2016.1141489	3
15	3	Zhang YT, 2017, Neural Plast	10.1155/2017/7351238	2 (2)
16	3	Pak ME, 2018, Exp Neurol	10.1016/j.expneurol.2017.11.014	2 (3)
17	2.9	Lee JY, 2013, PLoS ONE	10.1371/journal.pone.0073948	2 (3)
18	2.833	Liu J, 2017, Biomed Pharmacother	10.1016/j.biopha.2017.02.077	2 (1)
19	2.667	Li G, 2020, Neurosci Bull	10.1007/s12264-019-00442-0	2 (3)
20	2.636	Jia J, 2012, J Ethnopharmacol	10.1016/j.jep.2012.01.034	1
21	2.6	Zidan N, 2018, J Neurotrauma	10.1089/neu.2017.5485	3
22	2.5	Zhu XL, 2017, Brain Res	10.1016/j.brainres.2017.01.008	2 (1)
23	2.5	Prado C, 2019, Res Vet Sci	10.1016/j.rvsc.2019.01.011	3
24	2.5	Zhu Y, 2019, Ann Phys Rehabil Med	10.1016/j.rehab.2018.09.010	1
25	2.5	Xu H, 2021, J Neurotrauma	10.1089/neu.2020.7155	2 (3)

Category: 1 review; 2 (1) inhibition of apoptosis; 2 (2) improvement of the microenvironment; 2 (3) promotion of neural regeneration; 3 clinical research papers.

pro-inflammatory factors. In contrast, M2-type macrophages suppress inflammatory responses and promote tissue repair (35). In 2015 da Silva et al. found that manual acupuncture of Sanyinjiao (SP6) induced a phenotypic switch in muscle macrophages with a decrease in M1 macrophages and an increase in M2 macrophages and IL-10 in muscle to reduce pain, edema, and inflammation (36).

Neurotrophin-3 (NT-3) contributes to neuroprotection and axonal regeneration (37). There were two high annual citation papers on acupuncture increasing NT-3 expression in 2017. Zhao et al. found that EA at the acupoint inhibited M1 macrophages, TNF-α, IL-1β, and IL-6 levels, but enhanced the expression of IL-10, M2 macrophages, and NT-3 (38). These views were corroborated by the study of Zhao et al. This study showed that either tail nerve electrical stimulation or EA treatment could increase NT-3 and choline acetyltransferase expression, protect motor neurons, and reduce muscle atrophy in rats with thoracic SCI (39).

A study in 2019 found that SCI promoted anxiety and depression-like behaviors in adult female rats (40). This condition is associated with an imbalance between the production and release of pro- and anti-inflammatory cytokines, which acupuncture can help (41).

Promotion of nerve regeneration

Mechanisms that promote nerve repair have been a hot topic of research in acupuncture for SCI over the last few years. There are five related high-quality publications, which were published from 2015 to 2021 and all centered on EA. Nerve regeneration and repair can manifest as axonal lengthening, axonal remyelination, or neural stem cell differentiation (1).

Notch signaling is accomplished by transmembrane ligands on the cell activating transmembrane receptors on just cellular cells, which can regulate cellular transduction and participate in angiogenesis (42). In 2015, Geng et al. found that EA inhibited the Notch signaling pathway, promoted the proliferation of endogenous neural stem cells, and inhibited their differentiation to astrocytes (43).

Demyelination often occurs after oligodendrocyte necrosis and apoptosis and is one of the common pathological findings after SCI (44). A 2018 study discovered that EA in Baihui (GV20) and Zusanli (ST36) combined with treadmill exercise promoted

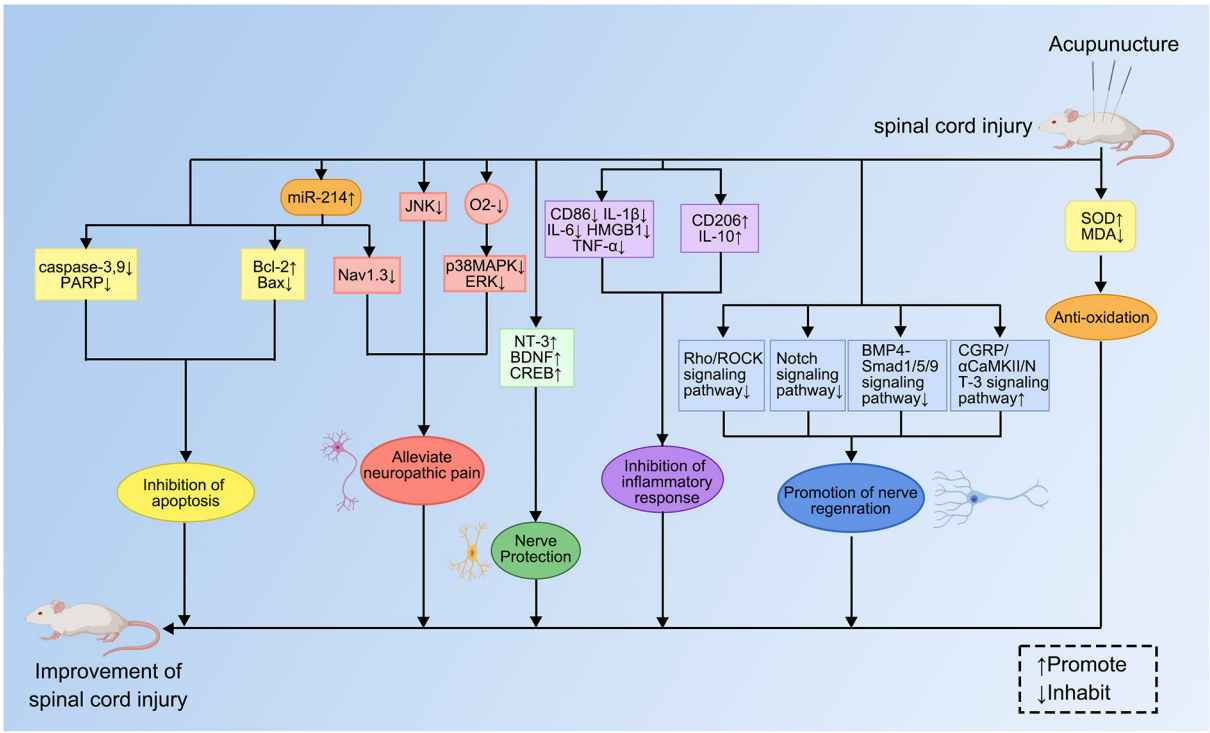

FIGURE 10
Specific mechanisms of acupuncture for SCI.

oligodendrocyte production in the corpus callosum of hypoxic-ischemic neonatal rats, induced the expression of mature brain-derived neurotrophic factor, and attenuated demyelination (45). This study corroborated that EA improved demyelination after SCI. Epidural spinal cord stimulation is an alternative electrical stimulation method to EA, in which electrodes are implanted in the epidural space of the spinal cord to stimulate the spinal cord tissue directly for therapeutic effect (46). In 2020, Li et al. found that this therapy enhanced oligodendrocyte survival and differentiation and protected myelin by inhibiting the BMP4-Smad1/5/9 signaling pathway after SCI (47).

In 2021, researchers found that EA in Yaoyangguan (GV3) and Dazhui (GV14) inhibited the Rho/ROCK signaling pathway, promoted axonal regeneration, and reduced inflammatory responses (48). In the same year, a study found that the EA in the governor vessel (*Du Mai*) increased NT-3 expression and activated the intrinsic growth capacity of spinal cord neurons after SCI through the CGRP/RAMP1/L-VGCC/NT-3 pathway, which promoted neuronal survival, axonal regeneration (12).

Clinical research papers analysis

In addition to the review and the experimental research papers, there are several highly annual cited clinical research papers in acupuncture for SCI, in both human and veterinary subjects, which are discussed together in this section. In 2016 Glaser et al. found that transcranial direct current stimulation helped to reduce the dose of analgesic drugs after SCI (49). In 2017 Estores used auricular acupuncture to treat NP after SCI and showed significantly improved numerical rating scale results compared to the baseline period (50).

The high annual citation publications included two veterinary clinical research papers on acupuncture for SCI (51, 52). The subjects of the two papers were canines with acute SCI functional recovery and chronic SCI. Treatment techniques included a pulsed electromagnetic field and a combination of stem cell and EA therapy with acupoints mainly from the governor vessel and the bladder meridian. Both therapies showed functional improvement in dogs with SCI. However, the sample size of both trials was <20 cases, and further validation is still needed.

Limitations

First, this bibliometric analysis did not include non-English databases, although the WOS database is reliably sourced and contains chiefly quality publications in acupuncture for SCI. Second, qualitative analysis is subjective to the researcher, and different observation perspectives may lead to different conclusions. Third, the publication of academic research lags

behind clinical practice. The results of this study reflect only the academic research trends in the field, being the primary purpose of this bibliometric study.

Discussion

The study conducted quantitative and qualitative analyses on 213 publications in the field of acupuncture for SCI in the WOS core database from 1979 to 2021.

Quantitative analysis shows a fluctuating upward trend in the number of publications and the average annual citation rate in this area. The authors are mainly from Asian and American countries, with China and U.S. as pivotal countries having extensive collaboration with other countries. China leads the world with more than four times the number of publications as the U.S., but it ranks second to the U.S. in terms of citations. It shows more Chinese authors in the field, but more quality publications come from the U.S. The most relevant author is Yuanshan Zeng from Sun Yat-sen University, China, with 12 publications on acupuncture for SCI. However, his author impact ranking is relatively low at seventh, with the top six coming from Massachusetts General Hospital, USA. The 20 most relevant publication sources are all academic journals, consistent with more than half of the publications being journal articles. Keyword analysis shows that EA has been a hot research topic in recent years.

In the qualitative analysis section, we analyzed 25 publications with an annual citation rate of no <2.5. These publications are divided into three categories based on content, including reviews, experimental research papers, and clinical research papers. A comprehensive analysis of the various publications according to publication time concludes that the efficacy and mechanism of acupuncture for NP after SCI is the first research hotspot, and EA is the most widely used technique. In addition, the most commonly used acupoints for EA are those located at the governor vessel. In the last 5 years, due to intensive basic research, the mechanism of acupuncture to improve the local microenvironment of SCI and promote nerve regeneration has become a new research trend. At the same time, as the efficacy of acupuncture has been generally confirmed, acupuncture is gradually used in various complications after SCI and the veterinary field.

Conclusion

The article provides an essential reference for understanding and predicting the direction of research in acupuncture for SCI. It is clear that research on acupuncture for SCI is still flourishing, and more research results based on EA to promote nerve repair and regeneration after SCI will be available in the future.

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

YH analyzed the data and edited the manuscript. KH designed the entire research. DF, FN, and BQ were responsible for data collection and participated in revising the manuscript. RM made significant contributions to the analysis and interpretation of the data. All authors read the manuscript and agreed to submit it.

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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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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.936744/full#supplementary-material

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Elucidating the mechanisms of post-stroke motor recovery mediated by electroacupuncture using diffusion tensor tractography

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Acupuncture has been commonly used for post-stroke patients, and electroacupuncture allows simultaneous application of acupuncture and electrical stimulation. We aimed to elucidate the mechanism of electroacupuncture on post-stroke motor recovery using diffusion tensor tractography. A total of 33 subacute stroke patients were recruited. The control group was subjected to conventional rehabilitation therapy. In contrast, the patients in the experimental group received electroacupuncture treatment for 30 min per session for 4 weeks in addition to the rehabilitation therapy. Fugl-Meyer assessment of the lower extremity (FMA_L), functional ambulation categories (FAC), and the Korean version of modified Barthel index (K-MBI) were used to compare behavioral outcomes between groups. The corticospinal tract (CST) was examined before and after the intervention *via* diffusion tensor tractography (DTT) to determine the motor recovery mechanism mediated by electroacupuncture. After 4 weeks of intervention, both the control and experimental groups showed a significant improvement with respect to FMA_L, FAC, and K-MBI. The level of improvement in FMA_L, FAC, and K-MBI did not vary significantly between the two groups. However, DTT results showed that the CST fractional anisotropy of the affected side (control: from 0.456 to 0.464, experimental: from 0.459 to 0.512) and its ratio (control: from 89.8 to 90.3, experimental: from 90.2 to 93.3) were significantly different between the two groups ($p = 0.032$ and $p = 0.018$). In addition, there were significant differences in the CST axial diffusivity of affected side (control: from 0.783 to 0.877, experimental: from 0.840 to 0.897) and its ratio variation (control: from 87.9 to 100.0, experimental: from 95.7 to 100.7) between the groups ($p = 0.003$ and $p = 0.001$). Electroacupuncture played a role in promoting brain plasticity and delaying neural degeneration in subacute period after stroke. Thus, electroacupuncture could be an effective adjuvant therapy in addition to conventional rehabilitation for motor recovery after stroke in a long-term perspective.

KEYWORDS

activities of daily living, acupuncture, cerebrovascular disorders, diffusion tensor imaging, gait, rehabilitation

Introduction

Stroke is the leading cause of mortality in South Korea and requires significant attention. The annual incidence of stroke is over 100,000 cases (1). Physical and psychological damage attributed to stroke is significant, and the disabilities attributed to stroke are observed across various locations of damaged lesions (2). To illustrate, well-known sequelae of stroke include hemiplegia, gait disturbance, language disorder, vascular cognitive impairment, and depression (3, 4). These aftereffects of stroke pose a significant challenge to the independence of the patient in daily routine and impose a significant burden on the family as well as the society (5, 6). To minimize such burden, rehabilitation therapy is performed at the hospital from the early days of the onset of stroke (7, 8), and a variety of evidence-based interventions are being used as adjuvants (9, 10). Among them, acupuncture has garnered significant interest.

Acupuncture involves the use of thin needles to stimulate specific pressure points linked to unwanted symptoms (11). Electroacupuncture, among various acupuncture techniques, is commonly used in combination with conventional stroke rehabilitation as it allows acupuncture and electrical stimulation to be simultaneously applied (12). The goal of electroacupuncture is to increase the potential therapeutic effects of standard acupuncture therapy (13). While acupuncture typically involves the use of a single needle on each point of interest during treatment, the modification in electroacupuncture involves the use of two needles (13). During the treatment, a weak current flows between the two needles that can mediate a stronger stimulation at the acupoint than the turning of the needle or other manual techniques used by the acupuncturist in general (11). For instance, the lower limb motor recovery in patients with stroke was reported to be more effective with the use of the combination of electroacupuncture and proprioceptive neuromuscular facilitation (PNF) rehabilitation therapy compared to that observed with the latter technique alone (14). In another study, the spasticity was significantly reduced when applied electroacupuncture (15). Nevertheless, there is a general lack of human studies investigating the mechanisms of motor recovery *via* electroacupuncture after stroke.

Diffusion tensor tractography (DTT), as a type of diffusion tensor imaging, is a technique that aids in the visualization of the 3D tracts of nerve bundles that are difficult to analyze with the conventional MRI (16). The DTT allows an in-depth analysis of the architecture and integrity of specific white matter tracts; hence, it is widely used in the prediction of post-stroke motor recovery and in the investigation of the mechanism of recovery (17). Therefore, the purpose of this study to investigate the therapeutic effects of electroacupuncture and to elucidate the mechanism of motor recovery mediated by electroacupuncture in subacute stroke patients using DTT.

Materials and methods

Subjects

The subjects in this study were subacute stroke patients diagnosed with ischemic or hemorrhagic stroke within 3 months. The diagnosis of stroke was performed based on BRAIN magnetic resonance imaging (MRI) or computed tomography (CT) performed at the emergency department by neurosurgeons or neurologists. The participants were between 18 and 80 years old and had moderate to severe motor weakness with a total score of Fugl-Meyer assessment 0–84. Patients with serious comorbidities or severe mental/cognitive disorders that are prohibited from using an electronic device in the body as part of electroacupuncture were excluded.

Study design

This study was conducted as a double-blinded randomized controlled trial where the subjects were divided into two groups: patients in the control group received conventional rehabilitation therapy, and patients in the experimental group received electroacupuncture treatment in addition to the rehabilitation. The patients were randomized between the two groups using a random number table generated by a computer program, based on 1:1 allocation between the control and experimental groups. The random number table was prepared by an investigator who did not participate in the study registration.

Electroacupuncture treatment

The patients in the experimental group received electroacupuncture therapy by acupuncturists. Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) were followed for the intervention of electroacupuncture (18). The protocol for performing electroacupuncture therapy in this study was employed in previous studies (13, 19). Disposable sterile needles were used (stainless-steel needle, 0.30 × 30 mm, Woojin Medical Device Inc. Boryeong, South Korea) for acupuncture. The needle shaft had a thickness of 0.3 mm and a length of 30 mm. The insertion was performed up to the depth of 2–20 mm (20). After the insertion, the electroacupuncture (STN-330, Stratek, Anyang, South Korea) was connected to the needle handle on the affected side. Then, electrical stimulation was induced via a bipolar symmetric wave at a pulse width of 55 μs, frequency of 30 Hz, and interval mode (13). The electroacupuncture was performed for 30 min per session and five sessions a week, thereby completing 20 sessions during 4 weeks.

Stroke rehabilitation therapy

Patients in the control group were subjected to conventional stroke rehabilitation therapy to restore motor function in the affected arm and leg and improve gait function. This conventional rehabilitation therapy was performed for 4 weeks with five sessions a week and 120 minutes per session. Besides, the control and experimental groups patients received stroke rehabilitation therapy equally, including physical and occupational therapy.

Behavioral outcomes

To compare the treatment effects between the control and experimental groups, the lower limb Fugl-Meyer Assessment (FMA_L), the Functional Ambulation Categories (FAC), and the Korean version of the Modified Barthel Index (K-MBI) were used. The FMA_L is a tool widely used for the evaluation of the impairment of sensory-motor function in patients with stroke (21). It is a numerical scale with three scores per item, and the maximum score for lower limb motor function is 34 (21). The FAC categorizes gait patterns according to the level of assistance into six stages: a score of zero indicates nonfunctional ambulation, a score of 1 indicates ambulation dependent on physical assistance, a score of 2 indicates ambulation with intermittent help from one assistant, a score of 3 indicates ambulation without physical assistance but with guidance or monitoring, a score of 4 indicates independent ambulation on flat surface but dependent ambulation on steps or uneven surface, and a score of 5 indicates independent ambulation (22). In this study, the patients were divided into two groups, those with $<$3-point FAC and those with $\geq$3-point FAC based on the level of independent ambulation.

The K-MBI consists of ten evaluation categories (personal hygiene, taking a bath, eating a meal, relieving oneself, climbing steps, getting dressed, control of feces, control of urine, gait, and chair-to-bed movement) (23). Each category is evaluated on a 5-point scale with the application of nine weight values depending on the significance of the category content (23). The scores ranged from 0 to 100, where higher scores indicated more advanced ability to independently perform daily activities.

The data pertaining to demographic factors were also collected as they may influence motor recovery. The factors included age, gender, stroke risk factors (underlying diseases such as hypertension, diabetes, or hyperlipidemia), lesion location, lesion direction, and cognitive function (24).

Diffusion tensor tractography analysis

The data pertaining to DTT were collected using the 3 Tesla MRI scanner. Using the single-shot diffusion-weighted echo-planar imaging sequence, a complete image of the brain was obtained from 33 patients enrolled in this study. The data set comprised 45 images with high diffusion weighting (b value = 1,000 s/mm^2) applied along 44 diffusion directions and one image with no diffusion weighting (16). Each image included 60 2.25-mm thick axial slices of 1.96 $\times$ 1.96 mm in-plane resolution (16).

Corticospinal tract (CST) fiber connectivity was evaluated using the fiber assignment by continuous tracking (FACT) algorithm and three-dimensional fiber reconstruction algorithm using PRIDE software (Philips Medical Systems, Best, the

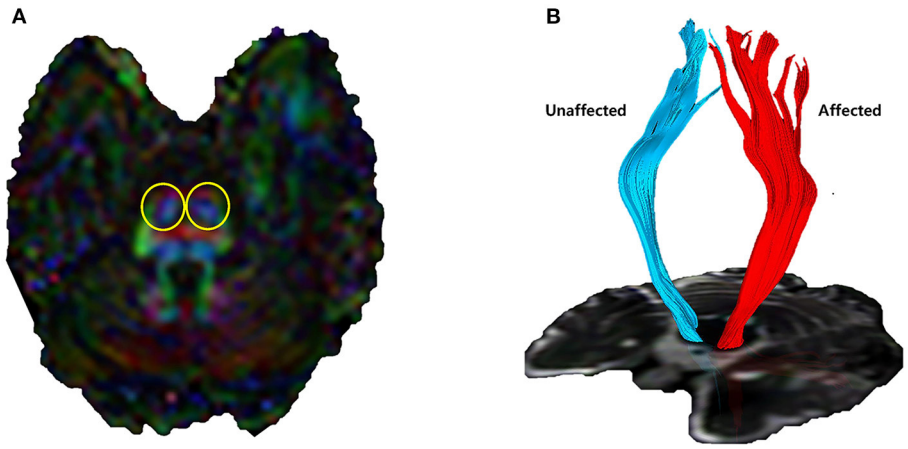

FIGURE 1
Corticospinal tract (CST) visualized by diffusion tensor tractography. **(A)** Lower anterior pons (yellow circles) and primary motor cortex were designated as regions of interest. **(B)** 3D reconstructed CST by fiber assignment by continuous tracking algorithm. Quantitative indicators such as the number of fiber tracts, fractional anisotropy (FA), and axial diffusivity (AD) can be identified.

Netherlands). Termination criteria for fiber tracking were set as follows: fractional anisotropy (FA) <0.2 and angle change >70° (25, 26). The two-region of interest (ROI) method was used for CST reconstruction, with ROIs including the motor cortex and lower anterior pons (Figure 1). We excluded fibers connected to the cerebellum (27). A quantitative analysis of ipsilateral CST parameters was performed by assessing FA, axial diffusivity (AD), and the number of fibers in the affected and unaffected CSTs. The FA ratio, AD ratio, and the ratio of the number of fibers were calculated by dividing the affected values by unaffected values, followed by multiplication of the resultant value with 100 (28).

Statistics

To test the normality of the data pertaining to demographics and outcome measures, the Kolmogorov-Smirnov test was used. To analyze the differences in demographics between the control and experimental groups, the independent *t*-test was used for continuous variables and the chi-squared test was used for categorical variables. To examine post-intervention changes in result indicators, the paired *t*-test was used. To compare the treatment effects between the two groups, the independent *t*-test was used. To analyze the indicators of categorical variables, the chi-squared test was used. The level of significance was set as $p < 0.05$, and the SPSS ver. 22.0 software package (IBMSPSS, Armonk, NY, USA) for statistical analyses.

Results

Demographics and baseline characteristics

A total of 35 patients participated in this study. The data for two patients were excluded due to aspiration pneumonia in the middle of the treatment. Thus, the data of 33 patients ($n = 17$ for the control group and $n = 16$ for the experimental group) were analyzed. The mean age of the study participants was 63 yrs, and the mean treatment length for acute stroke determined between the onset and the first day of the intervention was 37.3 days (Table 1). No significant intergroup differences were observed with respect to age, gender, lesion direction, stroke type, lesion location, the interval between the onset and the first day of the intervention, and the state of cognitive function on the first day of the intervention. No side effect of electroacupuncture was reported throughout the intervention period.

TABLE 1 Baseline characteristics.

	Control group ($n = 17$)	Experimental group ($n = 16$)	*p*-value
Age (yrs)	64.1 ± 9.1	62.0 ± 10.4	0.823
Gender (M: F)	10:7	11:5	0.469
Duration after onset (days)	36.4 ± 5.4	38.1 ± 6.2	0.672
Lesion side (Lt: Rt)	9:8	8:8	0.942
Location (supratentorial: infratentorial)	13:4	11:5	0.812
Comorbidity			0.782
Hypertension (%)	88	87	
Diabetes mellitus (%)	29	31	
Hyperlipidemia (%)	88	93	
MOCA	20.4 ± 5.4	19.2 ± 5.9	0.880

MOCA, Montreal Cognitive Assessment.

Behavior outcomes

Before the intervention, no significant differences were observed in FMA_L, K-MBI, or FAC scores between the two groups. Following 4 weeks of intervention, FMA_L scores showed a significant improvement from 16.2 ± 7.3 to 22.0 ± 6.5 ($p = 0.012$) in the control group and from 16.7 ± 8.4 to 22.5 ± 8.6 ($p = 0.014$) in the experimental group (Table 2). The level of improvement between the two groups did not vary significantly ($p = 0.630$). The K-MBI scores also showed a significant improvement in both control and experimental groups after the intervention; K-MBI of the control group increased from 41.7 ± 17.1 to 66.7 ± 11.4 ($p < 0.001$) and that of the experimental group increased from 51.5 ± 15.1 to 71.2 ± 10.4 ($p < 0.001$). The level of improvement, however, did not vary significantly ($p = 0.304$).

The number of patients with <3-point FAC was 15 and the number of patients with ≥3-point FAC was 2 for the control group before the intervention. However, after 4 weeks of intervention, the number of patients with <3-point FAC was 5, and the number of patients with ≥3-point FAC was 12, indicating a remarkable change. For the experimental group, the number of patients with <3-point FAC was 14, and the number of patients with ≥3-point FAC was 2. A clear change was observed after electroacupuncture therapy; the number of patients with <3-point FAC was 6 and the number of patients with ≥3-point FAC was 11. The between-group comparison, however, did not show a significant difference in FAC scores depending on the treatment methods ($p = 0.842$).

DTT outcomes

Through DTT, the CST fiber connectivity was analyzed before and after 4 weeks of intervention. With respect to baseline fiber numbers of the affected side, fiber ratio, FA of the affected side, FA ratio, AD of the affected side, and AD ratio,

TABLE 2 Comparison of behavioral outcome indicators in control and experimental groups after 4-weeks intervention.

	Control group ($n = 17$)		Experimental group ($n = 16$)		p-value[b]
	T0	T1[a]	T0	T1[a]	
FMA_L	16.2 ± 7.3	22.0 ± 6.5*	16.7 ± 8.4	22.5 ± 8.6*	0.630
K-MBI	41.7 ± 17.1	66.7 ± 11.4*	51.5 ± 15.1	71.2 ± 10.4*	0.304
FAC					
<3	15	5	14	6	0.842[c]
≥3	2	12	2	11	

FMA_L, Fugl-Meyer Assessment of lower limb; FAC, Functional Ambulation Categories; K-MBI, Korean version of the modified Barthel Index (K-MBI).
*$p < 0.05$.
[a]Paired t-test for within group change.
[b]Independent t-test for between group comparison.
[c]Chi-square test for categorical data analysis.

TABLE 3 Comparison of diffusion tensor tractography parameters in both groups after 4-weeks intervention.

	Control group ($n = 17$)			Experimental group ($n = 16$)			p-value[b]
	T0	T1	p-value[a]	T0	T1[a]	p-value[a]	
Fiber No., affected	586 ± 153	499 ± 139	0.012*	506 ± 157	431 ± 119	0.020*	0.442
Fiber ratio[c]	58.1 ± 17.7	39.1 ± 10.6	0.008*	60.4 ± 27.8	39.2 ± 12.6	0.008*	0.256
FA, affected	0.456 ± 0.073	0.464 ± 0.081	0.082	0.459 ± 0.077	0.512 ± 0.088	0.004*	0.032*
FA ratio[c]	89.8 ± 14.5	90.3 ± 14.9	0.241	90.2 ± 14.1	93.3 ± 17.1	0.012*	0.018*
AD, affected	0.783 ± 0.105	0.877 ± 0.089	<0.001*	0.840 ± 0.089	0.897 ± 0.112	0.032*	0.003*
AD ratio[c]	87.9 ± 11.7	100.0 ± 8.9	<0.001*	95.7 ± 9.1	100.7 ± 9.8	0.036*	0.001*

FA, fractional anisotropy; AD, Axial diffusivity.
*$p < 0.05$.
[a]Paired t-test for within group change.
[b]Independent t-test for between group comparison.
[c]The ratio was defined as dividing the affected side by the unaffected side then multiplying it by 100.

no significant differences were found between the control and experimental groups before intervention.

The CST fiber number of the affected side showed a significant decrease after intervention in both groups, with a decline from 586 ± 153 to 499 ± 139 ($p = 0.012$) in the control group and from 506 ± 157 to 431 ± 119 ($p = 0.020$) in the experimental group (Table 3). The fiber number ratio also showed a significant reduction after treatment in both groups, with a decrease from 58.1 ± 17.7 to 39.1 ± 10.6 ($p = 0.008$) in the control group and from 60.4 ± 27.8 to 39.2 ± 12.6 ($p = 0.008$) in the experimental group. The level of reduction, however, did not vary significantly between the two groups for both the CST fiber number and CST fiber ratio (p=0.442 and 0.256).

The FA of the affected side (from 0.459 ± 0.077 to 0.512 ± 0.088, $p = 0.004$) and FA ratio (from 90.2 ± 14.1 to 93.3 ± 17.1, $p = 0.012$) in the experimental group showed significant improvement after four weeks of electroacupuncture therapy. There were no significant differences in FA and FA ratio of the affected side CST in the control group ($p = 0.082$ and $p = 0.241$). Besides, the patients in the experimental group demonstrated a more significant increase in the FA and the FA ratio than those in the control group after the intervention ($p = 0.032$ and $p = 0.018$).

The AD of the affected side showed a significant increase after intervention in both groups; an increase was observed from 0.783 ± 0.105 to 0.877 ± 0.089 ($p < 0.001$) in the control group and from 0.840 ± 0.089 to 0.897 ± 0.112 ($p = 0.032$) in the experimental group. For AD, the level of increase significantly varied between the two groups ($p = 0.003$). The AD ratio also showed a significant increase in both groups; an increase was observed from 87.9 ± 11.7 to 100.0 ± 8.9 ($p < 0.001$) in the control group after treatment and from 95.7 ± 9.1 to 100.7 ± 9.8 ($p = 0.036$) in the experimental group after treatment. The level of increment was significantly higher in the control group ($p = 0.001$).

Discussion

The patients, either the control or experimental group, demonstrated significant improvement in behavioral outcomes, including motor function, gait capability, and activities of

daily life after 4 weeks of intervention. Regarding DTT, the patients who received electroacupuncture therapy showed a more significant increase in the FA and the FA ratio and a lower increase in AD.

We investigated the effect of electroacupuncture on motor network plasticity with DTT, which was performed for the first time to our best knowledge. The DTT provides various parameters for the analysis of the white matter fibers. The degree of FA in a white or gray matter region reflects the structural integrity of white or gray matter in that region (29). The number of fibers calculated via DTT indicates the volume of voxels with FA above a threshold for each depicted tract (30). Because FA values within CST correlate positively with the degree of motor function improvement in patients with better recovery, the FA may serve as an imaging biomarker during the recovery process (29). In this study, CST-wise DTI analysis has shown significant interactions for the FA and FA ratio between intervention types and time by increasing the diffusivity across time for the electroacupuncture group. Our results showed that electroacupuncture therapy collaborating with conventional rehabilitation therapy could play a long-term positive role in restoring lower extremity motor function in subacute stroke patients.

In addition, the value of AD was significantly less increased in the experimental group than in the control group. AD refers to the magnitude of diffusion parallel to fiber tracts (31). A decrease in AD may indicate axonal damage in the acute phase after injury, whereas an AD elevation may be attributed to degenerative processes in the chronic phase (30). In this study, patients showed a gradual increase in AD for 4 weeks after the intervention of adjunct electroacupuncture treatment. The AD steeply decreased, however, in patients who received stroke rehabilitation therapy only. This finding may indicate that electroacupuncture through stroke rehabilitation therapy delayed the degenerative process during the transition to the chronic phase (30). This finding implies that long-term combined treatment would lead to better functional recovery in patients with stroke than stroke rehabilitation therapy alone.

We used the FACT algorithm to analyze the CST change in DTT, which was the core of elucidating the mechanisms of electroacupuncture effects in stroke patients. A whole-brain analysis is an exploratory approach that can be applied to investigate global white matter changes or whether such changes are heterogeneous across patients within a study (32). The most popular method is voxel-based analysis (VBA) which compares DTT metrics in every brain voxel (32). The FACT algorithm is an example of a VBA and can easily change discrete voxel information in a continuous track line (16). The line propagates in the vector direction of the pixels with discrete coordinates and can follow the actual tract more precisely (15). This strategy has high reproducibility, is time-efficient, and provides excellent spatially localized information based on the atlases coordinates (32). An alternative is running a cluster-based analysis and correcting them instead of correcting voxel-by-voxel. Tract-based spatial statistics (TBSS) overcomes issues about alignment and smoothing in voxel-based analysis by focusing registration and statistical testing exclusively on the center of the tracts (33). However, TBSS is known to suffer from several methodological limitations that complicate outcome interpretation (34). Because the FACT algorithm is easier to use for a DTT analysis than probabilistic algorithms like TBSS (35), previous studies have used a DTT analysis with the FACT algorithm to predict motor recovery (16, 36, 37).

Several theories have been proposed for elucidating the mechanism of nerve cell recovery mediated by electroacupuncture. First, electroacupuncture was reported to promote neurogenesis and cell proliferation in the central nervous system during the rehabilitation of patients with ischemic stroke (11). It can also control cerebral blood flow, inhibit apoptosis, and regulate neurochemical substances (13). In another study, electroacupuncture was shown to exert a neuroprotective effect and a neuroregenerative effect (38). These effects were reported to be based on mechanisms such as (1) regulation of oxidative stress, (2) suppression of glutamate excitotoxicity, (3) maintenance of the blood-brain barrier integrity, (4) inhibition of apoptosis, and (5) production of cell growth factors (39). Another study reported that electroacupuncture enhances the neuroplasticity in post-stroke subcortical regions and the cortical motor areas that compensate for the motor defect (40). These mechanisms are presumed to have led to the effects of electroacupuncture in preventing nerve cell degeneration, and based on this, the combined treatment is anticipated to induce functional recovery in patients with stroke in the long term.

There are several limitations to this study. As follow-up monitoring was not performed for the behavioral outcomes and DTT parameters after the completion of the intervention, the long-term effects of electroacupuncture should be addressed in the future study. The results have shown a significant difference in FA and AD between the control and experimental groups, and it is thus possible that among the parameters of behavioral outcomes, the lower limb motor function and gait function would have significantly improved in patients who received the electroacupuncture therapy had the study been conducted for a longer duration. In addition, this study was conducted with a small sample at a single institution for the assessment of behavioral outcomes and neuroimaging analysis. In the future, a study recruiting a higher number of subjects based on a longitudinal design should be conducted to clearly identify the effects of electroacupuncture on post-stroke lower limb motor recovery.

In summary, after 4 weeks of intervention, the lower limb motor function and gait capability significantly improved in patients subjected to conventional rehabilitation therapy alone and patients subjected to electroacupuncture. The DTT results provided evidence that electroacupuncture can promote brain

neuroplasticity and delay the progression of neural degeneration over time. Thus, the treatment combining electroacupuncture with conventional stroke rehabilitation therapy could be a good protocol to promote motor recovery after stroke in the long term.

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/s.

Ethics statement

The studies involving human participants were reviewed and the study was conducted with the approval of the Institutional Review Board of the Wonkwang University Medical Center (IRB No. WKUIOMH-IRB-2020-14). The patients/participants provided their written informed consent to participate in this study.

Author contributions

J-ML and MJ: conceptualization. J-yA, S-sS, and BM: methodology. J-ML and S-sS: formal analysis. J-yA, BM, and MK: investigation. MK: writing. J-ML: editing. MJ: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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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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Case report: Tongdu Xingshen acupuncture for a patient with persistent vegetative state after herpes simplex virus encephalitis

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Introduction: A persistent vegetative state (PVS) can be caused by traumatic or non-traumatic brain injury. PVS is a complex clinical condition with numerous complications. Nursing care, medical treatment, and comprehensive rehabilitation are necessary to improve the outcomes of PVS. However, the prognosis remains unsatisfactory. Acupuncture therapy has been used as a rehabilitation strategy to treat patients with PVS in China, showing better results in the recovery of consciousness, intellectual capability, and motor function.

Case description: We present the case of a 4-month-long PVS after herpes simplex virus encephalitis (HSVE) in a 3.5-year-old boy who underwent Tongdu Xingshen acupuncture integrated with Western medicine and rehabilitation. The patient regained consciousness post-treatment. His intelligence and motor function gradually recovered after seven treatment sessions.

Conclusion: Tongdu Xingshen acupuncture is a potential complementary therapy to optimize clinical outcomes in PVS.

KEYWORDS

persistent vegetative state (PVS), herpes simplex virus encephalitis (HSVE), acupuncture, traditional Chinese medicine, case report

Introduction

Prolonged disorders of consciousness (PDoC) are defined as any disorder of consciousness that has continued for at least 4 weeks following sudden-onset brain injury. PDoC includes vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) (1). VS/UWS is defined as a state of unaware wakefulness in which there is a preserved capacity for spontaneous or stimulus-induced arousal—as evidenced by sleep–wake cycles and a range of reflexive and spontaneous behaviors.

Few studies have reported the epidemiology of VS. A systematic review reported that the prevalence of VS ranged from 0.2 to 6.1 patients with VS/UWS per 100,000 people (2). Studies on children found a prevalence rate of 6–80/million children (3).

The major causes of VS are trauma, vascular events, hypoxia or hypoperfusion, infection or inflammation, and toxic or metabolic disorders (1). Central nervous system infections account for 5–10% of pediatric persistent VS (PVS) (3). Viruses are responsible for 20–50% of all cases of encephalitis. Herpes simplex virus is the most common sporadic encephalitis worldwide (4). Herpes simplex virus encephalitis (HSVE) is fatal in more than 70% of patients if untreated. Antiviral treatment has decreased mortality to 20–30% (5), whereas most surviving patients continue to suffer from moderate-to-severe neurological sequelae including PVS. A previous study (6) reported that HSVE survivors experience amnestic difficulties (75%), global cognitive decline (25%), and personality and behavioral abnormalities (40–60%). It has also been reported that nearly 1% of pediatric patients are found to be in a VS at long-term follow-up evaluation (7, 8).

There are no established therapies for children with PDoC (9). Currently, the clinical evidence for therapies for children with PDoC is inadequate. Drugs such as amantadine, pramipexole, donepezil, and zolpidem are sometimes used in clinical practice (9, 10). Specialized neurological rehabilitation is recommended, and traditional Chinese medicine is used as a rehabilitation method (1). The prognosis for regaining consciousness and subsequent survival is poor, and long-term survival from PVS among the pediatric population is poor (11). Thus, the treatment of PDoC in the pediatric population deserves further research.

Here, we report the case of PVS after contracting HSVE in a young child. A combination of Tongdu Xingshen acupuncture therapy and Western medicine was adopted. The patient progressed favorably with respect to the level of consciousness and intelligent and motor function.

Case presentation

A 3.5-year-old boy showed perturbed consciousness with movement and intellectual dysfunction after suffering from HSVE and secondary epilepsy (Supplementary Video 1). He was administered antiviral and antiepileptic therapy, as well as immunomodulatory and neurotrophic agents. On admission, he was unsteady with his head upright and was able to roll over but unable to sit up independently. He was unable to actively or passively grasp objects. Although he was able to open his eyes, no visual tracking was observed. He was unable to follow any instructions. His left limb had involuntary activity sometimes accompanied by altered sleep–awake cycles. He was able to cry and make a "hum" sound through his nose. He required bolus nasogastric tube feedings due to dysphagia. His growth and development had proceeded normally until the onset of HSVE. Seizures were under control after taking levetiracetam tablets (Supplementary Video 1).

On initial physical examination, his vital signs were normal. He presented deficits in upright head/neck control and inability to support himself with his elbows and hands. Although he could roll over, he had problems controlling the movement of all four limbs, making it difficult for him to crawl, stand, and walk independently. He could not easily control shifts in position, e.g., from lying down to sitting up. His muscle tone was generally normal, but limb weakness grade was 3/5 (MRC strength scale). Adductor angle, popliteal angle, and dorsiflexion angle of his foot was 150°, 150°, and 70°, respectively. Knee/Achilles jerk reflexes were normal. Ankle clonus was positive. Neither the Babinski sign nor the meningeal irritation sign was positive.

His PVS score (12) was 5 (command execution = 0, body movement = 2, eye movement = 1, emotional reactions = 1, swallow = 0, and speech = 1). Gesell Developmental Schedules (GDS) scores (13) indicated a severe defect [gross motor (developmental quotient (DQ) = 4.4, fine motor (DQ = 0), adaptive behavior (DQ = 0), language (DQ = 0), and personal–social behavior (DQ = 0)]. Infants-Junior High School Students' Social Development Screening Test (14) (coarse score = 1 and standardized score = 6) indicated a severe abnormality, suggestive of movement and intellectual disorder. Gross Motor Function Measure-88 (GMFM-88) (15) was as follows: A = 82.4, B = 0, C = 0, D = 0, and total score = 16.5, indicating significant retardation in GMF.

Brain magnetic resonance imaging (MRI) showed that the sulcus in the bilateral cerebral hemispheres was slightly deeper than before, and the lateral ventricles were slightly enlarged. Some abnormal signals were observed around the bilateral ventricles. There were perivascular lesions in the bilateral frontal lobe and pachymeningeal enhancement (Figure 1). Video electroencephalogram (VEEG) demonstrated slow background activity. Numerous bilateral sharp waves and sharp wave complexes were observed in the posterior head and right rolandic area. Transcranial Doppler (TCD) indicated that the blood flow velocity of the bilateral middle cerebral artery was asymmetric, with its right side slightly slower. The anterior and posterior communicating arteries were unobstructed with compensatory capability. Visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) were normal.

The results of routine biochemical tests were normal. Immunologic tests found a high concentration of immunoglobulin G (IgG), while the concentration of IgA was decreased.

Diagnosis

Because the age of onset of PVS was >1 year after birth and the patient showed a normal development before HSVE, cerebral palsy and inherited metabolic disease were ruled out. According to the nervous system, physical examination, and the disease

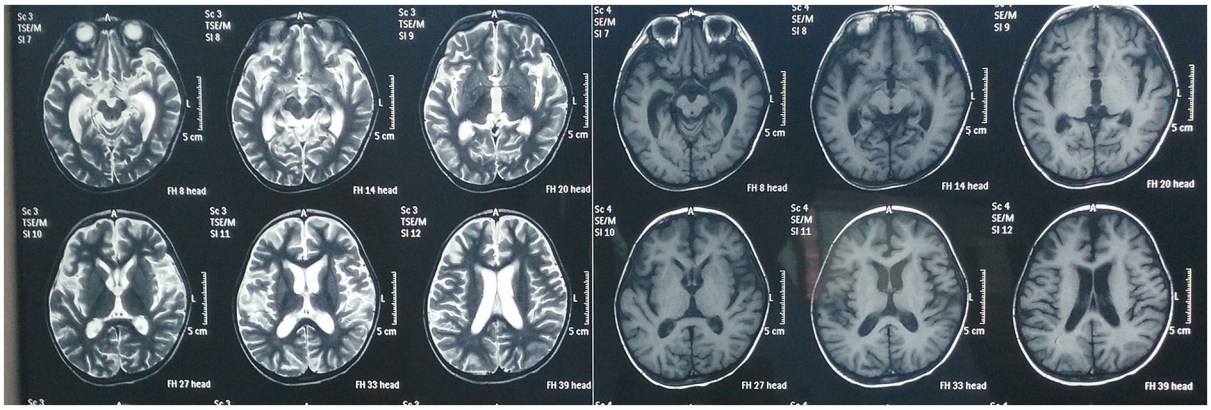

FIGURE 1
Magnetic resonance imaging of the brain before receiving Tongdu Xingshen acupuncture showed mild brain atrophy and pachymeningeal enhancement associated to meningitis.

being unprogressive, progressive muscular dystrophy was also ruled out.

The following diagnostic criteria for PVS (12), proposed at a meeting in Nanjing in April 1996, were applied: (1) no evidence of awareness of self or environment and inability to execute commands; (2) sufficiently preserved respiratory function and blood pressure; (3) intermittent wakefulness manifested by the presence of sleep–wake cycles; (4) no evidence of language comprehension or expression; (5)unconsciousness with eyes open; (6) no visual tracking; and (7) hypothalamic and brainstem autonomic functions sufficiently preserved to permit survival with medical and nursing care.

The patient's clinical presentations conformed to the abovementioned diagnostic criteria, and his PVS score of 5 indicated incomplete vegetative syndrome. VEEG activity demonstrated typically slow wave activity, and the patient had a history of HSVE. Therefore, he was diagnosed to be on PSV during convalescence from HSVE. Based on the case history, VEEG and MRI results, and medication history, a diagnosis of secondary epilepsy and brain atrophy was considered.

Treatment and outcomes

Routine treatment

The patient was given intravenous (IV) scopolamine (one time a day, 0.03–0.06 mg/kg; the IV was adjusted according to the patient's conditions in the first three treatment courses) compound Danshen tablets (two times a day with one tablet each time in the remaining four treatment courses) to improve brain microcirculation, and cattle encephalon glycoside and ignotin (CEGI) injection (one time a day, 2 ml, IV throughout the treatment period) to alleviate the nerve function injury. Regular rehabilitation therapy included exercise therapy, massage, and speech and cognitive training.

Acupuncture therapy

The acupuncture method used was Tongdu Xingshen acupuncture comprising scalp acupuncture and body acupuncture (Supplementary Table S1).

Treatment course

In the first four treatment courses, the selected acupoints were nine intelligent needles [Sishencong (EX-HN1) plus forehead five needles], temporal three needles, BaiHui (GV20), foot motor sensory area, motor area, balance area, second speech area, spirit-emotion area, YinTang (EX-HN3), Neiguan (PC6), Sanyinjiao (SP6), and Shenmen (HT7).

In the remaining three courses, acupoints were adjusted based on the previous four courses. The foot motor sensory area, motor area, and spirit-emotion area were removed. Areas of the heart and liver were added during these treatment courses.

Acupuncture manipulations

Acupuncture treatment was performed by an independent certified practitioner (acupuncturist) with 5 years of clinical experience.

Scalp acupuncture and Bai Hui (GV 20)

Disposable stainless steel needles (size 0.30 mm × 40 mm; Huatuo, Suzhou Medical Appliance, Suzhou, Jiangsu Province, China) were manually inserted at an angle of ∼15° to a depth of 20–35 mm. For a total of 120 min, the needles were twirled and rotated at 180–200 revolutions/min for 3 min every 30 min.

Body acupuncture

a. *Yin Tang*: The 0.30 mm × 25 mm acupuncture needles were inserted obliquely in the direction of the nasal root at an angle of ∼10–20° and an insertion depth of 10–15-mm.

b. *Bilateral Neiguan and Shenmen*: The needles were vertically thrust at depths of 10–15 (Neiguan) and 8–10 mm (Shenmen).

c. *Bilateral Sanyinjiao*: The 0.3 mm × 40 mm needles were vertically inserted at a depth of 15–20 mm.

d. *Manipulation*: The even reinforcing-reducing method was adopted by twirling the needles for at least 180 revolutions/min for 3 min every 10 min. The needle retention time was 30 min. "De qi" is an indication of effective needling. Acupuncturists will feel tightness around the needle when the qi arrives.

e. *Treatment course*: The patient received seven courses of acupuncture with an average of 19 days each course. Acupuncture was implemented every other day for 10 times per treatment course. If the patient caught a cold or other conditions that influenced acupuncture treatment, the course was prolonged.

The diagnosis and treatment process is illustrated in Figure 2.

Evaluation of therapeutic effect

PVS score scale

The curative effect was evaluated using a PVS score scale proposed at the meeting in Nanjing in April 1996 (12). The total score was calculated according to the sum of scores for six clinical features. The standard for the total score is as follows: complete vegetative state (PVS $\leq$ 3); incomplete vegetative syndromes (4 $\leq$ PVS $\leq$ 7); transitional vegetative syndromes (8 $\leq$ PVS $\leq$ 9); out-of-vegetative-state (10 $\leq$ PVS $\leq$ 11); and recovery of consciousness (PVS $\geq$ 12). A patient is in the out-of-vegetative-state if he can execute instructions.

Gesell developmental schedules

The Chinese version of the GDS (13) is used to evaluate neurodevelopmental symptoms in children, such as gross motor skills, fine motor skills, adaptability, language, and personal–social activity. The degree of mental development is classified according to the average DQ score: normal (DQ ≥6), borderline (DQ: 76≤ –≤85), mild defect (DQ: 55≤-≤75), moderate defect (DQ: 40≤-≤54), and severe and extremely severe defect (DQ ≤ 39).

Therapeutic effect

Approximately 1 week after the abovementioned treatment, the nasogastric tube was removed, and the patient was fed thick porridge and rice cereal. After 12 days of treatment, the patient smiled on his own. After completion of the first treatment course, the PVS score on the PVS rating scale increased to 8 (command execution = 0, body movement = 2, eye movement = 1, emotional reactions = 2, swallow = 2, and speech = 1) (Figure 3), indicating that the patient evolved favorably. The patient showed the ability to control his head and neck when he was upright and could sit independently. Muscle strength in his upper limbs gradually recovered, and he demonstrated his ability to support the upper body with his hands and elbows. He had a normal crying and laughing reaction to stimulation (Supplementary Video 2).

At the end of the second treatment course, the patient was out of VS (the PVS rating scale was 15) (command execution = 2, body movement = 3, eye movement = 3, emotional reactions = 3, swallow = 2, and speech = 2) (Figure 3). He was able to perform simple tasks with continuous eye tracking and eye contact. He could speak simple words like "mum" and "dad," sit up straight, stand up, and walk slowly by holding or touching a support surface. The grip strength of his hand increased. The urge to defecate gradually recovered. Four limbs muscle strength was gradually recovered (grade 4+/5) (Supplementary Video 3).

In the third treatment course, GDS was assessed (Figure 3). The score was 21.74, indicating a severe and extremely severe defect [gross motor (DQ = 17.9), fine motor (DQ = 21.9), adaptive behavior (DQ = 24.8), language (DQ = 23.2), and personal–social behavior (DQ = 20.9)]. MRI was rechecked after this course, demonstrating that mild atrophy-like changes in the bilateral cerebral hemispheres improved and the abnormal signal near the bilateral ventricles was basically absorbed. The abnormal signal in the white matter of bilateral frontal lobes indicated the possibility of poor myelination, and a follow-up review is advised to rule out focal demyelination. Bilateral temporal dura enhanced, indicating intracranial infection sequelae, for which short-term review is recommended (Figure 4).

After five treatment courses, the patient was able to resume a full diet. He could sit and walk independently and grasp objects flexibly. He demonstrated hand–mouth–eye coordination. He was able to communicate with others by talking short sentences of 5–6 words and could play a simple imitation game. GDS scores increased to 53.98, suggesting a moderate defect [gross motor (DQ = 51.2), fine motor (DQ = 48.1), adaptive behavior (DQ = 55.1), language (DQ = 58.6), and personal–social behavior (DQ = 56.9)] (Figure 3) (Supplementary Video 4).

In the last treatment course, the patient was able to follow instructions and play games. He exhibited fluency in routine verbal communication. He could not only sit, stand, and walk independently, but also run and jump. He exhibited hand–mouth–eye coordination and was able to stand upright independently. Muscle strength in all four limbs was generally normal. Ankle clonus was positive (Supplementary Video 5). No adverse or unanticipated events

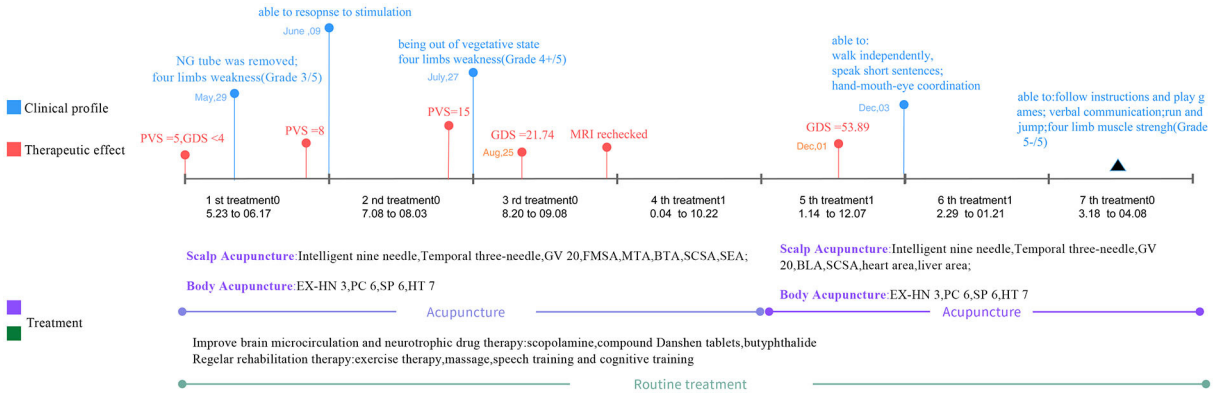

FIGURE 2
The timeline of diagnosis and treatment for this patient. NG tube, nasogastric tube; PVS, persistent vegetative state; GDS, Gesell Developmental Schedules; MRI, magnetic resonance imaging; FMSA, Foot motor sensory area; MTA, Motor area; BLA, Balance area; SCSA, Second speech area; SEA, Spirit-emotion area; GV 20, Baihui acupoint; EX-HN 3, Yintang acupoint; PC 6, Neiguan acupoint; HT 7, Shenmen acupoint; SP 6, Sanyinjiao acupoint.

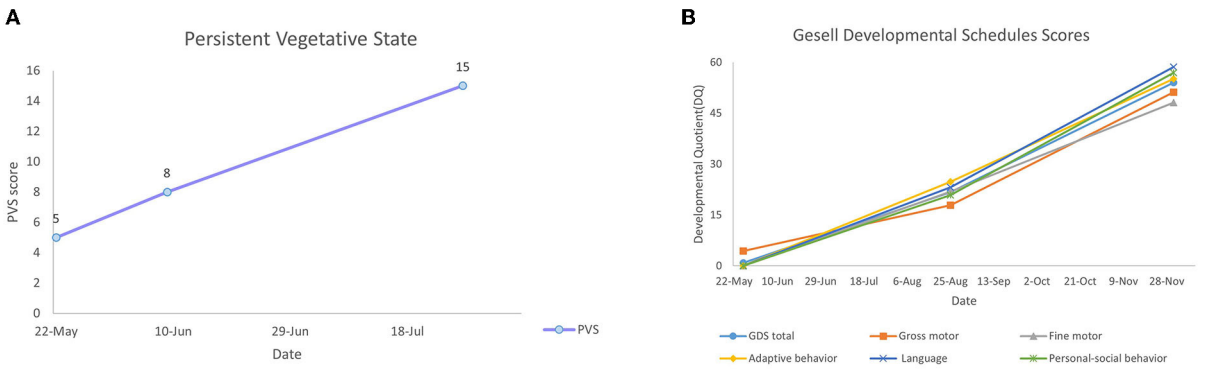

FIGURE 3
The therapeutic effect on PVS **(A)** and GDS score **(B)** of patient.

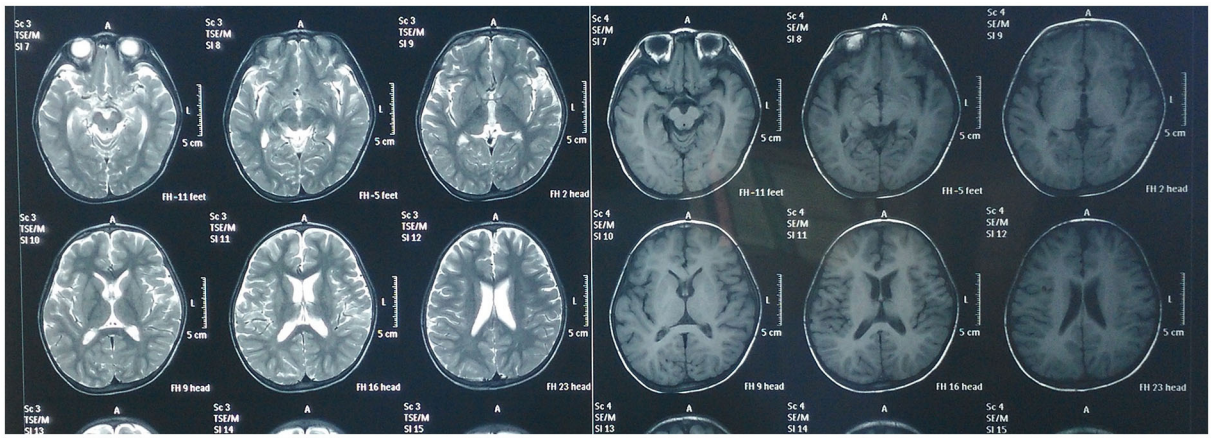

FIGURE 4
Magnetic resonance imaging of the brain after receiving Tongdu Xingshen acupuncture suggested mild brain atrophy and pachymeningeal enhancement associated to meningitis improved.

were reported throughout the treatment period. At the 1-year follow-up examination, ambulatory electroencephalography (AEEG) showed a paroxysmal complex of sharp–slow waves in bilateral brain areas. MRI demonstrated few bilateral lacunar ischemic foci in the subfrontal cortical white matter. The patient was studying in kindergarten and was able to actively communicate with other children and teachers.

Preventive measures during acupuncture

To avoid unexpected situations, the acupuncturists selected a comfortable posture for the needling and paid due attention to the manipulation. Parents were asked to carefully observe the patient during acupuncture to monitor for emergency conditions. If any adverse event occurred, appropriate measures were taken immediately.

Discussion

Evidence has shown that some of the factors involved in the prognosis of VS/UWS are etiology, age at the time of acute injury, and time spent in the same state. As for age, the recovery of consciousness and survival rates are higher in younger patients than in older ones; however, pediatric patients <1 year of age have been reported to show higher mortality (16). Better consciousness and independence outcomes are observed in traumatic causes than in non-traumatic ones (17). The correlation between time spent in VS/UWS and a better outcome is negative. Given that VS/UWS impairs neurological development among pediatric patients, many patients require long-term care. Therefore, effective and early intervention is indispensable for the long-term prognosis of VS/VWS.

Acupuncture is commonly used in various neurological conditions. The addition of acupuncture can alleviate consciousness disorders. It is reported that the addition of acupuncture can remarkably promote the recovery of the consciousness level (18) and improve motor function of the limbs. Further, computed tomography (CT) demonstrated a reduction in the width of the third ventricle (19) and apparently reduced the mean curing time (20). Only a few adverse events were reported. The abovementioned studies suggested that the addition of acupuncture is safe and effective.

Scalp acupuncture is a modern acupuncture technique that combines the traditional needling method with modern medical knowledge (21). It has been widely used to treat cerebral diseases in traditional Chinese medicine.

The mechanism underlying scalp acupuncture therapy in cerebral diseases remains elusive. However, the following are considered potential mechanisms: (1) increases cerebral blood flow; (2) improves cerebral oxygen metabolism; (3) reduces the deterioration of brain tissues as a result of free radicals and inflammatory factors (22); (4) enhances synaptic plasticity *via* the regulation of neurotrophic factors (23); and (5) regulates the brain microenvironment *via* nerve growth-related proteins (24).

Tongdu Xingshen acupuncture is developed based on Lin's scalp acupuncture, Jiao's scalp acupuncture, and our clinical practice. Our previous studies reported that Tongdu Xingshen acupuncture improved intelligence, language ability, social adaptive ability, and motor function (25–29). It exerts stimulation on the corresponding scalp projection area of the cerebral cortex including the frontal lobe (precentral gyrus), parietal lobule (postcentral gyrus), paracentral lobule, temporal lobe (posterior superior temporal gyrus), and acerebellar hemisphere. The effect of acupuncture transmitted through the cortical–thalamic–cortical pathway thereby positively modulates the corresponding areas of memory, the language center, the motor center, or balance. As for the retention time of the needle, a curative effect is positively associated with the length of the retention time. Retaining needles for 2 h is optimal for intellectual and gross motor development in children with cerebral palsy based on our previous research (30).

According to the basic theory of traditional Chinese medicine, the location of the disease in VS is the brain. The brain is made up of "marrow." It has been recognized that the functions of the sense organs and body motion are linked with the brain in *Errors on Medicine Corrected* (*Yilin Gai Cuo*). The governing vessel has a close relationship with the brain, spinal marrow, and kidneys. Tongdu Xingshen acupuncture mainly stimulates the governing vessel to nourish the brain *via* ascending Yang Qi and enriching the marrow beneficial for the recovery of consciousness and nerve repair.

This case report has some limitations. First, the latest version of the diagnostic criteria and clinical efficacy scales for PVS were not adopted, but we propose that this did not influence diagnostic accuracy. Furthermore, intervention adherence and tolerability were not accessed. Nevertheless, the patient and his parents strictly followed the treatment routine and were hospitalized on time, suggesting good intervention adherence and tolerability.

In this case presentation, a 3.5-year-old boy with PVS after HSVE recovered from VS, and his cognitive and motor function generally improved after receiving a combination of Tongdu Xingshen acupuncture and modern medicine. This showed that acupuncture as an adjunctive therapy is effective in the recovery stage of PVS. It is recommended that patients with PVS receive acupuncture therapy as soon as possible when vital signs become stable. Acupoints located on the head are frequently used to stimulate the scalp projection area of each brain functional area. Earlier application of acupuncture is associated with a higher probability of awakening and fewer neurological sequelae.

Patient's perspective

We sought medical help from Chinese medicine after receiving Western medicine therapy. Considering that the conditions were complex, we attempted to receive acupuncture in combination with routine treatment. After a week-long treatment, our son was able to swallow thick porridge or rice cereal. This favorable turnaround gave us confidence in the current treatment plan. The medical staff were patient and attentive. Throughout the therapy session, we were delighted to see his progress.

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/s.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

BJ contributed to data collection, the design of the case report design, data analysis, and interpretation. YT contributed to the design of the case report, writing the initial and subsequent drafts after they were revised by all involved authors, and submitting the final case report. YW contributed to data analysis and interpretation. ZL contributed to data analysis and interpretation, as well as critically revising this paper. All authors contributed to the article and approved the submitted version.

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.2022.896721/full#supplementary-material

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Effect of acupuncture for disorders of consciousness in patients with stroke: A systematic review and meta-analysis

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Background: Disorder of consciousness (DOC) is frequent in patients with stroke, which is the second most common cause of death and a leading cause of disability. Acupuncture has been used as a curative method for DOC treatment in China. Nevertheless, no critical systematic review of acupuncture's effect on DOC has been published. This review aims to evaluate the present evidence regarding the efficacy of acupuncture for DOC after stroke.

Methods: Seven databases were searched from their inception to November 1, 2021, containing three English databases (PubMed, Embase, and Cochrane Central Register of Controlled Trials) and four Chinese databases (CNKI, CBM, VIP, and Wanfang Database). The primary outcomes comprise the Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) before and after treatment. Secondary outcomes involve resuscitation rate, resuscitation time, and adverse events. Data synthesis was calculated by RevMan (V.5.4.1) software. According to the Cochrane Handbook, methodological quality was assessed with the risk of bias tool 2.0 (RoB2).

Results: Seventeen studies containing 1,208 patients were eventually included in our review. Overall, most trials were rated as high or had some concerns regarding the risk of bias. GCS was reported in 16 trials, and a meta-analysis showed that GCS improvement in the acupuncture group was greater than in the non-acupuncture group (MD 1.45, 95% CI 0.94–1.97, $P < 0.0001$). One trial reported that GOS improvement in the acupuncture plus medication group was greater than in the medication group (MD 0.58, 95% CI 0.11–1.05, $P = 0.01$). Another study reported that acupuncture plus medication was statistically more effective in shortening resuscitation time than medication alone (MD−0.89, 95% CI −1.53 to −0.25, $P = 0.006$). Four trials reported that the resuscitation rate in the acupuncture group was higher than without

acupuncture intervention (RR 1.68, 95% CI 1.30–2.18, I^2 0%, $P = 0.39$). Adverse events were reported in two studies, with one case in the acupuncture group suffering from subcutaneous hematoma.

Conclusion: Acupuncture may improve consciousness level, increase the resuscitation rate, and shorten resuscitation time for post-stroke patients with DOC. Adverse events from acupuncture were rare, tolerable, and recoverable. However, the results should be interpreted cautiously, and more rigorous RCTs with better methodology are warranted.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=289802, identifier 289802.

KEYWORDS

stroke, systematic review, DOC, GCS, GOS, acupuncture

Introduction

Stroke, a common acute cerebrovascular accident, can be clinically divided into two types according to pathogenesis: ischemic stroke and hemorrhagic stroke—the former accounts for about 62.4% and the latter, 37.6% (1). High incidence, morbidity, mortality, and recurrence rate constitute the significant characteristics of stroke. From a global perspective, stroke, in particular, has imposed a ponderous burden on developing countries (2). In 2017, the total number of stroke deaths worldwide was 6.16 million, while China accounts for about one-third of the total, with 2.1 million (3). Besides, the overall lifetime risk of stroke in China is 39.9%, the highest in the world, which means that about two out of five people may suffer from a stroke during their lifetime. In 2017, the per capita hospitalization expenses for patients with ischemic and hemorrhagic strokes in China were 9,607 and 18,525 Chinese yuan (CNY), an increase of 60 and 118%, respectively, compared with 2007 (4). Therefore, more attention should be paid to strokes.

Several complications could be involved in stroke, such as consciousness disorder, depression, dysphagia, cognitive impairment, and so on (5). The sequelae of a stroke may lead to a lengthy recovery period, high medical expenses, and a poor prognosis for post-stroke patients (6). Among various sequelae, a disorder of consciousness (DOC) occurs frequently. According to an evidence-based practice guideline for stroke, nearly one out of every three stroke patients suffers from DOC to varying degrees (7). Moreover, it was also shown that 40% of patients with DOC have difficulty regaining normal consciousness (8). In a clinical randomized controlled study involving 6,336 people, the results indicated that the hospital mortality rate of stroke patients with DOC was higher than those without (35.9 vs. 2.6%) (9).

Currently, stroke treatment is based primarily on surgery and drug thrombolytic therapy (10, 11). In terms of stroke sequelae, it has been pointed out that multidisciplinary cooperative rehabilitation units could achieve superior outcomes (12). As a relatively well-recognized traditional therapy, acupuncture has broadly been used in post-stroke rehabilitation in China (13). Studies have indicated that acupuncture treatment for stroke can adjust the stability of the human body environment through the influence of the nerve-endocrine-immune network (14). Specific to stroke, acupuncture affects the neurovascular unit through multiple levels to promote cerebral blood perfusion in the focal area of stroke patients and improve the function of damaged brain cells (15, 16). Furthermore, with respect to the therapeutic method regarding post-stroke patients with impaired consciousness, acupuncture has been carried out in correspondent clinical study (17).

However, no systematic review assessing the effect of acupuncture for DOC has been carried out until now. Consequently, we performed this review to explore whether acupuncture was an efficacious therapy for DOC.

Method

Study registration

Our review protocol has been registered on PROSPERO (No. CRD42021289802). The Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines were strictly complied with (18, 19).

Inclusion criteria for study selection

Types of studies

All clinical RCTs were included. Non-randomized or quasi-randomized controlled trials or case reports, case series, systematic reviews and meta-analyses, and animal studies were

excluded. For randomized crossover trials, we used the data before crossing.

Types of participants

Patients in the trial must be diagnosed with stroke with DOC, such as coma, vegetative state (VS), or minimally conscious state (MCS). The diagnosis was confirmed by an imagelogical examination, clinical signs, and symptoms. The qualified patients were enrolled in the review without regarding any information about their age, sex, race, education, or nationality. Studies focused on DOC due to other causes, such as traumatic brain injury, were excluded.

Types of interventions

Experimental interventions

Studies that label the intervention "acupuncture," for example, traditional acupuncture, auricular acupuncture, electro-acupuncture, warm needle, scalp acupuncture, manual acupuncture, fire needle, superficial acupuncture, wrist-ankle acupuncture, and abdominal acupuncture, were included. However, noninvasive methods such as laser acupuncture and point massage were excluded.

Control interventions

The control groups could use placebo acupuncture, repetitive transcranial magnetic stimulation (rTMS), hyperbaric oxygen, acupressure, no treatment, non-acupoint acupuncture, medication, massage, etc. Studies that compared acupuncture with another therapy with the same therapy alone were also included. Trials that only involved comparisons between different types of acupuncture were excluded.

Outcome measures

Primary outcomes

The Glasgow Coma Scale (GCS) score and Glasgow Outcome Scale (GOS) score are vital criteria for assessing a conscious state. Hence, the level of consciousness was measured by GCS and GOS before and after treatment. The GCS has three major items, a total of 15 points. The higher the score, the better the consciousness level. The GOS has five points in all; the higher the score, the better the awareness outcome.

Secondary outcomes

Resuscitation rate, resuscitation time, and adverse events related to the treatment were extracted from the study as secondary outcomes.

Search methods for the identification of studies

Electronic searches

The following databases were searched from their inception to November 1, 2021, including three English literature databases (PubMed, Embase, and Cochrane Central Register of Controlled Trials) and four Chinese literature databases (Chinese National Knowledge Infrastructure database, Chinese Biomedical database, VIP, and Wanfang Database). Terms of medical subjects (MeSH) and keywords were used individually or in combination during the query. Nonetheless, the search strategy for other databases was slightly modified. Besides, Chinese characters with the same meaning were used for literature retrieval in the Chinese databases. The overall search strategy is displayed in Supplementary Appendix 1.

Searching for other resources

Clinical trial registries, dissertations, and gray literature were additionally searched. Furthermore, the reference lists of selected studies were scanned for additional studies. We also searched the WHO International Clinical Trials Registry Platform (ICTRP; http://apps.who.int/trialsearch/), the ClinicalTrials.gov registry (http://clinicaltrials.gov/), the Chinese Clinical Trial Registry, and other relevant trial registries.

Data collection and analysis

Selection of studies

Before the selection of studies, all reviewers received professional training to understand the objective and process of the review. NoteExpress software was applied to upload the studies obtained from electronic databases and other resources. The selection of studies for the current review was performed independently by two reviewers (CYN and HZB) to screen the titles, abstracts, and keywords of all retrieved records separately. Any disagreement was resolved through discussion and adjudication to get a consensus and judged by an arbiter (LT). Details of the selection procedure for studies are shown in a PRISMA flow chart (Figure 1).

Data extraction and management

The following key information was extracted from each study: first author, publication year, sample size, characteristics of participants, disease duration, intervention and control, acupoints selected, duration and sessions of treatment, outcome measures, results reported, and adverse events. Study selection was scrutinized independently by two reviewers based on the predetermined inclusion criteria, with disagreement resolved by discussion and adjudication. When the data of articles were

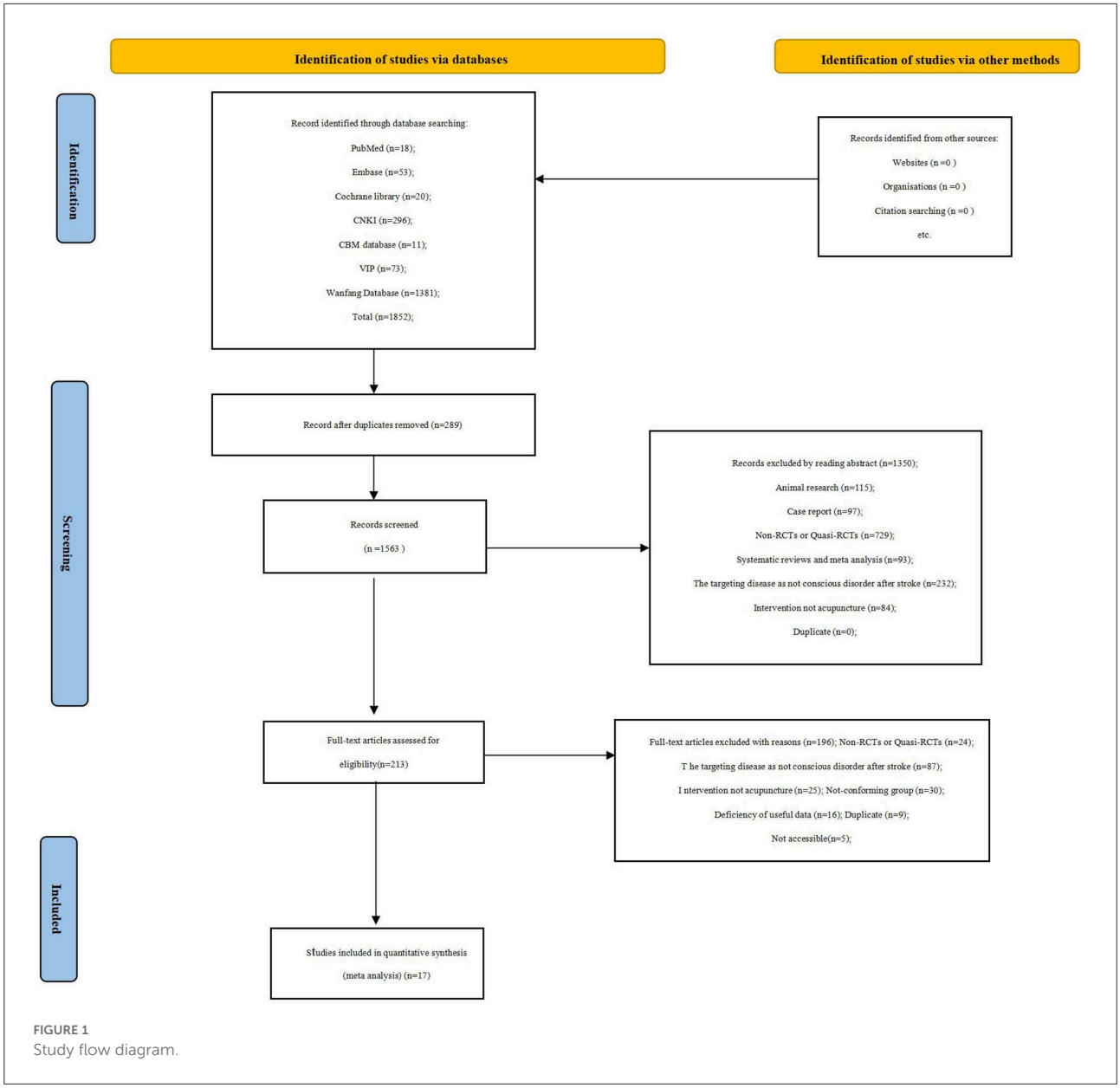

FIGURE 1
Study flow diagram.

insufficient or ambiguous, we tried to contact the corresponding authors for more information.

Assessment of the risk of bias in included studies

The research team conducted a risk-of-bias assessment using the risk of bias tool 2.0 (RoB2) from Cochrane. The assessment includes the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The overall judgment of each trial can be "low" or "high" or "some concerns" risk of bias. With any discrepancies resolved through discussion, the research team independently completed the risk-of-bias assessment for each study.

Measures of treatment effect

Outcome data were summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary outcomes, while mean difference (MD) with 95% CI for continuous outcomes. WMD with 95% CIs was applied if outcomes were assessed by the same scale, while SMD with 95% CIs was applied if outcomes were assessed by different scales. Revman (V.5.4.1) software was used.

Unit of analysis issue

Considering that some studies compared two or more intervention groups with a control group, the research team followed the recommended advice in the Cochrane Handbook version 6.2 (18) and combined groups to create a single pairwise comparison to avoid a unit-of-analysis error.

Dealing with missing data

If possible, we tried to contact the corresponding authors by e-mail or telephone to acquire the missing data. When we failed, we analyzed the available data and discussed the potential influence of the missing data in the discussion.

Assessment of heterogeneity

We first took the characteristics of patients (e.g., age, sex) and trial design (e.g., adequate sequence generation, blinding of assessors) into account to assess the clinical heterogeneity of the included studies. Then, we used the *I*-squared and Chi^2 tests to evaluate the statistical heterogeneity of the included studies. A random-effects model was used when $I^2 \geq 50\%$, while a fixed-effects model was applied when $I^2 < 50\%$. When significant clinical heterogeneity existed, we used sensitivity analysis and descriptive analysis.

Data synthesis and analysis

Review Manager Software (RevMan V.5.4.1) from Cochrane Collaboration was applied for data synthesis and analysis.

Assessment of publication bias

If the overall quantity of our study was more than 10, a funnel plot analysis was conducted to determine publication bias.

Subgroup analysis

We considered that different add-on treatments to acupuncture might influence the adjunctive effect of acupuncture. We conducted subgroup analysis for primary outcomes as follows: acupuncture plus medication therapy vs. medication therapy alone, acupuncture plus rehabilitation training therapy vs. rehabilitation training therapy alone, acupuncture vs. medication, and acupuncture vs. rehabilitation training therapy.

Sensitivity analysis

A sensitivity analysis was performed to identify the robustness of studies according to the comparison between different effect models.

Grading the quality of evidence

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was applied to evaluate the quality of confidence for primary outcomes in included studies (20). The evaluation was divided into four levels: high, moderate, low, or very low.

Results

Characteristics of included trials

Through a detailed search of seven electronic databases, a total of 1,852 related articles were obtained. After checking the duplication and reading the titles and abstracts, 213 articles remained. We further read the full text of these papers; a total of 17 studies containing 1,208 patients were eventually included in our systematic review (21–37). A manual review of the references in the included literature did not reveal additional studies of value.

All the included papers were RCTs and published in Chinese journals from 2013 to 2021 in China. The individual sample sizes of the studies ranged from 30 to 114. However, the exact calculation of the sample size was not mentioned in any of the studies. In all included studies, there was no statistically significant difference in the average age of males and females. The treatment course ranged from 7–90 days, and the treatment times of acupuncture ranged from 7–90. Of all the included studies, fourteen studies compared acupuncture plus medication therapy with medication therapy alone (21–35); two studies compared acupuncture plus rehabilitation therapy with rehabilitation therapy (including music therapy and repetitive transcranial magnetic stimulation) alone (36, 37), and three studies compared acupuncture to medication therapy (33–35). One study compared acupuncture to rehabilitation training therapy (repetitive transcranial magnetic stimulation) (37). All the general information is presented in Table 1.

Risk of bias within the trial

Two (11.8%) studies (26, 27) were rated as having a low risk of bias for the randomization process because they provided a detailed random sequence generation process, and the allocation sequence was concealed. Fifteen trials (88.2%) (21–25, 28–37) were rated as having a high risk of bias for the randomization process because none provided a specific randomization method or random sequence allocation concealment. Regarding deviations from intended interventions and missing outcome data parts, all studies could be assessed as having a low risk of bias according to the descriptions in the method and results in sections of the included trials. As for the measurement of the outcome part, one study (5.8%) (31) had a

TABLE 1 General information of the included trials.

First author	Year	Sample Size	Age (mean ± SD)	Sex (male/female)	Disease duration (day)	Acu retention	Regimen	Duration of treatment	Primary outcomes	Secondary outcomes	Adverse effects	Acupoint selected
He et al. (21)	2016	T:20	T: 47. 7 ± 11. 4	T: 15/5	T: 1. 5 ± 0. 6	20	T: MT + Acu	20 times,22 days	GCS	resuscitation rate		BaiHui(GV20), SiShenCong(EX-HN1), ShenTing(GV24), Parietal anterior slash, ShuiGou(GV26)
		C: 20	C:45. 6 ± 10. 0	C:13/7	C:1. 7 ± 0. 4		CMT					
Bi et al. (22)	2014	T:38	T:62.33 ± 8.73	T:23/15	T:1.3 ± 0.5	NR	T: MT + Acu	7 times, 7 days	GCS	resuscitation time		NeiGuan(PC6), RenZhong(GV26), SanYingJiao(SP6), JiQuan(HT1), ChiZe(LU5), WeiZhong(BL40)
		C:38	C:60.38 ± 8.26	C:20/18	C:1.2 ± 0.5		C: MT					
WU et al. (23)	2013	T:15	T:52.7 ± 1.3	T:11/4	5	30	T: MT + Acu	30 times,30 days	GCS	resuscitation rate		NeiGuan(PC6), RenZhong(GV26), SanYingJiao(SP6)
		C:15	C:50.1 ± 3.2	C:12/3			C: MT					
Tian et al. (24)	2016	T:50	T:65.61 ± 5.43	NR	≤3	30	T: MT + Acu	24 times,30 days	GCS			BaiHui(GV20), NeiGuan(PC6), ChiZe(LU5), WeiZhong(BL40), (ShuiGouGV26), QuChi(LI11), WanGu(GB12), JinJing(BL1), HeGu(LI4), LianQuan(RN23)
		C:50	C:64.18 ± 4.89				C: MT					
Duan et al. (25)	2012	T:20	T:62.20 ± 8.11	T:13/7	≤1	30	T: MT + Acu	23 times,30 days	GCS			YiFeng(SJ17), FengChi(GB20), YuYe(EX-HN13), NeiGuan(PC6). RenZhong(GV26), SanYingJiao(SP6), JiQuan(HT1), ChiZe(LU5) WeiZhong(BL40), QuChi(LI11)BaiHui(GV20), WanGu(GB12), JinJing(BL1),
		C:20	C:60.40 ± 7.85	C:14/6			C: MT					
Zhao (26)	2017	T:38	T:60.05 ± 10.34	T:22/16	T:2.5 ± 0.8	20	T: MT + Acu	20 times,26 days	GCS, GOS	resuscitation rate	ecchymoma	BaiHui(GV20), SiShenCong(EX-HN1), ShuiGou(GV26), SuLiao(DU25), NeiGuan(PC6)
		C:38	C:59.53 ± 9.51	C:23/15	C:2.3 ± 0.9		C: MT					
OuYang (27)	2018	T:33	T:60.39 ± 13.73	T:19/14	NR	20	T: MT + Acu	20 times, 26 days	GCS		Ecchymoma	BaiHui(GV20), SiShenCong(EX-HN1), TaiYang(EX-HN5), QuBing(GB7), ShuiGou(GV26)

(Continued)

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TABLE 1 (Continued)

First author	Year	Sample Size	Age (mean ± SD)	Sex (male/female)	Disease duration (day)	Acu retention	Regimen	Duration of treatment	Primary outcomes	Secondary outcomes	Adverse effects	Acupoint selected
		C:32	C:60.53 ± 9.54	C:20/12			CMT				stuck needle	JianYu(LI15), QuChi(LI11), ZhiGou(SJ6), WaiGuan(SJ5), HeGu(LI4), FuTu(ST32), XueHai(SP10), ZuSanLi(ST36), YangLinQuan(GB34), FengLong(ST40)
Gao (28)	2018	T:32	T:55.72 ± 7.13	T:15/17	T:2.7 ± 0.2	40	T: MT + Acu	24 times,26 days	GCS			ShuiGou(GV26), NeiGuan(PC6), SanYingJiao(SP6)
		C:32	C:63.52 ± 6.41	C:16/16	C:3..5 ± 1.4		C: MT					
Qi (29)	2020	T:40	T: 61.22 ± 11.05	T:25/15	T:45.3 ± 14.7	15	T: MT + Acu	90 times,90 days	GCS			ShuiGou(GV26), BaiHui(GV20), HeGu(LI4), LianQuan(RN23), TaiChong(LR3), FengChi(GB20), QuBing(GB7), TongLi(HT5)
		C:40	C:60.84 ± 10.39	C:24/16	C:44.7 ± 15.3		C: MT					
Huang (30)	2018	T:16	T:57	T:11/5	NR	25	T: MT + Acu	28 times,28 days	GCS			JianYu(LI15), Jianliao(SJ14), JianZhen(SI9), YangXi(LI5), QuChi(LI11), HouXi(SI3), HeGu(LI4), HuanTiao(GB30), FengShi(GB31), ZhongDu(LR6), ZuSanLi(ST36), YangLinQuan(GB34), JueGu(GB39)
		C:16	C:54	C:10/6			C: MT					
Liu et al. (31)	2021	T:33	T:63 ± 6	T:19/14	3–7	30	T: MT + Acu	21 times,21 days	GCS	resuscitation rate		YinTang(EX-HN3), ShuiGou(GV26), BaiHui(GV20), ShenTing(GV24), NeiGuan(PC6), SanYingJiao(SP6)
		C:32	C:63 ± 7	C:17/15			C: MT					
Zhang (32)	2015	T:40	T + C:61.2 ± 10.56	T + C:50/30	>0.4	30	T: MT + Acu	45 times, 51 days	GCS			YongQuan(KI1), BaiHui(GV20), SanYingJiao(SP6), ShiXuan(EX-UE11)
		C:40					C: MT					LaoGong(PC8), ShenMen(HT7), NeiGuan(PC6), FengFu(DU16), ShuiGou(GV26)

(Continued)

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TABLE 1 (Continued)

First author	Year	Sample Size	Age (mean ± SD)	Sex (male/female)	Disease duration (day)	Acu retention	Regimen	Duration of treatment	Primary outcomes	Secondary outcomes	Adverse effects	Acupoint selected
Wang et al. (33)	2021	T:38	T:65 ± 5	T:21/17	0.4 ± 0.1	30	T: ACU+EDA	10 times, 14 days	GCS			NeiGuan(PC6), SanYingJiao(SP6), ShuiGou(GV26), HeGu(LI4), WeiZhong(BL40), ChiZe(LU5), JiQuan(HT1)
		C1:38	C1:64 ± 5	C1:20/18			C1:EDA					
		C2:38	C2:64 ± 5	C2:22/16			C2:Acu					
Han (34)	2019	T:34	T:49.58 ± 6.52	T:19/15	≤1	30	T: ACU+NX	14 times, 14 days	GCS			NeiGuan(PC6), RenZhong(GV26), SanYingJiao(SP6)
		C1:33	C1:49. 72 ± 6. 31	C1:19/14			C1:NX					
		C2:33	C2:48.16 ± 7.24	C1:18/15			C2:Acu					
Yang et al. (35)	2013	T:36	T:58.5 ± 19	T:17/19	T:2.8 ± 0.5	NR	T: ACU+CM	14 times,14 days	GCS			HeGu(LI4), ShuiGou(GV26), LianQuan(RN23), SiShenCong(EX-HN1), NeiGuan(PC6), ZuSanLi(ST36), TaiChong(LR3)
		C1:36	C1: 56.7 ± 21	C1:16/20	C1:2.6 ± 0.7		C1:CM					
		C2:36	C2: 56.8 ± 20	C2:18/18	C2:2.7 ± 0.6		C2:Acu					
Li et al. (36)	2021	T:30	T:53.2 ± 8.2	T: 16/14	T:85 ± 3	30	T:ACU+rTMS	24 times, 28 days	GCS			BaiHui(GV20), RenZhong(GV26), ShenTing(GV24) NeiGuan(PC6), YongQuan(KI1)
		C1:30	C1:53.2 ± 5.2	C1:14/16	C1:85 ± 6		C1:rTMS					
		C2:30	C2:54.5 ± 2.2	C2:15/15	C2:86 ± 2		C2:Acu					
Li et al. (37)	2020	T:24	T:58.03 ± 3.58	T:14/10	3–10	80	T: ACU+HBO	30 times, 30 days	GCS			BaiHui(GV20), QianDing(DU21), HouDing(DU19), RenZhong(GV26), ShenShu(BL23) XinShu(BL15), TaiXi(KI3), TaiChong(LR3), ShenMen(HT7), TongLi(HT5)
		C:24	C:57.11 ± 3.61	C:13/11			C: HBO					

Acu, acupuncture; MT, medication therapy; RT, rehabilitation therapy; EDA, Edaravone; NX, Naloxone; CM, yiqixingshen fan; rTMS, repetitive transcranial magnetic stimulation; HBO, hyperbaric oxygen therapy; NR, not referred; Year, publication year; w, week; T, treatment group; C, control group; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale.

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high risk of bias because it measured the primary outcome in part of the population. In the evaluation of a selection of the reported results, all of the studies could be rated as having some level of concern about bias because of the absence of protocols of included trial. As for the overall bias, most of the trials (88.2%) (21–25, 28–37) were rated as having a high risk of bias, while the remaining two trials (11.8%) (26, 27) were rated as having some level of concerns about bias. The specific information is presented in Figure 2.

Outcomes of meta-analysis

The Glasgow Coma Scale

The GCS was reported in 16 articles (94.1%) (21–30, 32–37). Because of the considerable heterogeneity of the included studies, we used a random-effects model for the corresponding analysis. Results showed that the advancement of GCS scores in the acupuncture group was better than that in the non-acupuncture group (MD 1.45, 95% CI 0.94–1.97, $P < 0.0001$; Figure 3).

Glasgow Outcome Scale

Moreover, only one article reported GOS as the primary outcome (26). The experimental group applied acupuncture plus medication therapy, while the control group used medication therapy. The result indicated that the improvement of GOS scores in the acupuncture plus medication group was greater than in the medication group (MD 0.58, 95% CI 0.11 to 1.05, $P = 0.01$).

Resuscitation rate

Four studies reported the resuscitation rate as an indicator (21, 23, 26, 31). Included studies showed no significant heterogeneity, and the fix-effects model was used for the analysis. The result showed that the resuscitation rate was substantially higher in the acupuncture plus medication group than in the medication group (RR 1.68, 95% CI 1.30–2.18, I2 0%, $P = 0.39$; Figure 4).

Resuscitation time

Only one study reported resuscitation time (22). Results showed that acupuncture in conjunction with medication could significantly shorten resuscitation time than medication alone (MD −0.89, 95% CI −1.53 to −0.25, $P = 0.006$).

Adverse events

Two studies reported adverse events were reported in two studies (26, 27) (11.8%) reported adverse events. Both trials reported one case in the acupuncture group suffering from subcutaneous hematoma, respectively. Fortunately, the symptoms were obviously alleviated after general treatment.

Subgroup analysis

Acupuncture in conjunction with medication vs. medication

Fifteen (21–35) trials compared acupuncture plus medication with medication by GCS. However, one trial (31) only evaluated the GCS score of the awakened patients. So 14 trials (82.35%) (21–30, 32–35) with 898 participants were included in the final analysis. A random effects model assessed the effects due to significant heterogeneity. Results showed that GCS in the acupuncture plus medication group was significantly higher than in the medication group (MD 1.81, 95% CI 1.24–2.39, $P < 0.0001$; Figure 5).

Acupuncture in conjunction with rehabilitation vs. rehabilitation

Two (11.76%) (36, 37) trials with 108 participants compared acupuncture plus rehabilitation with rehabilitation by GCS. Considering the minor heterogeneity, we applied the fixed effects model to analyze the effects. The result showed that GCS in the acupuncture plus rehabilitation group was significantly higher than in the rehabilitation group (MD 2.48, 95% CI 1.42–3.53, $P < 0.0001$; Figure 6).

Acupuncture vs. medication

Three trials (17.65%) (33–35) with 214 participants compared acupuncture with medication by GCS. The fixed effects model was used because no obvious heterogeneity was found. The result showed no significant difference between the acupuncture and medication groups (MD −0.08, 95% CI −0.43 to 0.27, $P = 0.64$) (Figure 7).

Acupuncture vs. rehabilitation

One trial (5.88%) (37) with 60 participants compared acupuncture with rehabilitation by GCS. Results showed no significant difference between the acupuncture and rehabilitation groups (MD 0.17, 95% CI −1.34 to 1.68, $P = 0.82$).

FIGURE 2
Assessment of risk of bias (ROB2) using the Cochrane tool. **(A)** ROB graph and **(B)** ROB summary.

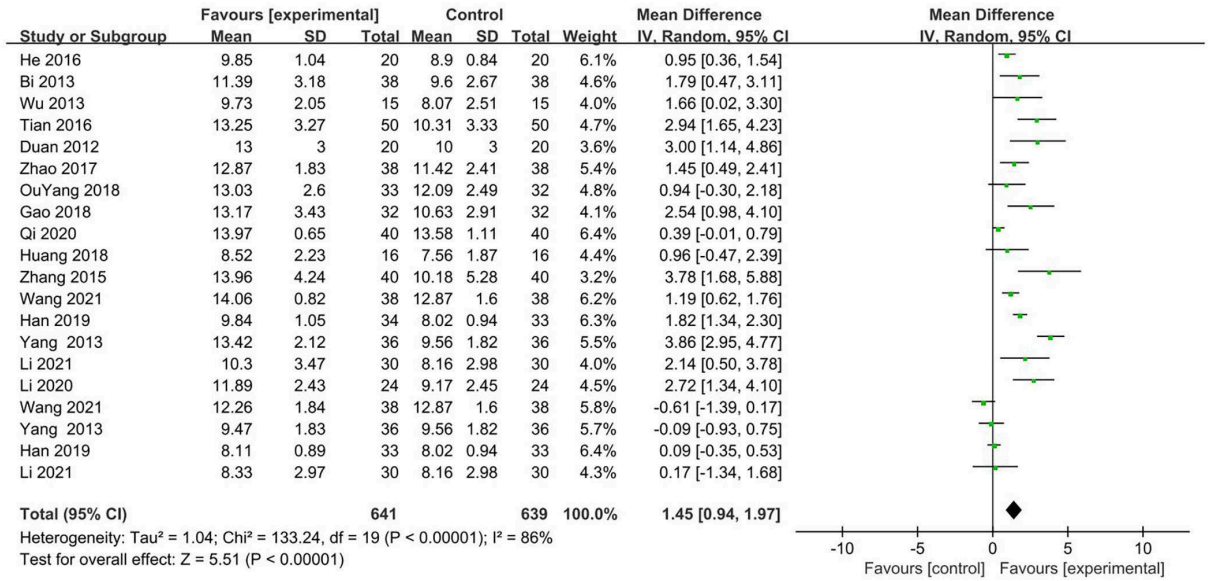

FIGURE 3
Forest plot and meta-analysis of GCS (Glasgow coma scale).

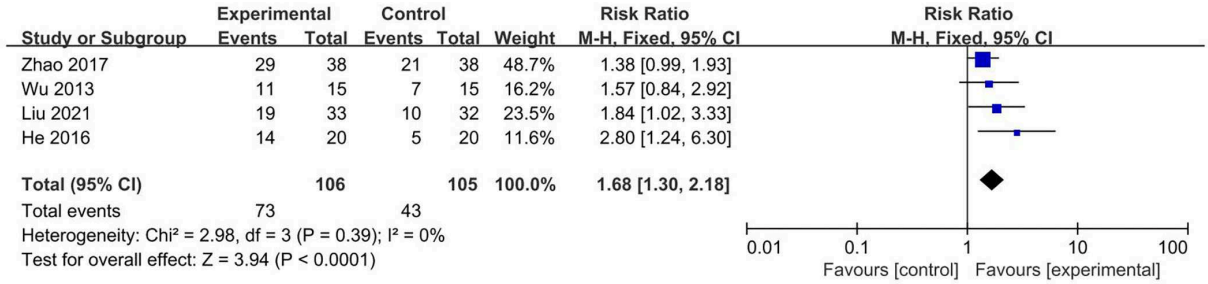

FIGURE 4
Forest plot and meta-analysis of resuscitation rate.

Sensitivity analysis

Different effect models may affect the analysis of the results; therefore, we tested the stability of the meta-analysis by comparing the difference between the fixed-effects model and the random-effects model. It showed that there were no significant differences between the two statistical models. The detailed results are shown in Table 2.

Quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of confidence for included studies. The results generally showed a very low level of evidence concerned with the fact that acupuncture can improve GCS, resuscitation rate, and resuscitation time in post-stroke patients with DOC. Although the level of evidence is moderate regarding the effect of acupuncture in promoting GOS, this result is limited by the small sample size. Specific information is listed in Table 3.

Publication bias

Publication bias was evaluated with a funnel plot. The results showed that the distribution of the funnel plot failed to be symmetrical, and the lower part of the graph was vacant. According to the results, included studies may have potential publication bias (Figure 8).

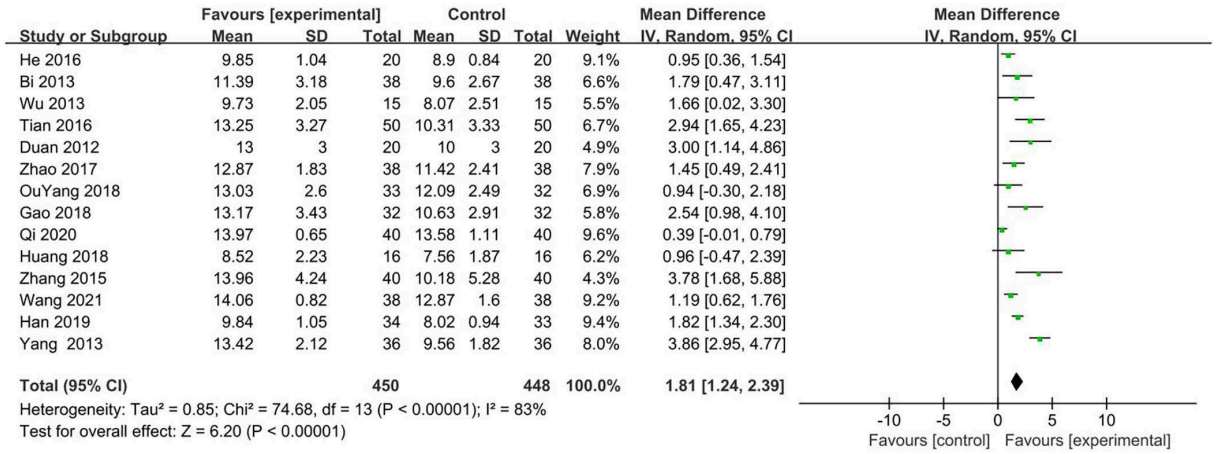

FIGURE 5
Forest plot of GCS (Glasgow coma scale) comparing acupuncture plus MT (medication therapy) vs. MT (medication therapy) alone.

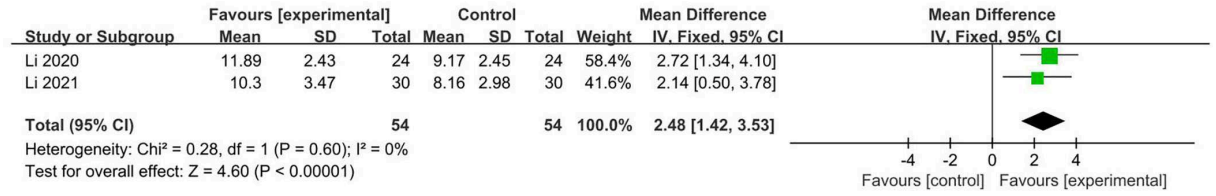

FIGURE 6
Forest plot of GCS (Glasgow coma scale) comparing acupuncture plus RT (rehabilitation therapy) vs. RT (rehabilitation therapy) alone.

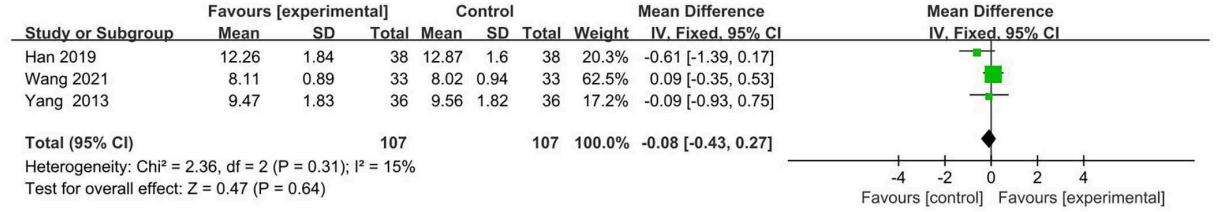

FIGURE 7
Forest plot of GCS (Glasgow coma scale) comparing acupuncture vs. MT (medication therapy) alone.

Discussion

In our systematic review, 17 RCTs involving 1,208 patients were eventually included for meta-analysis. Results showed that acupuncture might be more effective in improving consciousness, increasing resuscitation rate, and shortening resuscitation time than those patients without acupuncture intervention. According to our subgroup analysis, compared to medication and rehabilitation alone, acupuncture plus medication and acupuncture plus rehabilitation had more advantages in improving GCS for stroke patients with DOC. Additionally, two studies reported acupuncture-related adverse events, which were mild subcutaneous hematoma and obviously alleviated after general treatment. The results of sensitivity analysis showed that the effect of acupuncture was relatively stable, but the findings in our study had been influenced by methodological flaws and should be considered with caution.

It is worth mentioning that our results suggest that acupuncture combined with drugs and rehabilitation therapy is far more effective than drugs and rehabilitation alone. There may be two reasons for this: one is the superposition of the therapeutic effects of acupuncture itself, and another may be

TABLE 2 Results of the sensitivity analysis.

Study type	Study quantity	Participants		Study heterogeneity				Analysis model	MD (95% CI)	*P*-value
		Experiment group	Control group	chi^2	*df*	I^2,%	*P*-value			
GCS										
Acu plus MT vs. MT	14	450	448	74.68	13	0.83	<0.0001	Random	1.81 (1.24, 2.39)	<0.0001
								Fixed	1.34 (1.13, 1.55)	<0.0001
Acu plus RT vs. RT	2	54	54	0.28	1	0	0.60	Random	2.48 (1.42, 3.53)	<0.0001
								Fixed	2.48 (1.42, 3.53)	<0.0001
Acu vs. MT	3	107	107	2.36	2	0.15	0.31	Random	−0.11 (−0.51, 0.29)	0.60
								Fixed	−0.08 (−0.43, 0.27)	0.64
Acu vs. RT	1	30	30	*	*	*	*	Random	0.17 (−1.34, 1.68)	0.82
								Fixed	0.17 (−1.34, 1.68)	0.82
Resuscitation rate										
Acu plus RT / RT	4	106	105	1.38	3	0	0.71	Random	3.33 (1.86, 5.97)	<0.0001
								Fixed	3.34 (1.87, 5.95)	< 0.0001

Acu, acupuncture; MT, medication therapy; RT, rehabilitation therapy; CI, confidence interval; df, degrees of freedom; MD, mean difference; GCS, Glasgow Coma Scale.
*Insufficient data.

the possible synergistic effect between acupuncture and other therapies. A study by Xia et al. (38) explored the synergistic effects of electro-acupuncture and bone mesenchymal stem cell transplantation on repairing thin endometrial injuries in rats and found that electro-acupuncture promotes the paracrine effect of BMSCs at the site of local injury and improves the ability of BMSCs to differentiate into cells required for tissue regeneration. Another study by Zhou et al. (39) discussed the synergistic and attenuated effects of electro-acupuncture for aconitine in the treatment of heart failure and concluded that electro-acupuncture achieves the synergism/attenuation effect of aconitine for the improvements in heart failure probably by upregulating the expression of SERCA2a and downregulating the expression of PLB. The research team led by Zhou et al. (40) found that acupuncture can significantly improve the respiratory function of asthmatics and increase metallothionein-2 (MT-2) protein content, which was validated as a new target for bronchial asthma. All these findings suggest that acupuncture might represent a good alternative or complementary treatment to conventional management in clinical settings by the same or unique mechanism, which is worth further discussion and exploration.

Several acupoints could be applied in acupuncture manipulation, as shown in Table 1. In all the included studies, the most commonly used acupoints were Shuigou acupoint (GV26), which was used in 16 studies; Neiguan acupoint (PC6), used in 12 studies; Sanyinjiao acupoint (SP6), used in nine studies; and Baihui acupoint (GV20), used in 10 studies. Several studies have revealed that acupuncture could achieve satisfactory treatment effects on stroke, especially for DOC (41, 42). Najem's study (43) indicated that acupuncture could reduce the efficacy of secondary brain injuries by reducing systemic and local inflammation, oxidative stress, intracellular calcium overload, neuronal regeneration, and growth factor release. Tang's research also revealed that acupuncture could activate genes modulating neuronal projections (P2rx7, P2rx3, Trpv1, Tacr1, and Cacna1d), protein secretion (Exoc1, Exoc3l1, Fgb, and Fgr), and dopamine (DA) receptor D3 (Drd3) in the ventral periaqueductal gray (vPAG), as well as the expression and excitability of DA and P2RX7 neurons (44). These may be the potential mechanisms of acupuncture for consciousness improvement in patients following stroke.

Previous systematic reviews have paid attention to the effect of acupuncture on disorders of consciousness after traumatic brain injury (45, 46). Their pooled analyses indicated that acupuncture might have a superior effect on GCS score, GOS score, efficacy rate, ADL, and mortality. However, no review has reported the efficacy of acupuncture on consciousness disorders after stroke. To the best of our knowledge, this meta-analysis of 17 clinical types of research is the first systematic review to address this topic. Therefore, this is a big step forward. We rigorously carried out this meta-analysis according to the Cochrane Collaboration and PRISMA guidelines. Eligible RCTs in seven electronic databases were extensively searched. As the primary outcome measures, GCS and GOS scores have been widely used in the clinic to assess consciousness in stroke patients. However, only one article applied GOS to evaluate the prognosis of the patient, which was a pity. Despite its simplicity, GOS is still the most widely used instrument for measuring the outcome of DOC (47, 48). Therefore, future research is required to focus on this indicator to better observe the outcome of

TABLE 3 Summary of findings and strength of evidence for outcomes.

Acupuncture for disorders of consciousness in patients with stroke

Patient or population: patients with the conscious disorder after stroke

Settings:: Hospitals in mainland China

Intervention: Acupuncture

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	GCS				
GCS		The mean gcs in the intervention groups was One higher (0.82 to 1.17 higher)		1,280 (16 studies)	⨁⊖⊖⊖ very low1,2,3	
GCS - Acu plus MT vs. MT		The mean gcs - acu plus mt vs. mt in the intervention groups was 1.34 higher (1.13 to 1.55 higher)		898 (14 studies)	⨁⊖⊖⊖ very low1,2,3	
GCS - Acu plus RT vs. RT		The mean gcs - acu plus rt vs. rt in the intervention groups was 2.48 higher (1.42 to 3.53 higher)		108 (2 studies)	⨁⊖⊖⊖ very low1,2,3	
GCS - Acu vs. MT		The mean gcs - acu vs. mt in the intervention groups was 0.08 lower (0.43 lower to 0.27 higher)		214 (3 studies)	⨁⊖⊖⊖ very low1,2,3,4	
GCS - Acu vs. RT		The mean gcs - acu vs. rt in the intervention groups was 0.17 higher (1.34 lower to 1.68 higher)		60 (1 study)	⨁⊖⊖⊖ very low1,2,4	
GOS		The mean gos in the intervention groups was 0.58 higher (0.11 to 1.05 higher)		76 (1 study)	⨁⊖⊖⊖ moderate3	
Resuscitation rate		Study population	OR 3.34 (1.87 to 5.95)	211 (4 studies)	⨁⊖⊖⊖ very low1,2,3	
	410 per 1,000	698 per 1,000 (565 to 805)				
	Moderate					
	390 per 1,000	681 per 1,000 (545 to 792)				
Resuscitation time		The mean resuscitation time in the intervention groups was 0.89 lower (1.53 to 0.25 lower)		76 (1 study)	⨁⊖⊖⊖ very low1,2,3	

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; OR, odds ratio.

GRADE Working Group grades of evidence. High quality: Further research is unlikely to change our confidence in the effect estimate. Moderate quality: Further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

1 The overall quality of rob is low. 2Two fail to provide the study protocol, and the study design and data collection have obvious shortcomings. 3 see the result of publication Figure 5. 4 NO so related to the study found.

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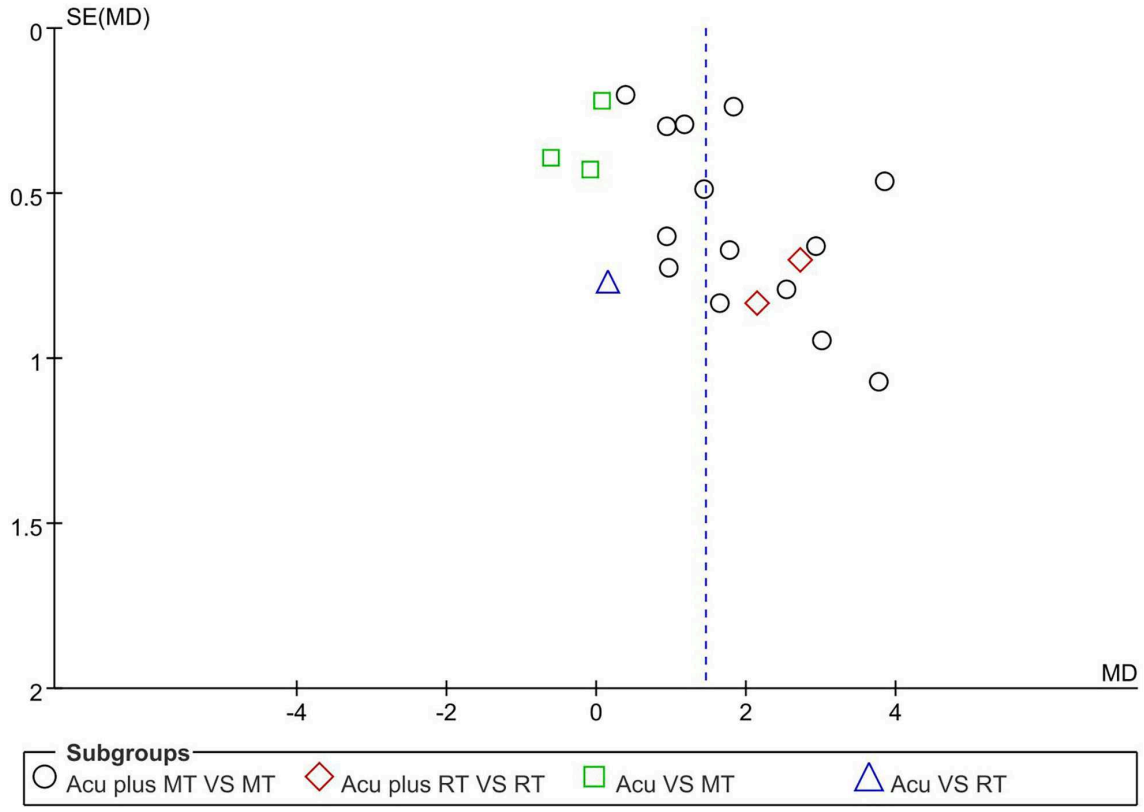

FIGURE 8
Funnel plot of GCS (Glasgow coma scale).

patients and provide more comprehensive data for future meta-analysis. To some extent, our findings provide evidence for the clinical application of acupuncture in stroke patients with DOC.

However, there are still some limitations in our research. Our results were encouraging but not convincing because most trials had a high risk of bias, which may have caused an overestimation or underestimation of the true treatment effect. Firstly, all the included 17 articles were published in China, which may affect the generality of the results. Secondly, the result of the funnel graph also showed a potential publication bias; this could be that most of the included articles were of positive results, and articles with negative results were more difficult to publish. Then, some research results may be against the interests of the funder, forced to be stranded, and cannot be published. Thirdly, the number of studies included was extremely limited, with only 17 papers included in the total, with a maximum sample size of only 114. The treatment duration, frequency of acupuncture, and acupoint selection also varied a lot. Fourthly, allocation concealment and blinding methods were ignored in most studies, with only two (26, 27) studies specifying the allocation concealment and blinding method. Fifthly, despite subgroup analysis, there is still heterogeneity in some comparisons, such as Figure 5, which compared acupuncture plus medication with medication by GCS. The reason may be different drugs or different selected acupoints, and we hope that as more and more studies appear, more accurate analyses and conclusions can be drawn. All the above factors may lead to large heterogeneity, which limits the reliability of the results. Thus, to obtain a more definitive answer to the question of the efficacy of acupuncture for DOC, the field needs more carefully designed and conducted trials. Researchers should use adequate randomization methods and ensure that the group assignment is adequately concealed. Those techniques are both critical to avoiding systematic differences between the baseline characteristics of the compared groups. Because it is almost impossible for a therapist to be blinded to the acupuncture intervention, it may be important to blind the participants and the outcome assessor.

Conclusion

Acupuncture may be more effective in improving consciousness level, increasing the resuscitation rate, and shortening resuscitation time than in patients without acupuncture intervention. Adverse events from

acupuncture were rare, tolerable, and recoverable. However, the results should be interpreted cautiously, and more rigorous RCTs with better methodology are warranted in the area.

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

TL was responsible for the study's design, supervision, and manuscript revision. ZH and YC contributed equally by both drafting the manuscript and undertaking the trial registration. QX, WK, KL, YJ, XW, WQ, and YL were involved in the interpretation of the study findings. All authors commented on early drafts and approved the final version of the manuscript.

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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.2022.930546/full#supplementary-material

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Decision tree model based prediction of the efficacy of acupuncture in methadone maintenance treatment

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Background: Patients with MMT often face difficulties such as sleep disturbance, headaches, and difficulty in complete abstinence from drugs. Research has shown that acupuncture can mitigate side effects while attenuating methadone dependence. It also has a synergistic and attenuated effect on methadone maintenance treatment (MMT). Exploring the predictors of the efficacy of acupuncture intervention in MMT might help clinicians and patients promote acupuncture-assisted participation in MMT, and improve clinical treatment strategies for MMT.

Objective: To describe the effect of potential predictors on MMT after acupuncture intervention by building a decision-tree model of data from *A Clinical Study of Acupuncture-assisted MMT*.

Design, setting, and participants: In this randomized controlled trial, 135 patients with MMT underwent acupuncture at the Substance Dependence Department of Guangzhou Huiai Hospital in Guangzhou, Guangdong Province, China.

Intervention: A total of 135 patients were 1:1 randomly assigned to either an acupuncture plus routine care group (acupuncture plus methadone) or a routine group (methadone only) for 6 weeks, and followed up for 10 weeks. Sex, age, education level, route of previous opioid use, years of opioid use, and MMT time were recorded before the trial.

Outcome measurements and statistical analysis: All analyses were based on the intention-to-treat (ITT) population. The two decision tree models used the change of methadone dosage and the VAS score for opioid desire as response variables, respectively, and the evaluation criteria were positive effect (decreased by ≥20%) and no effect (decreased by<20%, or increased). We generated the respective feature weights for the decision tree and evaluated the model's accuracy and performance by Precision-Recall.

Results: The overall accuracy of methadone reduction and psychological craving VAS scoring decision trees were 0.63 and 0.74, respectively. The Methadone Dosage Efficacy decision tree identified years of opioid use (weight = 0.348), acupuncture (weight = 0.346), and route of previous opioid use (weight = 0.162) as key features. For the VAS Score decision tree, acupuncture (weight = 0.618), MMT time (weight = 0.235), and age (weight = 0.043) were the important features.

Conclusion: Exploratory decision tree analysis showed that acupuncture, years of opioid use, route of previous opioid use, MMT time, and age were key predictors of the MMT treatment. Thus, acupuncture-assisted MMT strategy should consider the relevant influencing factors mentioned above.

Patient summary: Understanding patient characteristics and the impact of acupuncture regimens on methadone dosage reduction in MMT patients may help physicians determine the best treatment regimen for patients. An analysis of data from our clinical trial showed that acupuncture, years of opioid use, route of previous opioid use, age, and MMT time were key predictors of progressive recovery in patients with MMT. Eligible patients may benefit most from the MMT rehabilitation that reduces consumption and psychological cravings for methadone.

Clinical trial registration: http://www.chictr.org.cn/index.aspx, identifier: ChiCTR1900026357.

KEYWORDS

methadone maintenance treatment, machine learning, decision tree, feature importance, acupuncture

Introduction

Global drug abuse presents several serious challenges. Nearly 275 million people were drug addicts in 2021 (1). In North America, opioid overdoses and deaths have been declared public health emergencies (2, 3). Currently, methadone maintenance treatment (MMT) is the mainstay of treatment for opioid abuse. Patients need to take methadone over the long term, or even for life, which often causes symptoms such as sleep disturbance, dry mouth, sweating, fatigue, constipation, and mental desire (4, 5). Due to the above adverse reactions, methadone patients often take a variety of drugs. Methadone often attenuates the effects of these other drugs, which in turn leads to withdrawal and an increased risk of relapse (6). Thus, patients generally have a strong desire for methadone reduction.

In recent years, extensive research has been conducted on how acupuncture improves the quality of life for patients with MMT, reduces heroin craving (7, 8), and facilitates methadone dose reduction. Additionally, acupuncture-assisted MMT has the advantages of affordability, reliable efficacy, and safety (9). Studies have shown that acupuncture, especially body acupuncture and electroacupuncture, can prolong patients' drug withdrawal time. Moreover, they were two times less likely to relapse than sham groups, and they have also reported mental benefits during withdrawal, such as relief from anxiety, depression, and insomnia (10–12). Acupuncture-assisted MMT can also improve desire, affect expectations, and quality of life for patients taking methadone. It also can facilitate reductions in methadone doses (13, 14).

Our previous studies, and those of other teams, have demonstrated the effects of acupuncture-assisted MMT (3). Yet it remains unclear which acupuncture-based factors influence methadone reduction. Determining this would be of utmost importance in decision-making for acupuncture-assisted MMT treatment. Machine learning offers a way to uncover the relationship between various factors and analyze the associated variables' degree of influence (15). Many machine learning algorithms are black-box theories, and the decision tree model is an important machine learning tool for decision analysis, due to its visualization and interpretability characteristics (16). In this study, we use a decision tree model to analyze data from a randomized controlled trial (RCT) to investigate the effects of acupuncture on MMT. This could help clinicians identify which patients may have varying degrees of influence on treatment outcomes.

For these reasons, this study aims to use a decision tree, a classic algorithm for machine learning, to explore the influence of methadone reduction factors and the relationship between

the variables of methadone reduction and craving (acupuncture, age, sex, education level, route of previous opioid use, years of opioid use, and MMT time).

Materials and methods

Study design

The data we selected came from our previous clinical RCT, which was a study of acupuncture-assisted methadone reduction. A total of 135 patients with MMT were recruited from the methadone outpatient clinic at the Substance Dependence Department of Guangzhou Huiai Hospital, from October 2019 to September 2020. We randomly divided them into an acupuncture plus routine care group and a routine group (the acupuncture plus routine care group used body acupuncture plus methadone; the routine group used methadone alone). This was done *via* a central randomization system (SAS 9.4) at a 1:1 ratio, and the two groups included 68 and 67 patients, respectively. The trial lasted 6 weeks and was followed up for 10 weeks. Details about the study design for the RCT are provided in the Supplementary materials. We then established decision tree models of daily methadone consumption and visual analog scale (VAS) score, respectively, and generated weights for each feature to evaluate acupuncture's influence on methadone reduction. The protocol was approved by the Ethics Committee at the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. Y-2019-241), and registered in the Chinese Clinical Trial Registry (ChiCTR1900026357).

Predictor selection

The dosage of methadone is related to factors such as patients' sex, age, education, and psychological stress (17, 18). Combined with the researchers' judgment on the clinical efficacy and clinical trial design of our previous RCT, we chose acupuncture, age, sex, education level, route of previous opioid use, years of opioid use, and MMT time as our feature index ultimately.

Outcomes

Daily dosage of methadone

Patients' daily methadone consumption from the baseline to the 2nd, 4th, and 6th weeks was recorded on a computer by the prescribing physician at the clinic. We observed changes in methadone dose from baseline to the 6th week.

VAS score for methadone craving

Participants were asked to mark their level of craving on a 100 mm line, with 0 representing no craving and 100 representing strong craving (19). VAS scores were recorded from the baseline to the 2nd, 4th, and 6th weeks. We observed changes in VAS scores from baseline to the 6th week.

Efficacy evaluation criteria were divided into two categories

Comparison of the differences between methadone dosage and VAS score before and after 6 weeks of treatment; decreased by $\geq$20% was a positive effect, decreased by <20% or increased was no effect. These classification criteria are based on a guideline that say in the process of methadone reduction, there should be a 5–10 ml reduction within every 1-2 weeks or a reduction of 10% of the current dose. (20). Our RCT lasted 6 weeks. Patients with a 20% reduction in the methadone dosage and the VAS score generally show improvement in sleep status and heart disease relief. Therefore, we chose 20% as the basis for division.

Statistical analysis

Baseline characteristics and results comparison

In this study, all analyses were based on the intention-to-treat (ITT) population. We conducted a descriptive statistical analysis of the description of the baseline characteristics and the comparison of the results. Measurement data were described by means, and to compare the means between the two groups, we used an independent sample *t*-test. Enumeration data were described by frequency, and comparisons of differences between the two groups were assessed with a χ^2 test. All statistical tests were analyzed in SPSS version 25 (IBM SPSS Statistical Software, New York, USA). $P < 0.05$ (two-sided) was considered statistically significant.

Decision tree model

We performed decision tree modeling on data from the ITT population to describe and visualize the impact of potential predictors on methadone dosage based on acupuncture interventions.

In the decision tree, the data set consisted of a series $\{(x_1, y_1),(x_2, y_2),\ldots, (x_n, y_n)\}$. Each iteration contains an input x_i, which may include multiple characteristics (for example, age, sex, education...) and a class y_i, (for example positive or no effects…). This data set is called the training set. Classification tasks must meet the following functions: $f(x_i) = y_i$, which means each input has a corresponding category. To obtain a high-performance generalization model, f needs to satisfy the generalization function. When given a data point m that is not in the training set, $f(m)$ should output the correct label.

Generating a decision tree is a recursive process that does a good job of breaking up our data, and the basic flow follows a simple "divide and conquer" strategy. The decision tree consists

of a root node, several leaf nodes, and several internal nodes. All decision trees start at a root node at the top of the tree, dividing the dataset into a hierarchy of subsets, represented by branch-like segments, and ending with the leaves of the described subsets. The root node contains the complete set of samples, the leaf node corresponds to the decision result, and the path from the root node to each leaf node corresponds to a decision test sequence. The splitting selection of nodes is based on the minimum Gini coefficient to produce the possible attributes and possible values.

A total of 135 people participated in our study. After cleaning and normalizing the data in the database, we took the sex, age, education level, participation in acupuncture treatment or not, years of opioid use, route of previous opioid use, and MMT time as independent variables, and methadone reduction and VAS score (positive or no effect) as dependent variables to establish a database. In the two classification attributes, the data are roughly evenly distributed. In the methadone reduction and VAS score data set, 72 samples and 68 samples had a positive effect, and 63 samples and 67 samples had no effect, respectively. As there was no missing data, the missing value was not filled. We randomly divided the 135 participants into two groups: one to serve as the training set to build the decision tree model (consisting of 80% of the total), and the other to verify the model's accuracy (the other 20%).

In the process of building a decision tree, we used the grid search method to iterate over the parameters of the decision tree and used the 10-fold cross-validation method to perform multiple verifications, with the highest scoring parameters as the results of the grid search. After the test, we selected Precision, Recall, F-1 score, and Accuracy as indicators to evaluate the decision tree model's performance. Precision is the number of real positive samples among the total positive samples, reflecting the model's ability to predict the accuracy of the positive samples. Recall rate is the samples predicted to be positive and which actually are positive, accounting for all positive samples, reflecting the model's ability to predict the completeness of the positive samples. The *F1* score is the weighted harmonic average of precision and recall. The closer the three metrics are to 1, the better the model performance, and the closer to 0, the worse the model performance. Finally, we obtain the optimal parameter values for the decision tree. Figure 1 shows the study design and technical roadmap. For decision tree construction, we used the scikit-learn Python package version 1.0.1 (21).

Results

Patient disposition and baseline characteristics

During the trial period, 135 patients were randomly assigned at a ratio of 1:1 to either an acupuncture plus routine care group or a routine group. The patient baseline characteristics are listed in Table 1. There were no statistically significant differences in age, sex, years of opioid use, MMT time, education, or route of previous opioid use between the two groups ($P > 0.05$). This indicated that the baseline data for the two groups were balanced and comparable.

Outcomes of effectiveness

As shown in Table 2, we used the methadone dosage efficacy and the VAS score efficacy as observational outcomes. They were also the output variables in the decision tree.

Methadone dosage efficacy

In the acupuncture plus routine care group, 48 patients (70.6%) had a positive effect of reducing methadone dosage by more than 20% over 6 weeks, while in the routine group, only 24 patients (35.8%) had a positive effect. Twenty (29.4%) patients in the acupuncture plus routine care group did not reduce methadone by more than 20% (no effect). Among the routine group, there were 43 (64.2%) such patients. Statistical analysis of the differences between the two groups showed $P<0.001$, indicating that the efficacy of methadone reduction was significantly different between the two groups. Additionally, the acupuncture plus routine care group had significantly better efficacy in reducing methadone dosage than the routine group.

VAS score efficacy

Sixty patients (88.2%) in the acupuncture plus routine care group had a positive effect (VAS score had decreased more than 20% over 6 weeks), while there were eight of such patients (11.9%) in the routine group. In comparison, eight (11.8%) patients in the acupuncture plus routine care group and 59 (88.1%) patients in the routine group had no effect <a 20% decrease in the VAS score. Statistical analysis showed that there was a statistical difference in the VAS score efficacy between the two groups ($P < 0.001$), and the acupuncture plus routine care group had better efficacy in relieving methadone craving.

Model performance

Model evaluation

We built the decision tree based on the trained model, and the model evaluation results are shown in Table 3.

We used test sets to evaluate the decision tree model's accuracy. The precision, recall, and *F1* score of the two decision tree models are summarized in Table 3. The test set is the data that has not been utilized in training the decision tree.

The accuracy of the methadone dosage efficacy decision tree model was 0.63, while the VAS score efficacy decision tree model was 0.74.

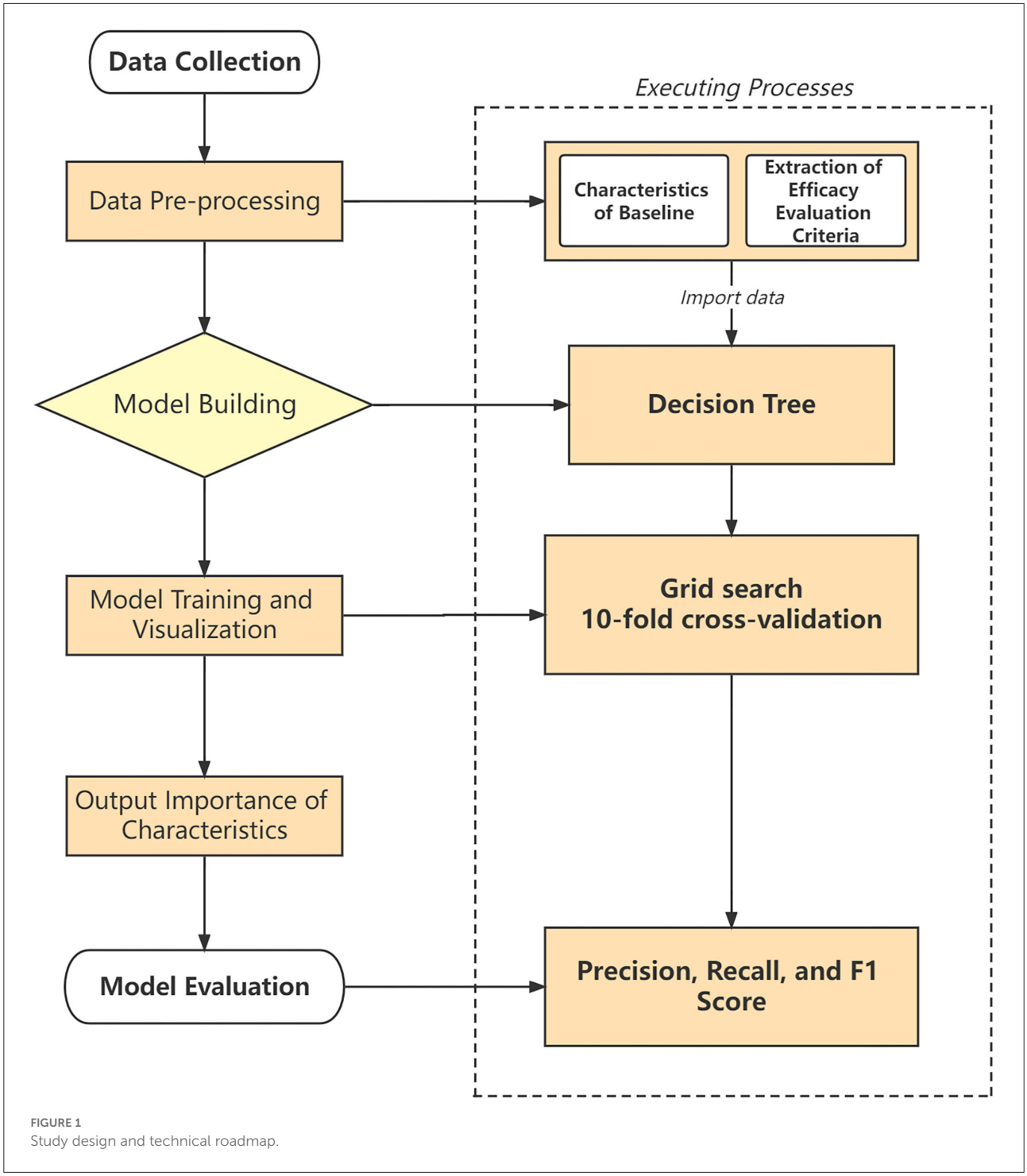


FIGURE 1
Study design and technical roadmap.

Constructing the decision tree model

As Figures 2, 3 show, the decision trees are constructed in pairs because there are two efficacy criteria based on the effect of acupuncture on the methadone effectiveness index and VAS index. The closer it is to the top of the decision tree, the more important the feature is; the closer it is to the bottom of the decision tree, the less the factors are correlated.

The criteria of the Methadone Dosage Efficacy decision tree model were evaluated by the Gini coefficient, while the VAS score efficacy decision tree was evaluated by the Entropy coefficient. In the methadone reduction model, the maximum

TABLE 1 Baseline characteristics of the study.

Variable	Acupuncture plus routine care group ($n = 68$)	Routine group ($n = 67$)	*P*-value
Age, mean ± SD	51.47 ± 4.72	49.46 ± 8.24	0.401
Sex (%)			0.371
Male	55 (80.9)	58 (86.6)	
Female	13 (19.1)	9 (13.4)	
Years of opioid use (year), mean ± SD	16.72 ± 5.86	15.60 ± 8.58	0.246
MMT time, (year), mean ± SD	8.34 ± 3.87	7.13 ± 3.38	0.071
Education (%)			0.468
primary school	13 (19.1)	18 (26.9)	
Middle school	28 (41.2)	22 (32.8)	
High school or university	27 (39.7)	27 (40.3)	
Route of previous opioid use (%)			0.146
Injection	51 (75)	41 (61.2)	
Nasal	14 (20.6)	18 (26.9)	
Oral	3 (4.4)	8 (11.9)	

SD, standard deviation.

TABLE 2 Outcomes of efficacy evaluation criteria.

	Acupuncture plus routine care group	Routine group	*P*-value
	($n = 68$)	($n = 67$)	
Methadone dosage efficacy (%)			<0.001
Positive effect	48 (70.6)	24 (35.8)	
No effect	20 (29.4)	43 (64.2)	
VAS score efficacy (%)			<0.001
Positive effect	60 (88.2)	8 (11.9)	
No effect	8 (11.8)	59 (88.1)	

depth of the decision tree was 4, and the maximum leaf nodes were 6. In the VAS model, the maximum depth of the decision tree was 5, and the maximum leaf nodes were 7.

As shown in Figure 2, acupuncture can significantly reduce methadone dosage when (1) the MMT time is ≤12.48 years, or (2) the MMT time is > 12.48 years, and opioid use is > 22.5 years. In short, judging from the positive effects of the acupuncture plus routine group, the shorter the MMT time, the easier it is for acupuncture to produce good results; when the MMT time as well as the opioid use time are both longer, the acupuncture can produce a positive effect.

As shown in Figure 3, acupuncture can reduce patients' methadone psychological craving when (1) the patient's age is > 43.5 years and the MMT time is ≤ 7.565 years, or (2) the patient's age is > 43.5 years and the MMT time is > 7.92 years. In general, in the acupuncture plus routine care group, when the patient is older and the MMT time is longer or shorter, acupuncture can produce positive results.

Feature importance

Figure 4 shows the factors that influenced the methadone dosage and the VAS score of psychological cravings. Figure 4A summarizes the most significant factors in the methadone dosage efficacy, they are (1) years of opioid use (weight = 0.348); (2) acupuncture (weight = 0.346); (3) route of previous opioid use (weight = 0.162); and (4) MMT time (weight = 0.143). Figure 4B summarizes the feature importance of the attributes that affect the VAS score: (1) acupuncture (weight = 0.681); (2) MMT time (weight = 0.235); (3) age (weight = 0.043); and (4) years of opioid use (weight = 0.041).

TABLE 3 P-R value and *F 1* score for each class.

	Precision	Recall	*F 1* score	Accuracy
Methadone dosage efficacy				0.63
Positive effect	0.60	0.69	0.64	
No effect	0.67	0.57	0.62	
VAS score efficacy				0.74
Positive effect	0.76	0.81	0.79	
No effect	0.70	0.64	0.67	

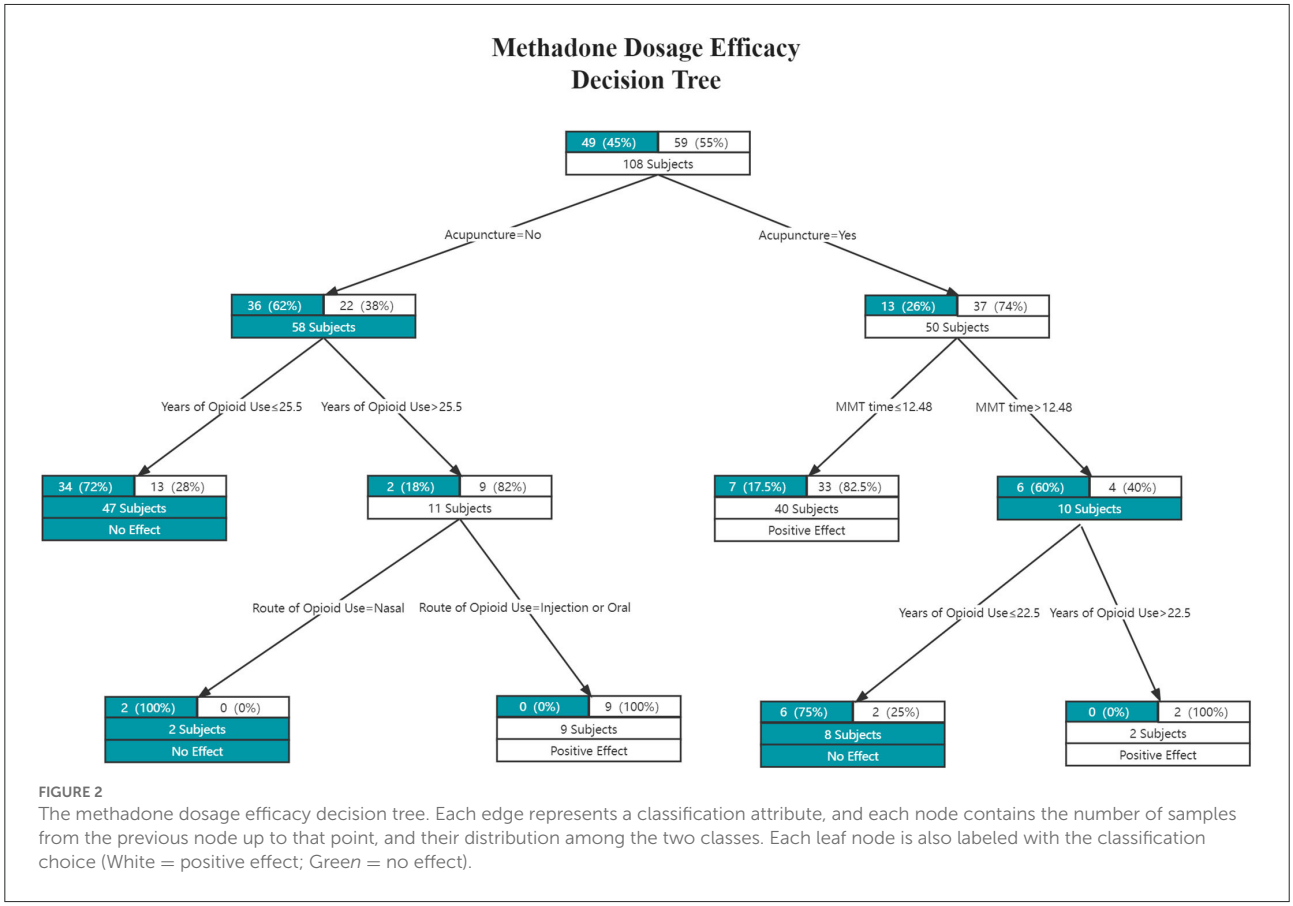


FIGURE 2
The methadone dosage efficacy decision tree. Each edge represents a classification attribute, and each node contains the number of samples from the previous node up to that point, and their distribution among the two classes. Each leaf node is also labeled with the classification choice (White = positive effect; Green = no effect).

Discussion

This study explores the important role of acupuncture in reducing methadone dosage and psychological cravings in patients with MMT. This is the first time that a decision tree algorithm has been used to explore the importance of acupuncture in the experimental process.

An exploratory decision tree model of this clinical trial data identified acupuncture, opioid use time, route of opioid use, age, and MMT time as common key predictors of recovery from MMT. Patients who meet these criteria appear to benefit the most from acupuncture initiated early in treatment.

In the two decision trees, we selected patients' age, sex, education, opioid use time, route of opioid administration, time on methadone, and whether they participated in acupuncture as predictors. In terms of the importance of feature contribution, the following feature values are all 0: for the characteristics of the methadone reduction index, education, age, and sex; in terms of psychological craving: sex, education, and the previous route of opioid use. They did not appear in Figure 4, suggesting that they did not play an important role in reducing methadone dosage and psychological craving.

In this study, characteristic importance analyzed by the decision tree revealed that the important features of both decision tree models were acupuncture, years of opioid use,

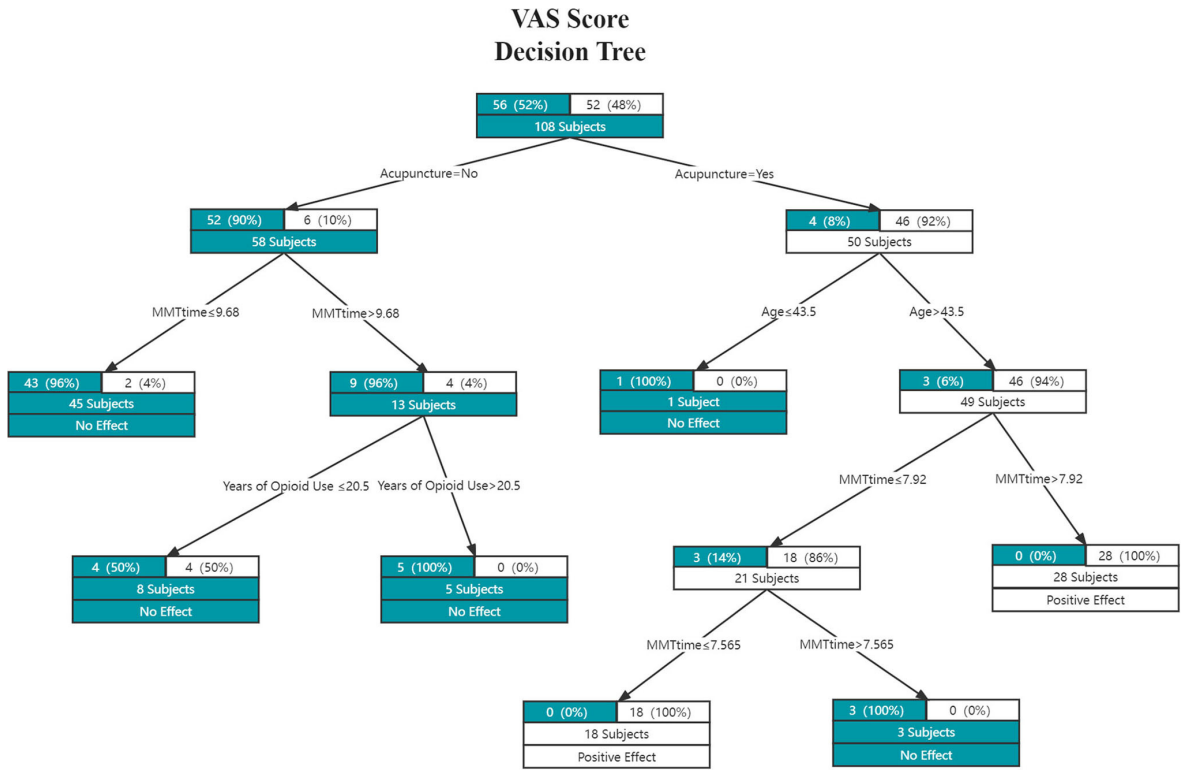
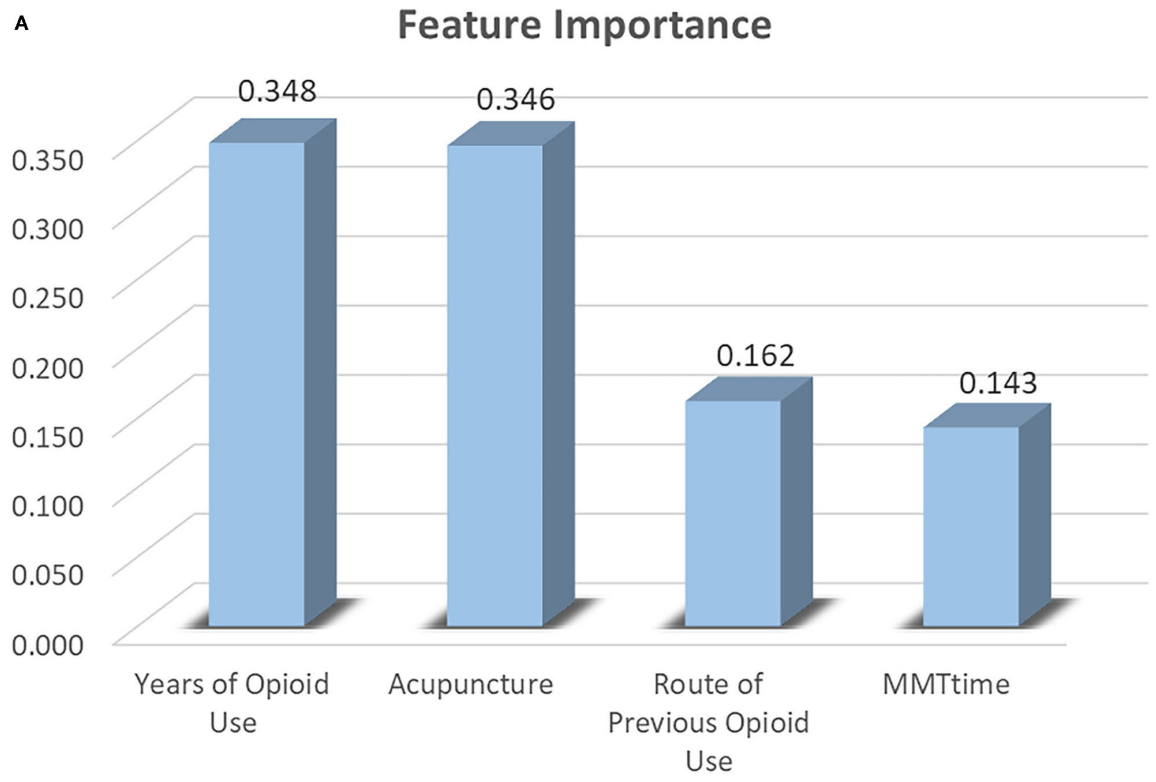


FIGURE 3
The VAS score efficacy decision tree. Each edge represents a classification attribute, and each node contains the number of samples from the previous node up to that point, and their distribution among the two classes. Each leaf node is also labeled with the classification choice (White = positive effect; Green = no effect).

and MMT time. We can speculate on the duration of opioid use, the duration of MMT treatment, and whether or not acupuncture has a significant impact on the VAS score and methadone reduction effect. In addition, acupuncture was at the forefront, playing the most important role in reducing patients' psychological craving for methadone, and in reducing methadone dosage. The findings of this study align with those of previous studies. After acupuncture intervention, the daily dose of methadone can be significantly decreased (7), and methadone patients' sleep quality significantly increases (8). At the same time, acupuncture as adjuvant therapy for MMT patients has the advantages of affordability, reliable efficacy, and safety (9). Additionally, body acupuncture plays a greater role than ear acupuncture, electro-acupuncture, transcutaneous electrical stimulation, Western medicine, and traditional Chinese medicine (22). These results are encouraging, as they offer guidance on combining opioid use time and MMT time so that acupuncture can play a greater role. They also provide specific guidance for clinical application.

Our decision tree model offers an upgrade to outcomes produced from a focus on MMT alone. Today, machine learning is widely used to assess opioid overdose risk, and to predict opioid use and relapse (23–25). David et al. established an "extreme random forest" prediction model to provide timely recommendations for local public health interventions to prevent drug overdose deaths (26). Dong et al. achieved high-precision automated predictions to support the healthcare industry in responding to the opioid crisis (27).

In machine learning, there are many ways to meet this requirement. The main reasons we chose the decision tree are: (1) The decision tree algorithm's calculation process is simple and clear, and it can generate easy-to-understand visual images. Unlike Logistic Regression (LR), Naïve Bayes Classification (NBC), Support Vector Machine (SVM), the Stochastic Gradient Boosting method (SGB) (28–31), Artificial Neural Network (ANN), K-Nearest Neighbor (KNN), and other learning algorithms; the decision tree can display the decision-making and classification process for each step. In the other aforementioned algorithms, it is difficult to know the specific training process, leaving researchers with a "black box". (2) It allows us to assess each feature's importance. In decision tree images, features closer to the root node tend to be more important than those located toward a leaf node. Since the decision tree algorithm always selects the optimal decision in which to split at each node, it plays an important role in predicting the main factors of event occurrence. Adway et al.



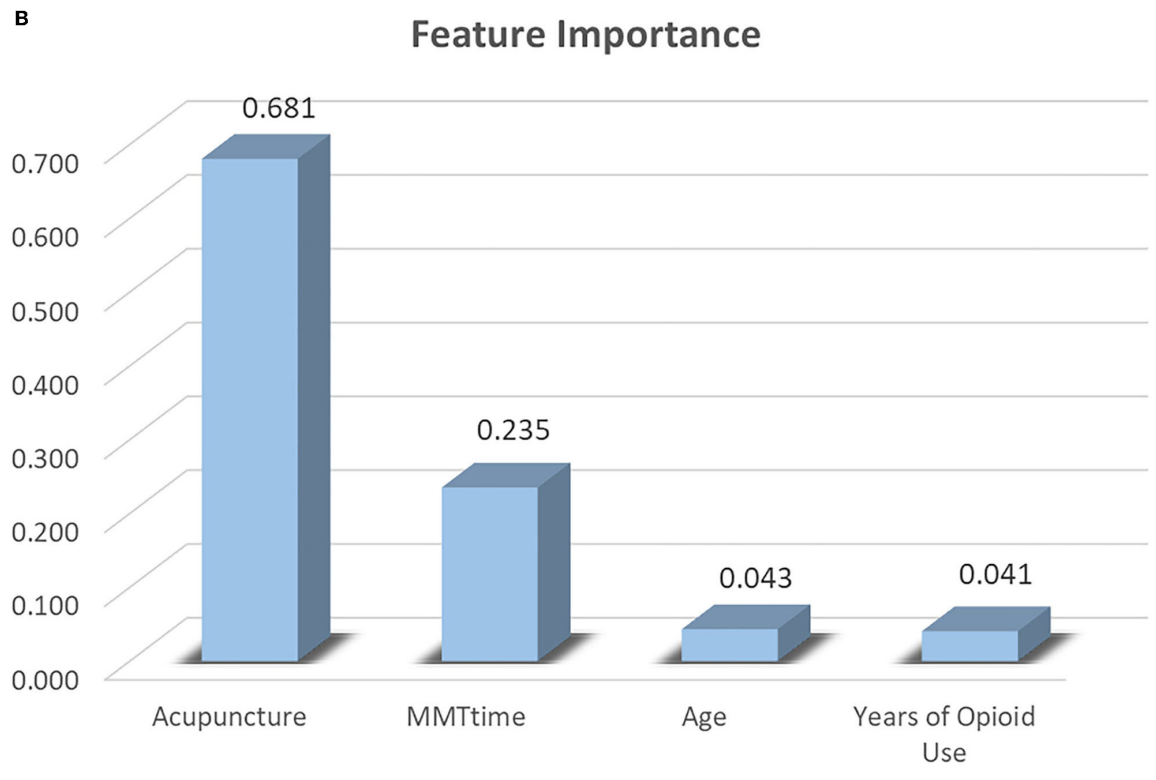


FIGURE 4
Feature importance. **(A)** Methadone dosage efficacy. **(B)** VAS score efficacy.

used a decision tree to explore the influence of the time factor for marijuana use on personal risk (32). Mehdi et al. used decision trees to explore the cost of purchasing drugs, age of first drug use, history of smoking cessation, MMT patients' medication frequency, methadone treatment frequency, and other factors that are associated with drug relapse (33). While most of the above studies have focused on the risks posed by opioids, in our study, we focused on patients' quality of life during MMT and explored the role of acupuncture with the help of a decision tree algorithm.

This study has several advantages over similar studies. First, we conducted a rigorous randomized controlled trial in the study's early stages, in which we obtained real MMT patient data to reflect the status of real individuals undergoing MMT. In addition, our study supplements the outcome measure of acupuncture-assisted methadone treatment reducing psychological craving in patients. We assessed this from both psychological and physical perspectives. Second, this is the first time that machine learning algorithms have been used to analyze methadone use among MMT patients under acupuncture intervention, whereas previous machine learning algorithms have tended to focus on opioid use. We expect that the construction of the decision tree will produce new ideas for rehabilitation management in clinical MMT. Third, this clinical study provides a new treatment for opioid overdose, suggesting a focus on clinical treatment. At the same time, the decision tree technique analyzed and verified the therapeutic value of acupuncture in the treatment of MMT patients, and the character analysis also suggested other important roles affecting MMT efficacy.

However, this study has several limitations. First, due to the small sample size and the lack of specific quantitative relationships between acupuncture and MMT time and opioid use time, the decision tree model in this study is exploratory. Thus, it can only facilitate the exploration of the approximate distribution of each predictor. Second, in this study, there was no comparison of the outcomes of multiple acupuncture methods (such as electro-acupuncture, ear acupuncture, etc.), acupuncture time, or acupuncture frequency differences. In future research, the acupuncture process could be further refined to rectify this shortcoming. Third, MMT patients are often plagued by sleep disturbance, anxiety, depression, etc., and these ailments also affect treatment efficacy in MMT patients. This was not included in our study. In the future, machine learning algorithms could also be used to explore acupuncture treatment of these diseases in greater depth. In future research, we plan to conduct a larger sample, treatment, and longer follow-up trial to confirm the clinical efficacy of acupuncture-assisted MMT.

Conclusion

This trial and decision tree algorithm demonstrated that acupuncture therapy showed a positive effect on methadone reduction and psychological craving in MMT patients. Additionally, the decision tree model based on the VAS score efficacy was highly accurate. This provides reference suggestions for MMT clinics to promote the application of acupuncture- and MMT-related guidelines.

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 human participants were reviewed and approved by the Ethics Committee of the First affiliated Hospital of Guangzhou University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EY, JZe, HW, and LL contributed to the conception and design of the study. YD drafted the manuscript. EY, LL, HW, and BF contributed to the critical revision of the article for important intellectual content. HW, XW, JZe, RC, and JZh performed the acupuncture treatment for patients. YD and BF analyzed the data. XW and RC collected and registered data. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.2022.956255/full#supplementary-material

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Does acupuncture therapy affect peripheral inflammatory cytokines of major depressive disorder? A protocol for the systematic review and meta-analysis

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Background: Acupuncture is widely used as adjuvant therapy for major depressive disorder (MDD). There is robust evidence that inflammation is closely associated with MDD. To date, only a few numbers of studies have investigated the potential relationship between acupuncture and the change of inflammatory biomarkers in patients with MDD. Additionally, the results are inconsistent among studies. The current study aims to provide a comprehensive, systematic review of the association between acupuncture and changes in peripheral inflammation of patients with MDD, and clarify the alterations of inflammatory cytokines before and after acupuncture treatment by meta-analysis.

Methods and analysis: This study will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Eligible randomized controlled trials (RCTs) reporting acupuncture, with inflammatory cytokines as the outcome measured before and after intervention in patients with MDD, were searched in electronic databases, such as PubMed, Embase, Cochrane, SINOMED, Wanfang, China national knowledge infrastructure (CNKI), and Chongqing VIP (CQVIP). Primary outcomes of interest will be validated to measure the levels of inflammatory cytokines before and after acupuncture treatment in patients with MDD.

Discussion: Acupuncture can drive anti-inflammatory effects, as well as symptom changes in MDD, which may represent a viable, multi-faceted treatment approach in MDD.

Systematic review registration: [PROSPERO], identifier [CRD42021289207 on 04 December 2021].

KEYWORDS

major depressive disorder, acupuncture, peripheral inflammatory cytokines, anti-inflammatory, selective serotonergic reuptake inhibitors (SSRI)

Background

Major depressive disorder (MDD) is a common mental illness, with more than 264 million people affected (1). Inflammatory cytokines are thought to contribute to the pathogenesis of MDD (2). More precisely, it is supposed that cytokines could be responsible for changes in the brain's circuits and neurotransmitter systems and consequently for behavioral changes in MDD (3). Both preclinical and clinical studies manifested that significantly higher concentrations of peripheral pro-inflammatory cytokines were found in animal depression models and patients with MDD (4). According to a recent meta-analysis (5), levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) significantly increased in patients with MDD. Three other meta-analyses have also shown that inflammatory marker levels, such as high sensitivity C-reactive protein (hs-CRP) and IL-1, increased in patients with MDD (6–8). These findings facilitate the hypothesis of inflammation during the depression and predict that inflammation plays a role in the formation, progression, and perpetuation of MDD.

Acupuncture is one of the most popular complementary therapies. Accumulating evidence shows that acupuncture alone or combined with SSRIs/SNRIs have been more and more widely used in the field of antidepressant therapy and have embodied the double advantages of effectiveness and safety (9, 10). Acupuncture involves inserting thin and sterile needles into the skin at acupoints. Numerous meta-analyses have evaluated acupuncture-related strategies to treat MDD (11–14).

Recent studies illustrated that acupuncture may also contribute to the reduction of chronic low-grade peripheral inflammation, which is similar to antidepressant medication (15). Results from animal experiments manifested that there was a multitarget antidepressant effect of acupuncture, which may be related to inflammatory pathways (16). Mounting evidence shows that they have an anti-inflammatory effect, which is important for their therapeutic effects on anti-depression (6). Meanwhile, growing evidence supporting an inflammatory etiology of MDD has led to numerous studies which have evaluated the anti-inflammatory efficacy of acupuncture. A study reported that abdominal acupuncture stimulation amplifies an endogenous anti-inflammatory system mediated by NPYDBH-marked splenic noradrenergic neurons (17). Somatosensory autonomic reflexes allow acupuncture to modulate body physiology at distant sites (e.g., suppressing severe systemic inflammation) (18). Results from animal experiments manifested that there is a multitarget antidepressant effect of acupuncture, which may be related to inflammatory pathways (16, 19).

However, the underlying biological processes of acupuncture effects on MDD are still not fully depicted and remain inconsistent. Therefore, it is worth conducting a systematic review and meta-analysis to summarize the most updated research results for the role of acupuncture treatment in the inflammation of MDD.

Aims and objectives

We conducted a meta-analysis using data from all relevant randomized controlled trials (RCTs) that compared the peripheral inflammatory cytokines of acupuncture in treating MDD. The purpose of this study is to provide evidence that acupuncture can be used as an adjunctive treatment to anti-depressants, which may be associated with increased anti-inflammatory effects. From the previous evidence, we hypothesized that the levels of hs-CRP, IL-1, IL-6, IL-10, and TNF-α in serum are decreased o increases in MDD individuals with acupuncture treatment by meta-analysis.

Methods

Search strategy

The systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20). Figure 1 summarizes the study selection as a PRISMA flowchart.

Search methods for identification

We searched the following electronic databases: five Chinese electronic databases: SINOMED, Wanfang database, CNKI, CQVIP, and Chinese Clinical Trial Registry and four English electronic databases: Cochrane Library, Medline (*via* PubMed), Web of Science, and Embase from their inception to November 2021. The search was restricted to English- and Chinese-language studies. The search strategy combined medical subject headings (MeSH) terms with keywords. To ensure the comprehensiveness of the search, we included all clinical studies of acupuncture on MDD for screening. The search strategy of PubMed is shown in Table 1.

Selection criteria

The studies conducting the within-group comparisons of the peripheral levels of cytokines and chemokines in patients with

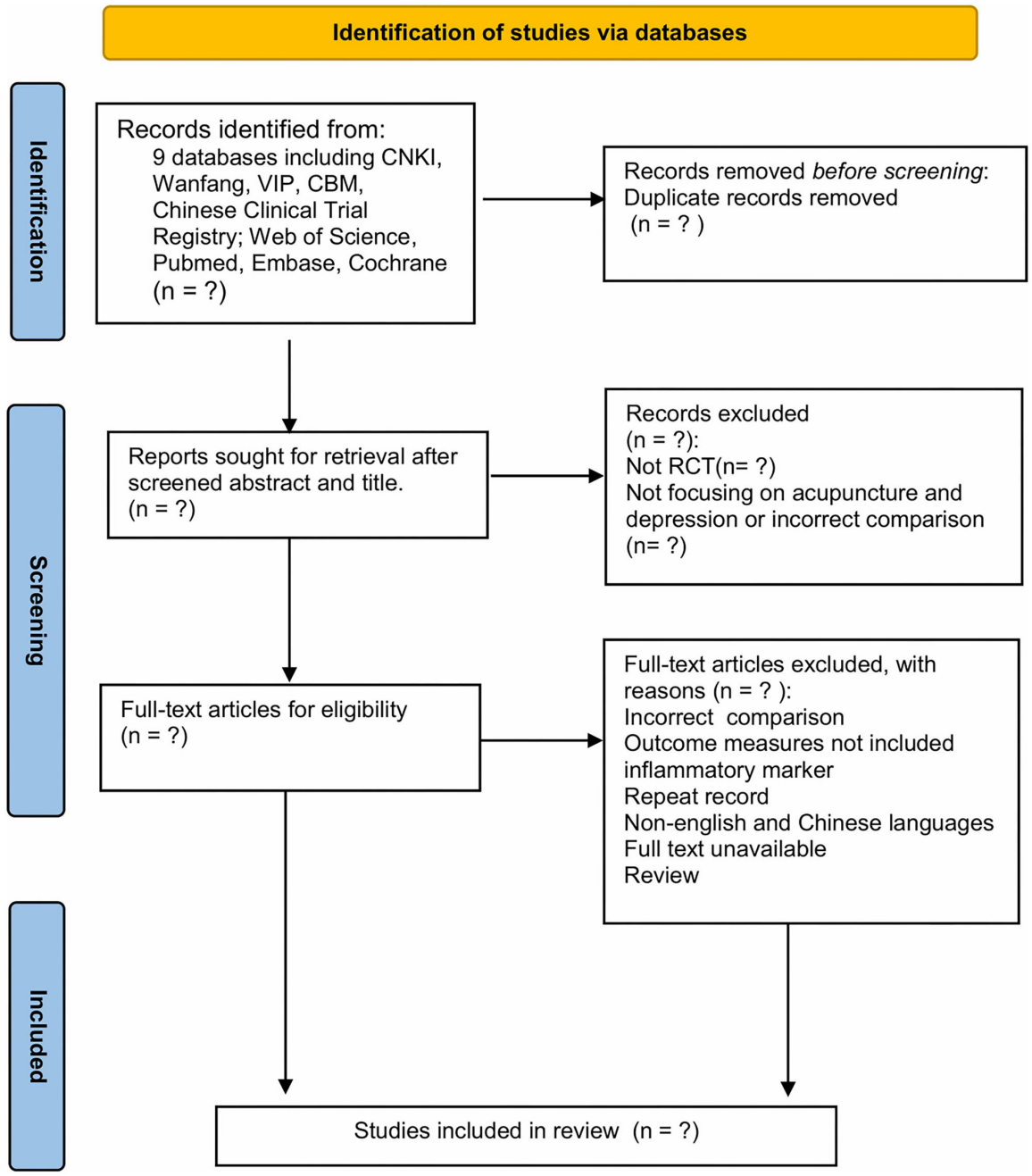

FIGURE 1
PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

MDD at baseline and after acupuncture will be included in the current meta-analysis.

Types of studies

A study with a longitudinal design including RCTs with double-blind, single-blind, or non-blind designs in English and Chinese will be included. Animal studies or studies with incomplete data will be excluded.

Participants

Adult patients of both sexes with MDD as confirmed by the Diagnostic and Statistical Manual (DSM-III/DSM-IV/DSM-V)

TABLE 1 Search strategy for PubMed.

Search number	Query
#1	"major depression" [Title/Abstract] OR "major depressive disorder" [Title/Abstract] OR "depressive symptom*" [Title/Abstract] OR "symptom, depressive" [Title/Abstract] OR "depress*" [Title/Abstract] OR "dysphor*" [Title/Abstract] OR "dysthym*" [Title/Abstract] OR "adjustment disorder*" [Title/Abstract] OR "mood disorder*" [Title/Abstract] OR "affective disorder" [Title/Abstract] OR "emotional depression*" [Title/Abstract]
#2	"Depression" [Mesh] OR "Depressive Disorder" [Mesh] OR "Depressive Disorder, Treatment-Resistant" [Mesh] OR "Depressive Disorder, Major" [Mesh]
#3	#1 OR #2
#4	"auricular acupuncture" [Title/Abstract] OR "electroacupuncture" [Title/Abstract] OR "hand acupuncture" [Title/Abstract] OR "acupuncture therapy" [Title/Abstract] OR "auriculotherapy" [Title/Abstract]
#5	"acupuncture" [Mesh]
#6	#4 OR #5
#7	#3 and #6

(21–23), the International Classification of Disease (ICD-10) (24), and the Criteria for Classification and Diagnosis of Mental Diseases (CCMD-2/CCMD-3) (24, 25) without major physical illness (diabetes, heart disease, cancer, etc.).

Types of interventions

Interventions with acupuncture vs. sham acupuncture, acupuncture combined with SSRIs/SNRIs vs. SSRIs/SNRIs alone, acupuncture vs. SSRIs/SNRIs, and acupuncture vs. psychological intervention in an acute treatment phase (treatment duration between 4 and 12 weeks) of an MDD episode.

Types of outcome measures

Primary outcomes

- Inflammatory cytokines: IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, hs-CRP, TNF-α, and IFN-γ in peripheral blood points. When multiple data points were available post-intervention (pre-treatment, post-treatment, or follow-up), post-treatment data were used as the primary time point;
- Severity of MDD measured on HAMD/MADRS scale.

Secondary outcomes

- QoL: evaluated mainly by the Medical Outcomes Study Short Form 36;
- Safety: the adverse events measured on SERS.

Study selection and data extraction

The outcome of this meta-analysis will be the changes in inflammatory cytokines before and after acupuncture treatment in patients with MDD, and their concentrations were measured by the standard mean differences (SMDs). EndNote V.X8.2 will be used to manage studies. First, duplicate literature will be excluded by electronic-based and manual-based steps in EndNote. Second, two reviewers will independently screen the titles and abstracts and select the studies which meet the eligibility criteria. If there are disagreements, the third reviewer will be consulted. The evaluators will read the full text of the included literature and then preliminarily extract the relevant data, mainly including the following information: first author, publication year, study design, sample size/female, mean age, gender, diagnostic criteria, acupuncture treatment (frequency, each session duration, total period, and acupoints protocol), control treatment, and inflammatory cytokines.

Assessment of the risk of bias

According to the Cochrane Handbook for Systematic Reviews of Interventions, version 6 (26), the risk of bias 2.0 (ROB 2.0) tool will be used to mean the methodological quality and the risk of bias of the included studies. One researcher assessed the ROB of included studies by using ROB 2.0 and another researcher confirmed the judgment. If there are any differences, the third researcher will be asked to solve the problem.

Quality assessment

The quality of evidence for main outcomes will be assessed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Two reviewers will do this independently through GRADEpro Guideline Development Tool. GRADE approach provides guidance for rating the quality of evidence and grading the strength of recommendations for healthcare. There are four quality levels: high, moderate, low, and very low. We also assessed the reporting quality by using the CONSORT and the STRICTA by two investigators.

Publication bias

STATA V.14.0 will be used to evaluate publication bias. Begg's test and Egger's test will be used to assess the publication bias of the included trials and form the publication bias plot.

Assessment of heterogeneity and sensitivity analysis

We will use the I^2 statistic to assess the heterogeneity. If the I^2 value is below 50%, the fixed effect model will be used. Otherwise, sensitivity analysis will be conducted to explore the main sources of heterogeneity, after which, the random effect model will be used if the I^2 is still equal to or >50%. Both types of effect sizes will be presented with 95% Cis, and p-values < 0.05 will be regarded as statistically significant.

Subgroup analysis

Subgroup analysis will also be conducted to explore the main sources of heterogeneity. We performed four subgroup analyses according to the frequency of treatment (once a day vs. every other day), study duration (4 vs. 8 weeks), treatment protocol of acupuncture points (semi-standardized vs. fixed-standardized), and types of antidepressant medications (SSRIs vs. SNRIs) to explore their impact on the levels of peripheral inflammatory cytokines.

Statistical analysis

We will use the Review Manager software provided by the Cochrane Collection (RevMan5.4.1). The SMD with 95% CI will be used for continuous outcomes and not actual mean differences to measure effect sizes. While a P-value < 0.05 was considered statistically significant. The extent of heterogeneity will be assessed using the Chi-square test and the Higgins I^2-test. A value of $P< 0.10$ or $I^2 > 50\%$ indicated that the heterogeneity of effect estimates within each group of studies will be statistically significant. As the potential clinical heterogeneity among the included studies, the random effects model will be used to pool the studies. All two-tailed $P < 0.05$ will be defined as statistical significance.

Patient and public involvement

Patients will be not involved in the development of this systematic review protocol. The data for this systematic review will be collected from previously published studies.

Ethics and dissemination

Formal ethical approval is not required, as primary data will not be collected with the systematic review and meta-analysis. Data from previously published studies will be retrieved and analyzed. This study including protocol development will be conducted from November 2021 to October 2022. The results will be disseminated through a peer-reviewed publication and inform the most up-to-date evidence of the roles of acupuncture treatment for MDD.

Discussion

Our current systematic review and meta-analysis will provide comprehensive evidence for the association between acupuncture and the inflammation of individuals with depression. We will use the PRISMA guidelines and checklist in the publication process. The quantitative data will be summarized and presented in tables, forest plots, and charts. The alterations of inflammatory cytokines pre- and post-acupuncture treatment in patients with MDD will be presented.

A "dose" of acupuncture is made up of multiple components. The exact components of a dose differ slightly between acupuncturists but consist of: (a) a neurophysiological dose, which includes the retention time and the treatment protocol of acupoints (fixed, semi-standardized, and individualized acupuncture) and (b) a cumulative dose, made up of the frequency (once a day, every other day, etc.) and total treatment duration (4, 6 weeks, etc.) (27–29). These multiple components not only affect the effect but also potentially affect the level of peripheral inflammatory cytokines in patients with MDD (18). Furthermore, there remain many unanswered questions concerning what might be considered optimal acupuncture.

The current study is anticipated to have some limitations. First, we might not find a sufficient number of original studies to perform the analyses. Second, the potential high heterogeneity between studies in the exposure of interest and restriction to studies in English- and Chinese-language will lead to selection bias and also decrease the reliability of our results. Third, the treatment schedule, such as the number of acupoints and frequency of treatment, will vary among studies. Fourth, large-scale studies will be required to yield stable and consistent effect sizes.

To the best of our knowledge, this will be the first meta-analysis exploring the association between acupuncture and peripheral inflammation of individuals with MDD. From our findings, we can provide the latest evidence to assist in decision-making among patients, caregivers, and clinicians in treating patients with MDD by acupuncture and as a foundation for future studies.

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

Y-NZ and P-JR had the idea for the article. SZ, YC, and Z-XZ performed the literature search. Y-NZ and SZ drafted the manuscript. P-JR and YW critically revised the work. Y-TD, HC, and S-YL helped conceptualize the study. CX and LL embellished the language of the manuscript. Y-FW provided valuable advice on writing the manuscript. All authors read and approved the final manuscript.

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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.2022.967965/full#supplementary-material

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Comparative efficacy of acupuncture-related techniques for mild cognitive impairment: A Bayesian network analysis

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Background: A comparison and ranking of the clinical effects of various acupuncture and acupuncture-related therapies on patients with mild cognitive impairment.

Methods: Using network meta-analysis, we assessed the direct and indirect evidence from relevant research. Seven databases [PubMed, Web of Science, Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), VIP Database, and Wanfang database] were examined to find randomized controlled trials of acupuncture-related therapies for individuals with mild cognitive impairment. Two researchers independently reviewed the literature, retrieved the data, and evaluated the risk of bias in the included studies. The data were analyzed using Stata15.0 and R3.6.1 software.

Results: A total of 27 randomized controlled trials involving 2,210 patients were included. Bayesian NMA showed that manual acupuncture combined with conventional therapy, moxibustion combined with conventional therapy, manual acupuncture, and electroacupuncture were most effective in improving the MMSE score. The most effective interventions related to the MoCA score were moxibustion combined with conventional therapy, followed by manual acupuncture combined with conventional therapy, acupressure combined with conventional therapy, and manual acupuncture combined with moxibustion. Manual acupuncture combined with moxibustion was dominant in the cluster ranking. The results of the node splitting method revealed that direct and indirect evidence were consistent ($P > 0.05$). In addition, publication bias was detected.

Conclusion: This research will add to the body of knowledge about the safety and efficacy of acupuncture-related therapies in the treatment of mild cognitive impairment. The results of this study will also assist in the choice of clinical guidelines that optimize acupuncture treatment for patients with mild cognitive impairment.

KEYWORDS

acupuncture, network meta-analysis, mild cognitive impairment, acupuncture—therapy, systematic (literature) review

Introduction

The core cognitive abilities of people, such as memory, reaction time, visuospatial ability, and executive cognitive functions, decline as they age (1). Individuals with mild cognitive impairment (MCI), not exceeding the threshold for dementia diagnosis, are characterized as having focal or multifocal cognitive impairment with limited impact on activities of daily living (ADL) (2). According to a study in the United States (3), the 2020 US Census-adjusted prevalence of clinical Alzheimer's disease (AD) was 11.3% (95% confidence interval [CI] = 10.7–11.9). The study also demonstrated that in 2020, 6.07 million people (95% CI = 5.75–6.38) were living with clinical AD, and this is predicted to increase to 13.85 million (95% CI = 12.98–14.74) by 2060. MCI is a neurocognitive disorder with a higher prevalence than dementia and can be considered a risk factor for dementia (4, 5). While some individuals with mild cognitive impairment appear to stabilize or return to normal over time, more than half of those with moderate cognitive impairment develop dementia within 5 years (6, 7). Severe cognitive impairment occurs as MCI progresses to dementia, which substantially impacts peoples' daily life and livelihoods (8).

Given the lack of drug therapy options, at least 40% of MCI patients have increasingly turned to complementary and alternative therapies to alleviate their symptoms (9, 10). Research in recent years has focused on alternative medicines to improve outcomes for patients. Alternative treatments for MCI, such as acupuncture, tai chi, CHEIs, placebo, exercise, cognitive training, golf training, music therapy, and Vitamin E, have been shown to provide possible clinical or theoretical benefits for patients (11). Acupuncture-related therapy is one of the most often used adjuvant therapies for MCI patients (12), and according to a previous NMA study, acupuncture-related therapy may be the best and safest complementary and alternative therapy for improving cognitive function in people with Alzheimer's disease (13).

Acupuncture-related therapy has been widely used to treat MCI, with many studies confirming its efficacy (14–16). However, due to the great diversity of acupuncture-related therapies, few studies have directly compared different acupuncture techniques; it remains unclear which acupuncture method is optimal for treating MCI. As a result, determining the most effective acupuncture treatment for MCI is a challenging task. Although the term "acupuncture" has been given many different definitions, we have used the definition provided by the World Health Organization (17), which states that acupuncture means "needle pricking." However, acupuncture therapy could also entail applying different forms of stimulation to specific areas. The term "acupuncture" will be used broadly throughout this essay to refer to any type of conventional acupunctures that replicate specific spots using needles, lasers, electricity, or pressure. Acupressure, ear (auricular) acupuncture, auricular pressure, scalp acupuncture, Bee Venom Acupuncture (BVA), conventional body needling, manual acupuncture, electroacupuncture, acupoint catgut embedding, and electroacupuncture are the specific acupuncture methods covered in this manuscript (18). The term "acupuncture-related therapies" refers to practices such as warm needling, acupoint injection, hydroacupuncture, or herbal decoction that combine moxibustion or medication with acupuncture (19).

To provide a comprehensive evaluation of the use of various acupuncture techniques in MCI patients, this study covers trials evaluating a number of different types of acupuncture procedures. NMA was utilized to assess and rank the best acupuncture treatment for MCI based on data from a variety of available databases.

Methods

Protocol and registration

The data gathering and analysis protocol used in this study was derived from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (20), and the protocol has been registered on the INPLASY website (registration number: INPLASY202240140: https://inplasy.com/inplasy-2022-4-0140/).

Search strategy

The Bayesian Network Meta-Analyses statement and the Cochrane handbook were used to conduct this study (21). PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), Cochrane Library, VIP Periodical Resource Integration Service Platform, and Wangfang Databases were searched from 4 March 2002 until 4 March 2022, with a combination of MeSH terms and free words.

Study selection and intervention definitions

Types of studies

All randomized controlled trials (RCTs) of acupuncture-related therapies for MCI were used with either English or Chinese as the language option, regardless of blinding, publication, status, or length of the trial. Non-randomized uncontrolled trials were excluded. Additionally, case reports, animal experiments, individual cases, research advances, expert experience, conference articles, and duplicate articles were excluded.

Participants

The participants in this study were MCI patients who had been diagnosed with neurodegeneration rather than mild cognitive changes relating to potential causes, such as metabolic, vascular, and systemic. Patients with psychiatric disorders, such as those defined by the American Psychiatric Manual of Psychiatry and Statistics diagnostic criteria for MCI (22), the MCI Clinical Diagnostic Standards revised by Petersen in 2018 (23), the Reference Standard of Deficiency Syndrome Differentiation in traditional Chinese Medicine (24), and the 2018 Chinese Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Impairment, were excluded (25).

Interventions

Studies that used a combination of acupuncture-related therapies and conventional therapy (CT) were included in the study. Classic acupuncture (with or without electrical stimulation and manual or scalp acupuncture), ear (auricular) acupuncture, auricular pressure, Bee Venom Acupuncture (BVA), abdominal acupuncture, acupoint catgut embedding, and acupressure, moxibustion (including direct and indirect moxibustion, and warm needling), and acupoint injection were all included in the definition of acupuncture-related therapies. The control group received conventional therapy or a placebo (sham acupuncture or other placebo treatments). These interventions were used alone or in combination. The current conventional-therapy strategy for MCI consists of conventional medicines (including Donepezil, Nimodipine, Huperzine, Perphenazine, Duxil, and Hydergine) and cognitive training.

Outcomes

We used the MoCA, MMSE, and ADL scales as the outcome indicators to assess the effects of acupuncture on cognitive function. The main outcomes were global cognitive function and behavioral abnormalities, which were assessed using recognized and standardized scales, such as the Mini-mental State Examination (MMSE) score, the Montreal Cognitive Assessment (MoCA) score, and the Activity of Daily Living (ADL) score.

Data extraction and quality assessment

Two reviewers screened the full texts, extracted the correlated information from all the included studies, and cross-checked the data for consistency and accuracy of the extraction. We extracted the general information (e.g., publication year, author, sample size, gender, and age), intervention measures (e.g., experimental group: the types, acupoints, frequency and duration of acupuncture-related therapies; control group: conventional treatment, placebo or conventional treatment plus other acupuncture therapy), and outcomes (MMSE, MoCA, and ADL). The reviewers independently assessed the risk of bias in the studies using Cochrane's risk of bias tool 5.1.0 to evaluate the methodological quality of the research (26). The Cochrane Risk of Bias tool contains seven items: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other sources of bias. Each trial was graded as either "low", "high", or "unclear" risk. A third reviewer resolved conflicts during trial selection when data extraction and quality evaluation scores were inconsistent.

Statistical analysis

Given the potential for clinical heterogeneity among the included studies, the datasets were merged using a random effect model (21). The Cochrane risk of bias tool 5.1.0 was used to assess the quality of the studies. The Bayesian hierarchical model inference with Markov Chain Monte Carlo (MCMC) algorithm was employed in the Bayesian meta-analysis and was performed with R software (version 3.6.3) (27) and STATA (version 14.0) (28). The Aggregate Data Drug Information System (ADDIS Version1.16.8) package was used in the R software. This software uses the Bayesian framework as a base combined with the Markov chain Monte Carlo method to evaluate research data. We used 200,000 iterations, and the first 5,000 iterations served as a burn-in for annealing to eliminate the impact of the initial value. Four chains yielded 20,000 iterations and a factor of 2.5. The two models for estimating the ADDIS effect size were consistency and inconsistency. A consistency assessment calculated the ranking probability for all the interventions and made judgments about the sizes of the interventions that were included. By using node-splitting analysis and an inconsistent model, the consistency test was evaluated. When the node-splitting p-value was higher than 0.05, a consistency mode was chosen—if not, an inconsistency model was applied. Otherwise, continuous outcomes were represented by standardized mean differences (SMDs) and 95% confidence intervals (CIs). The model convergence was assessed using the potential scale reduction factor (PSRF). The convergence improved as the PSRF value approached 1. If the PSRF value was <1.2, the model convergence was nevertheless considered satisfactory. We calculated the ranking probability for every intervention for every potential rank. Acupuncture methods were ranked by the surface under the cumulative ranking curve (SUCRA). Finally, a cluster ranking plot was created to assess the comprehensive ability of acupuncture methods to relieve symptoms in MCI patients.

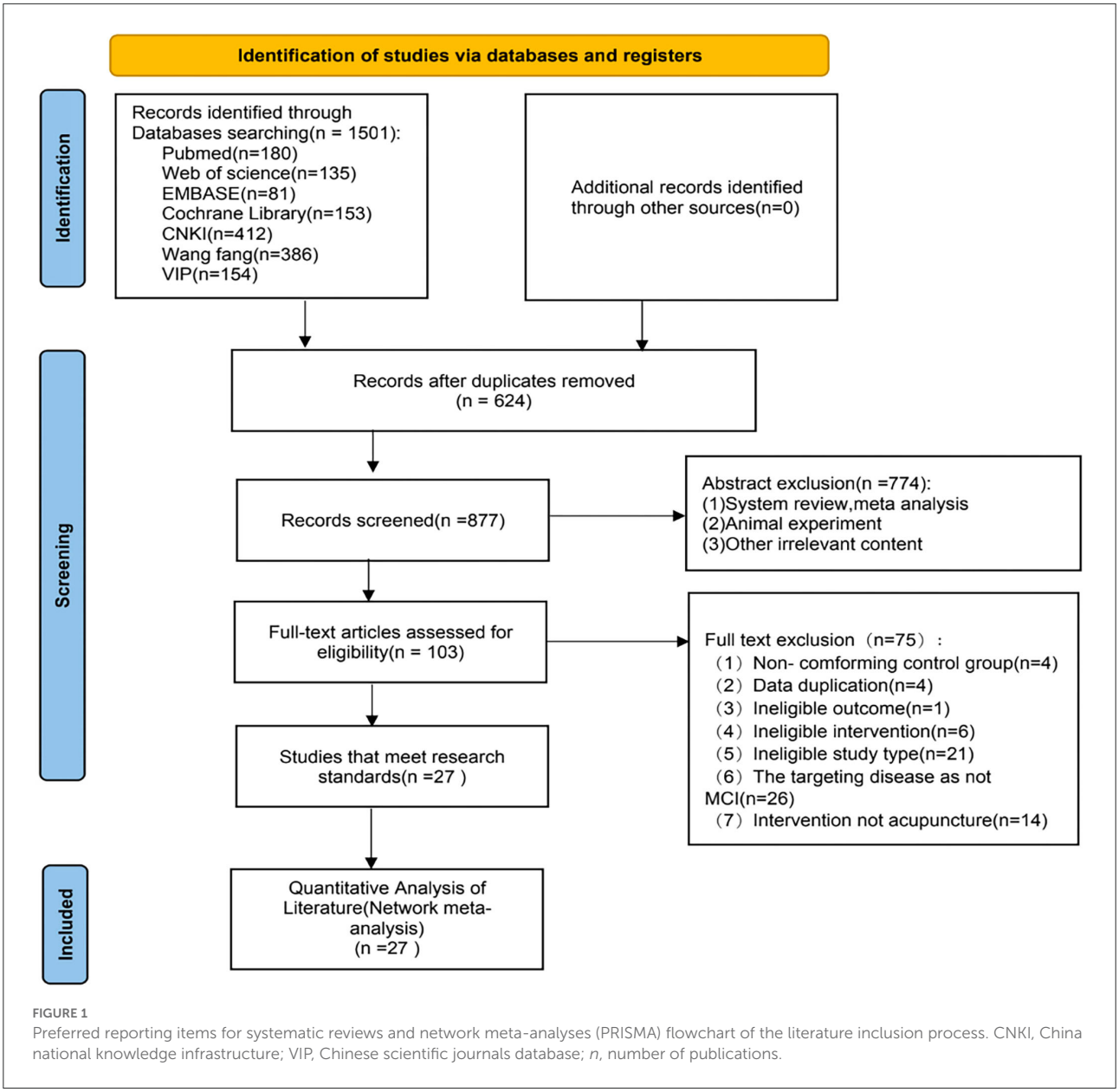

FIGURE 1
Preferred reporting items for systematic reviews and network meta-analyses (PRISMA) flowchart of the literature inclusion process. CNKI, China national knowledge infrastructure; VIP, Chinese scientific journals database; *n*, number of publications.

Results

Characteristics of study

A total of 1,501 articles of probable relevance were obtained with 624 duplicates. The PRISMA flow diagram of the search process is shown in Figure 1. Seven hundred and seventy-four studies were excluded after a preliminary review of the titles and abstracts for the following reasons: unconnected studies ($n = 495$); animal experiments ($n = 205$); system reviews and meta-analysis ($n = 74$). A total of 103 RCTs were retrieved for full-text evaluation. The retrieved articles were analyzed using deep reading. A total of 75 records were excluded from the study based on the following criteria: (1) non-conforming control group ($n = 4$); (2) data duplication ($n = 4$); (3) the targeting disease was not MCI ($n = 26$); (4) ineligible study type ($n = 21$); (5) ineligible intervention ($n = 6$); (6) ineligible outcome ($n = 4$); (7) intervention was not acupuncture ($n = 14$). Finally, 27 studies (16, 29–54) were included in this study (Table 1).

The studies included in this investigation comprised 27 RCTs, with 26 trials from China and one from South Korea. Twenty-two trials were published in Chinese (81.48%), and five in English (18.52%). There were 25 double-arm RCTs and two three-arm RCTs in the trials. The network analysis comprised 1,797 people from 25 two-arm studies and 231 from

TABLE 1 Main characteristics of included RCTs.

Study	Country	Arms	Group	Sample size (n)	Average age (years)	Interventions	Acupoints	Frequency (t/w)	Retention (min)	Follow-up	Aderverse events	Measurement time points	Outcomes
Chen et al.	China	2	G1	32	71 ± 5	SA	GV20,GV24,GV29,EX-HN1	3	30	√	×	8w	①②
			G2	32	71 ± 5	MA	GV20,GV24,GV29,EX-HN1	3	30			8w	①②
Yang	China	2	G1	40	71.61 ± 8.166	CT	/	7	NA	√	×	8w	①
			G2	40	73.51 ± 8.964	MO + CT	GV20,CV8,K13	4 + 7	20			8w	①
Chen et al.	China	2	G1	30	70.23 ± 6.92	CT	/	7	NA	×	×	4w	①②③
			G2	30	67.77 ± 5.96	MA + CT	BL23,ST25,ST41,K13	6 + 7	40∼60			4w	①②③
Huang	China	2	G1	40	67 ± 3	CT	/	21	NA	×	×	12w	①③
			G2	40	68 ± 3	MA	GV20,GV24,GV29,GB13,EX-HN1,BL15	6	30			12w	①③
Yu	China	2	G1	56	70.170 ± 4.475	CT	/	21	NA	√	√	4w	①③
			G2	56	68.309 ± 7.333	EA	GV20,EX-HN1,GB20,GV24	3	30	√	√	4w	①③
Cao	China	2	G1	30	NA	CT	/	6	40	×	×	8w	②
			G2	30	NA	CT + MA	/	6	360			8w	②
Wang et al.	China	2	G1	30	68.43 ± 6.16	CT	/	6	30	×	×	8w	②③
			G2	30	66.83 ± 6.72	CT + MA	/	6	30			8w	②③
Wang	China	2	G1	30	54.43 ± 3.081	CT	/	18	NA	×	√	1w	①②③
			G2	30	53.43 ± 2.725	CT + MA	GV26,GV24,GV20	6 + 2	30			1w	①②③
He et al.	China	2	G1	30	66 ± 6	CT	/	7	NA	×	×	12w	①②③
			G2	30	64 ± 7	WA	GV20,GV14,GV9,GV4	7	60			12w	①②③
Zhu et al.	China	2	G1	30	NA	CT	/	18	NA	×	×	5w	①②③
			G2	30	NA	MA + MO	CV4,GV4	6	30			5w	①②③
Wang et al.	China	2	G1	105	70.3 ± 9.4	CT	/	7	NA	√	√	8w	①②
			G2	105	72.3 ± 8.6	MO	GV20,CV8,K11	4	20			8w	①②
Liu	China	2	G1	18	69.32 ± 6.86	CT	/	7	NA	×	×	30d	①②
			G2	18	66.00 ± 6.84	EA	GV20,GB20,BL23,GB39,K13	7	NA			30d	①②
Liu et al.	China	2	G1	9	77 ± 6	CT	/	7	NA	×	×	4w	①

(Continued)

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TABLE 1 (Continued)

Study	Country	Arms	Group	Sample size (n)	Average age (years)	Interventions	Acupoints	Frequency (t/w)	Retention (min)	Follow-up	Aderverse events	Measurement time points	Outcomes
			G2	8	73 ± 8	EA	EX-HN1,GB20,BL23,HT7,GB39,K13	7	20			4w	①
Jin	China	2	G1	16	73.67 ± 3.266	CT	/	21	NA	×	×	45d	②
			G2	14	72.54 ± 7.067	EA	EX-HN1,BL23,GB20,K13	7	20			45d	②
Li et al.	China	2	G1	39	61.9 ± 6.8	CT	/	7	NA	×	×	3m	①②
			G2	39	62.8 ± 5.9	CT + EA	GV16,GV23,BL62,PC7	3.5	30 min			3m	①②
Li	China	3	G1	32	61.14 ± 9.05	CT	/	7	NA	×	√	8w	①②
			G2	32	65.10 ± 8.76	MO	GV20,CV8,K11	3.5	20 min			8w	①②
			G3	32	64.87 ± 9.23	MO + CT	GV20,CV8,K11	3.5	20 min			8w	①②
Su	China	2	G1	35	67.05 ± 6.10	CT	/	3.5	NA	×	√	4w	①②
			G2	35	63.85 ± 6.32	MO	GV20,CV4,ST36,GB39	7	NA			4w	①②
Liu	China	2	G1	65	70.24 ± 9.378	CT	/	7	NA	×	√	8w	①②
			G2	65	72.15 ± 8.418	MO	GV20,CV8,K11	3.5	20 min			8w	①②
Yu et al.	China	2	G1	32	66.75 ± 6.41	CT	/	7	NA	×	×	4w	①②③
			G2	32	64.13 ± 6.02	MO	GV20,CV4,ST36,GB39	3.5	30 min			4w	①②③
Du	China	2	G1	20	68.25 ± 5.80	CT	/	7	NA	×	×	8w	①②③
			G2	20	69.03 ± 5.47	MA	GV20,GV14,GV23,GV24,GV16,GV15,EX-HN1,K13,ST36,GB39,K14	6	40 min			8w	①②③
Yu	China	2	G1	25	63.32 ± 8.61	SA + CT		2	60 min	×	√	8w	①②③
			G2	25	65.48 ± 7.47	MA + CT	GV20,EX-HN1,GV24,GV16,GV14,BL23,BL18	2	60 min			8w	①②③
Zhu et al.	China	2	G1	30	74 ± 7	CT	/	21	NA	×	×	12w	①②
			G2	30	69 ± 7	MO	GV20,GV14,GV24,GV11	6	20 min			12w	①②
Zhao et al.	China	2	G1	30	58.14 ± 9.15	CT	/	21	NA	×	×	8w	①②
			G2	30	55.34 ± 8.48	MA + CT	GV20,EX-HN1,GV24,GB20,GB13	4	NA			8w	①②
Sun et al.	China	3	G1	45	NA	AP + CT	GV20,GB20,GV24,EX-HN1,EX-HN5	5 + 15	1 min 10 s	√	×	6m	①②
			G2	45	NA	CT	/	5	NA			6m	①②

(Continued)

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TABLE 1 (Continued)

Study	Country	Arms	Group	Sample size (n)	Average age (years)	Interventions	Acupoints	Frequency (t/w)	Retention (min)	Follow-up	Aderverse events	Measurement time points	Outcomes
			G3	45	NA	AP	GV20,GB20,GV24,EX-HN1,EX-HN5	15	1 min 10 s			6m	①②
kim jh,cho et al.	Korea	2	G1	16	67.25 ± 5.15	MA	GV20,EX-HN1,GB20,GV24	3	30	×	×	8w	②
			G2	16	64.63 ± 4.47	EA	GV20,GV24,EX-HN1,GB20	3	30			8w	②
Zhao et al.	China	2	G1	96	67 ± 6	EA	GV24,GV20,EX-HN1,GB20	3	30	√	√	4w	①③
			G2	96	69 ± 7	CT	/	21	NA			4w	①③
Wang et al.	China	2	G1	16	64.56 ± 5.25	SA	EX-HN1,GV29,PC6,K13,ST40,LR3	5	NA	√	×	4w	①②
			G2	16	65.88 ± 4.66	MA	EX-HN1,GV29,PC6,K13,ST40,LR3	5	NA			4w	②

two three-arm studies. Seven of the 25 trials compared electro-acupuncture (EA) and conventional therapy (CT), five trials compared manual acupuncture (MA) and conventional therapy (CT), and the two-arm investigations focused on moxibustion (MO) vs. conventional therapy (CT). Three trials compared manual acupuncture (MA) combined with conventional therapy (CT), two trials compared manual acupuncture (MA) vs. Sham acupuncture (SA), and one trial compared manual acupuncture (MA) vs. electro-acupuncture (EA), warm acupuncture (WA) vs. CT, moxibustion (MO) combined with conventional therapy (CT) vs. conventional therapy (CT), and manual acupuncture (MA) combined with moxibustion (MO) vs. conventional therapy (CT). Acupressure (AP) combined with conventional therapy (AP+CT), moxibustion (MO) combined with manual acupuncture (MO + MA), and moxibustion combined with conventional therapy (MO + CT) were compared in two three-arm experiments. The MMSE was reported in 22 trials and the MoCA in 21 trials as an end measure. In addition to conventional drugs, cognitive training, and placebo, the research included 12 acupuncture intervention modalities. A summary of the detailed information from the 27 RCTs can be found in Table 1.

Methodological quality assessment

Twenty studies randomized participants using a random number table, five studies used computer-generated random numbers, and two studies provided no information regarding the randomization procedure. Eight studies used sealed opaque envelopes for allocation concealment, whereas the remaining nineteen studies made no mention of their randomization procedures. Patients and researchers were only blinded in two trials. The result evaluators in four trials were blinded. Since the study did not explain why two examples were eliminated, one experiment was rated an "uncertain" risk of bias. The risk of bias for all studies with no indication of the study procedure or the influence of selective reporting was rated as "uncertain." No other bias was detected in the included studies (Figure 2).

Outcomes

Mini-mental state examination (MMSE) score

Twenty-two studies reported MMSE scores, resulting in four closed loops: AP-AP + CT – CT, MA – EA – CT, MO – MA + CT – CT, and MO – MO + CT – CT (Figure 3). Since the PSRF values tended to 1 and the incongruity model results were similar to the congruity model, which suggests the indicator stability and consistency were good, the MCMC congruity model was selected for network meta-analysis MMSE scores. Node-split was utilized to identify inconsistency and heterogeneity for the MMSE scores. Due to a P-value of >0.05,

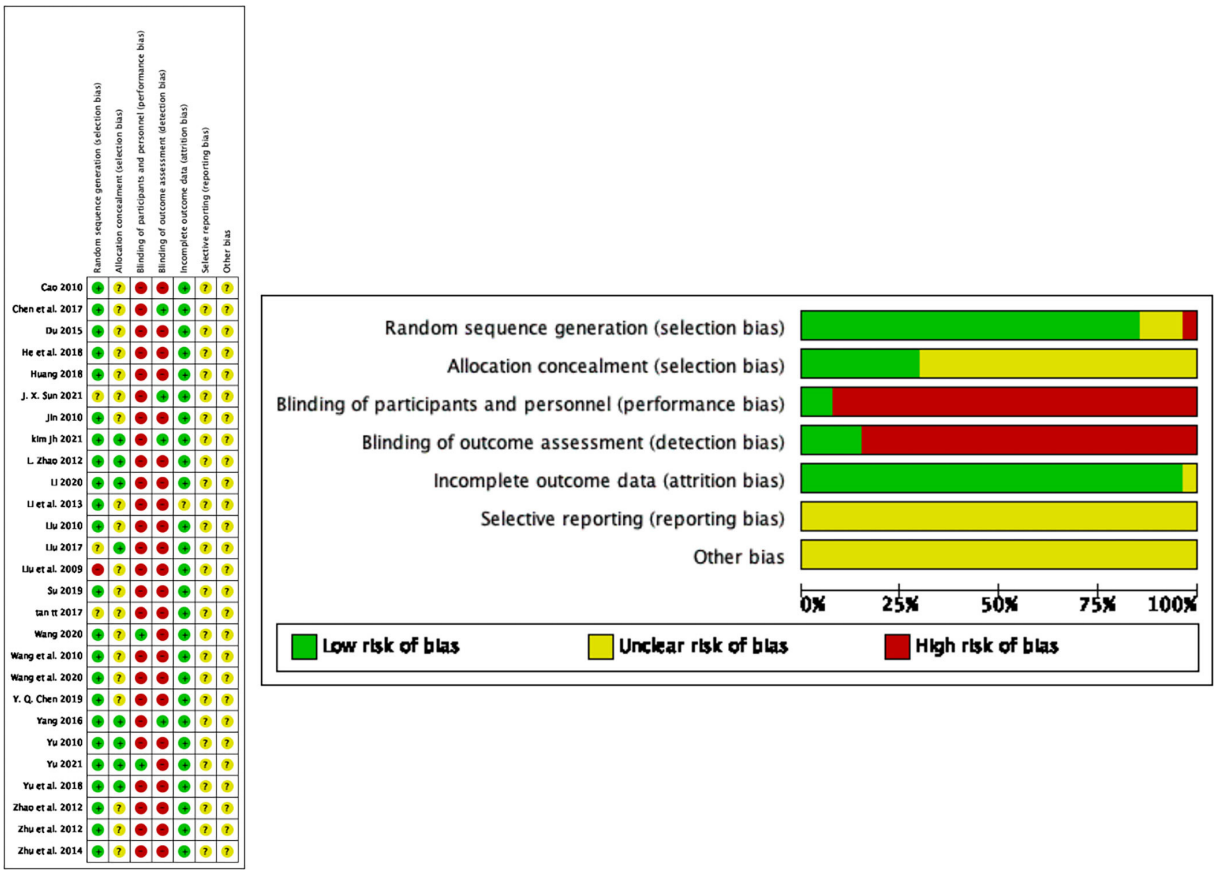

FIGURE 2
Risk of bias graph and summary.

the direct evidence approximated the indirect evidence. The node-split plots demonstrate that each comparison's direct and indirect evidence had hardly any heterogeneity or inconsistency (Supplementary Figure S1). In the comparisons, SA was the least efficacious among all interventions (Figures 4, 5). The ranking probability of MMSE (Figure 6A) showed that MO + MA had the highest probability (28%) of being the best treatment for MCI, followed by MA + CT (22%) and MO + CT (14%). According to cumulative probability, MO + MA had the highest probability (82.2%) to be the most efficacious treatment for MCI (Figure 7).

Montreal cognitive assessment (MoCA)

Twenty-one studies reported MoCA scores, forming seven closed loops: AP–AP + CT – CT, MA – EA – CT, MA – EA – SA, MA – EA – WA, CT – SA – WA, CT – MO – MO + CT, and CT – MA + CT – SA + CT (Figure 3). The MCMC congruity model was used for network meta-analysis of MoCA scores since convergence assessment demonstrated that PSRF values tended to 1. The results of the incongruity model were identical to those of the congruity model, which suggests the indicators' stability and consistency were good. The node-split plots demonstrated that each comparison's direct and indirect evidence had hardly any heterogeneity or inconsistency in MoCA scores (Supplementary Figure S2). In the comparisons, CT was the least efficacious among all interventions (Figures 4, 5). The ranking probability of MoCA (Figure 6B) showed that MO + CT had the highest probability (52%) of being the best treatment for MCI, followed by MA + CT (28%) and MO + MA (9%). According to cumulative probability, MO + CT had the highest probability (91.4%) to be the best treatment for MCI (Figure 7).

Activity of daily living (ADL)

Activity of daily living (ADL) scores were used to assess self-care ability after the intervention. Four studies involving 124 participants in the treatment group and 124 in the control group assessed the ADL scale score (MD = 3.08, 95% CI [0.66,

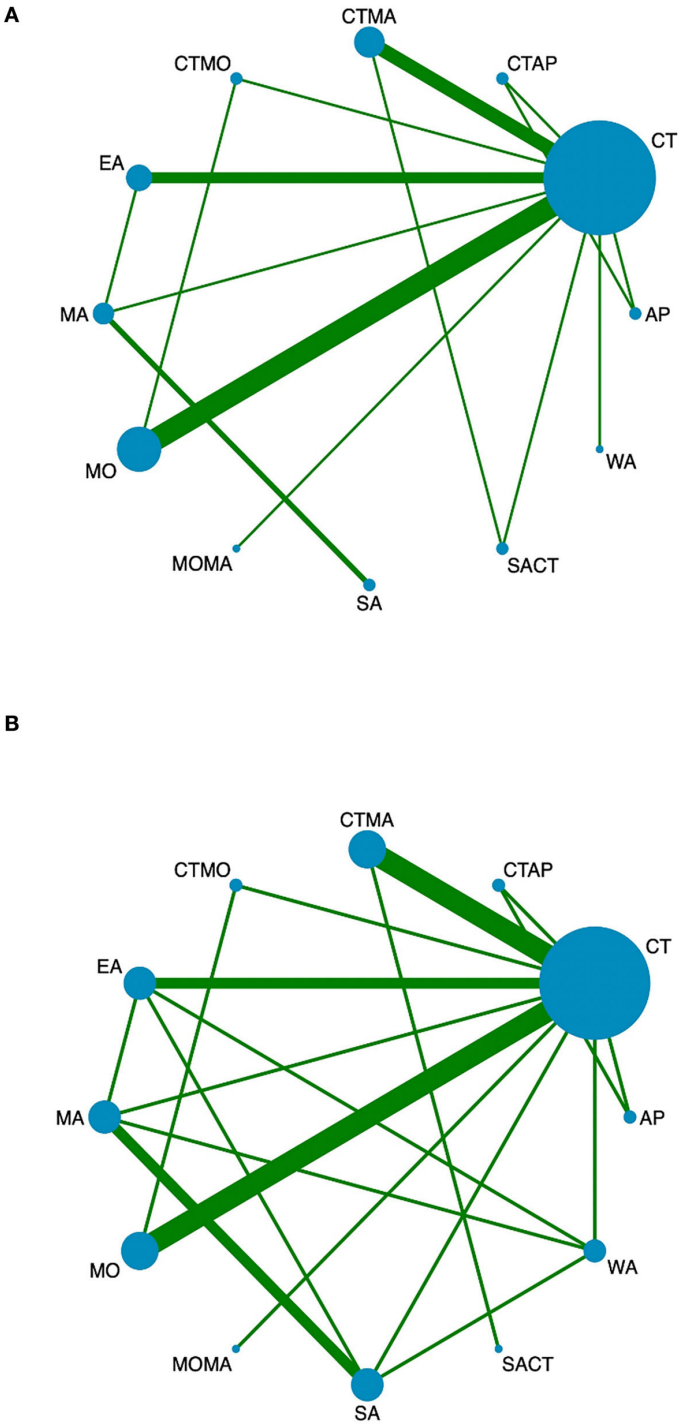

FIGURE 3
Network diagrams of comparisons of different outcomes of treatments in patients with MCI. **(A)** Network meta-analysis of multiple acupuncture-related treatments for MMSE. **(B)** Network meta-analysis of multiple acupuncture-related treatments for MoCA. Each node represents an intervention and the size of each node represents the number of randomly assigned participants. Each line represents a direct comparison between interventions and the width of the lines represents the number of studies. MMSE, mini-mental state examination; MoCA, montreal cognitive assessment.

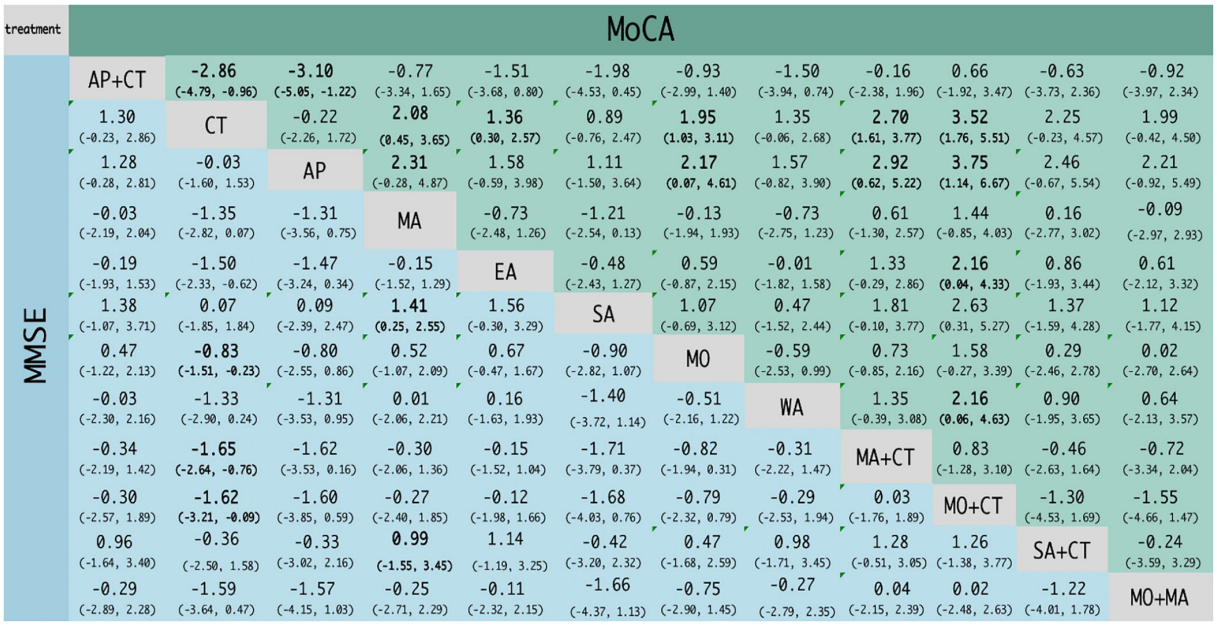

FIGURE 4
Network meta-analysis results for MMSE and MoCA scores. The bold font indicates a statistical difference.

5.49], $P > 0.05$). The data heterogeneity test ($I^2 = 94.8\%$, $I^2 > 70\%$) could not be used for the meta-analyses because of the high heterogeneity (Supplementary Figure S3). We also implemented sensitivity analysis by omitting a single study by step, and the result showed that one trial might be the likely source of heterogeneity, which changed the sensitivity analysis result when it was excluded from the pooled process (55, 56) (Supplementary Figure S4). After the study was removed, the robustness of the synthesized result changed (MD = 1.23, 95% CI [0.75, 1.70], $P > 0.05$) (Supplementary Figure S5), which showed that our result had high sensitivity and the treatment group combined with acupuncture-related therapy did not improve the ADL scale score.

Publication bias

A comparison-adjusted funnel plot was used to analyze MMSE and MoCA publication bias. No publishing bias is present when the distribution points in the funnel plot are symmetric (Figure 7). Most of the points were evenly distributed on both sides of the midline and concentrated in the central area. The majority of the research included had moderate sample sizes, and the funnel plot indicated that these studies were biased to a low degree. However, a few locations outside the two dashed lines indicate that this research might be potentially heterogeneous.

Adverse events

According to the studies utilized, adverse events were minor, did not require medical evaluation or specific intervention, and primarily consisted of skin irritation, slight headache, stomachache, and nausea from the application of the treatment. Out of 27 trials, adverse events were reported in nine studies. Adverse events were reported in five out of nine trials and were related to patients complaining of transient dizziness or headache after the first treatment. Two trials reported that a total of six subjects had slight skin reddening and mild swelling at the end of the stimulation procedure, and the side effects subsided spontaneously. Mild scalding of the skin also was observed in two trials after the first moxibustion treatment.

Acupoint selection

Therapy patterns and classic acupuncture points were among the details we examined (Figure 8). The most frequently used acupoints were GV20 (85.71%), EX-HN1 (57.14%), GV24 (53.57%), and GB20 (35.71%), as shown in Figure 3. Even though researchers used various acupoint selection and combination techniques, most high-frequency acupoints for MCI treatment were focused on the craniofacial area. The original studies were all administered by hospital employees, with acupuncture treatments administered by medical professionals. The time of therapy varied between 30 and

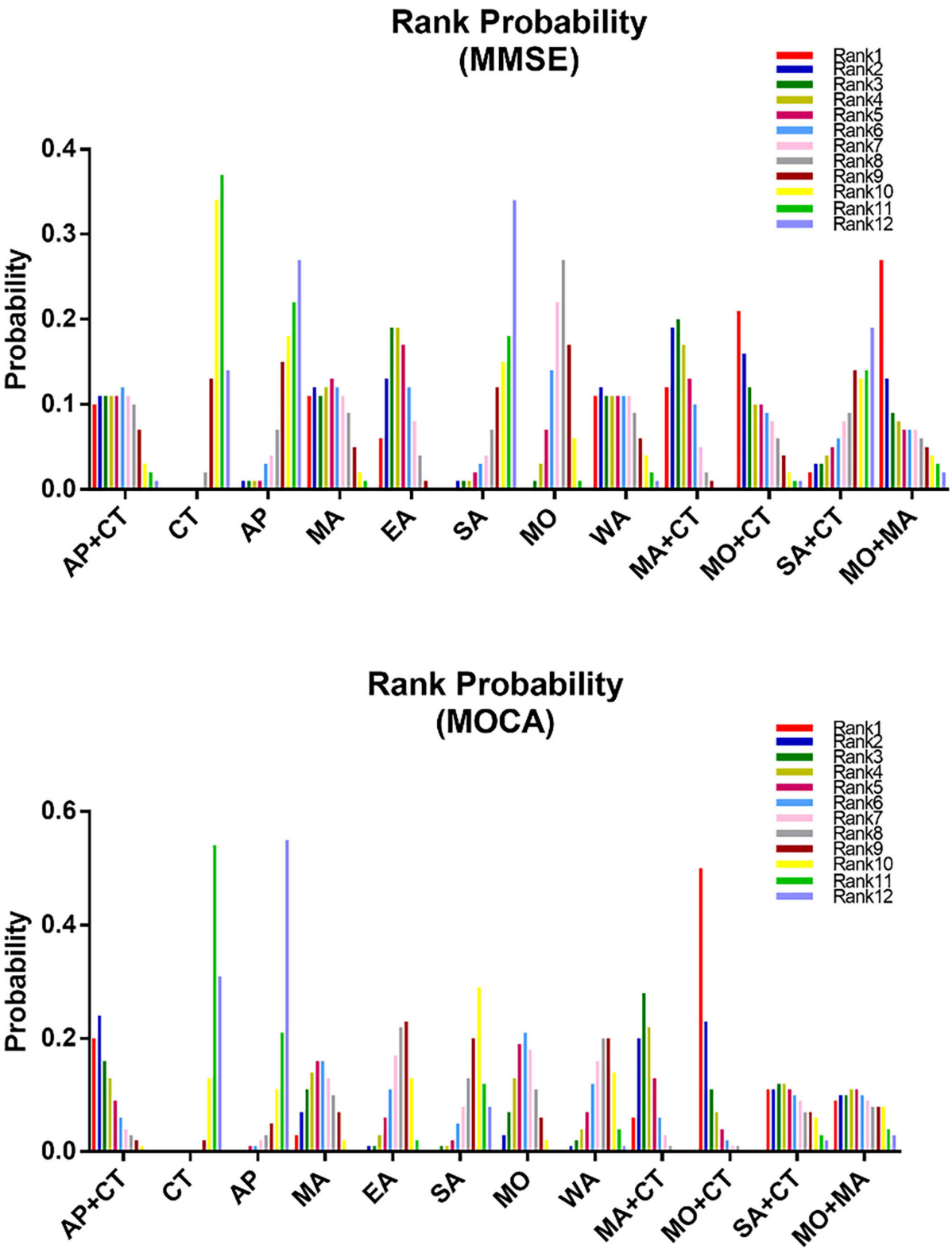

FIGURE 5
Rank probability plot of network meta-analysis for MMSE and MoCA.

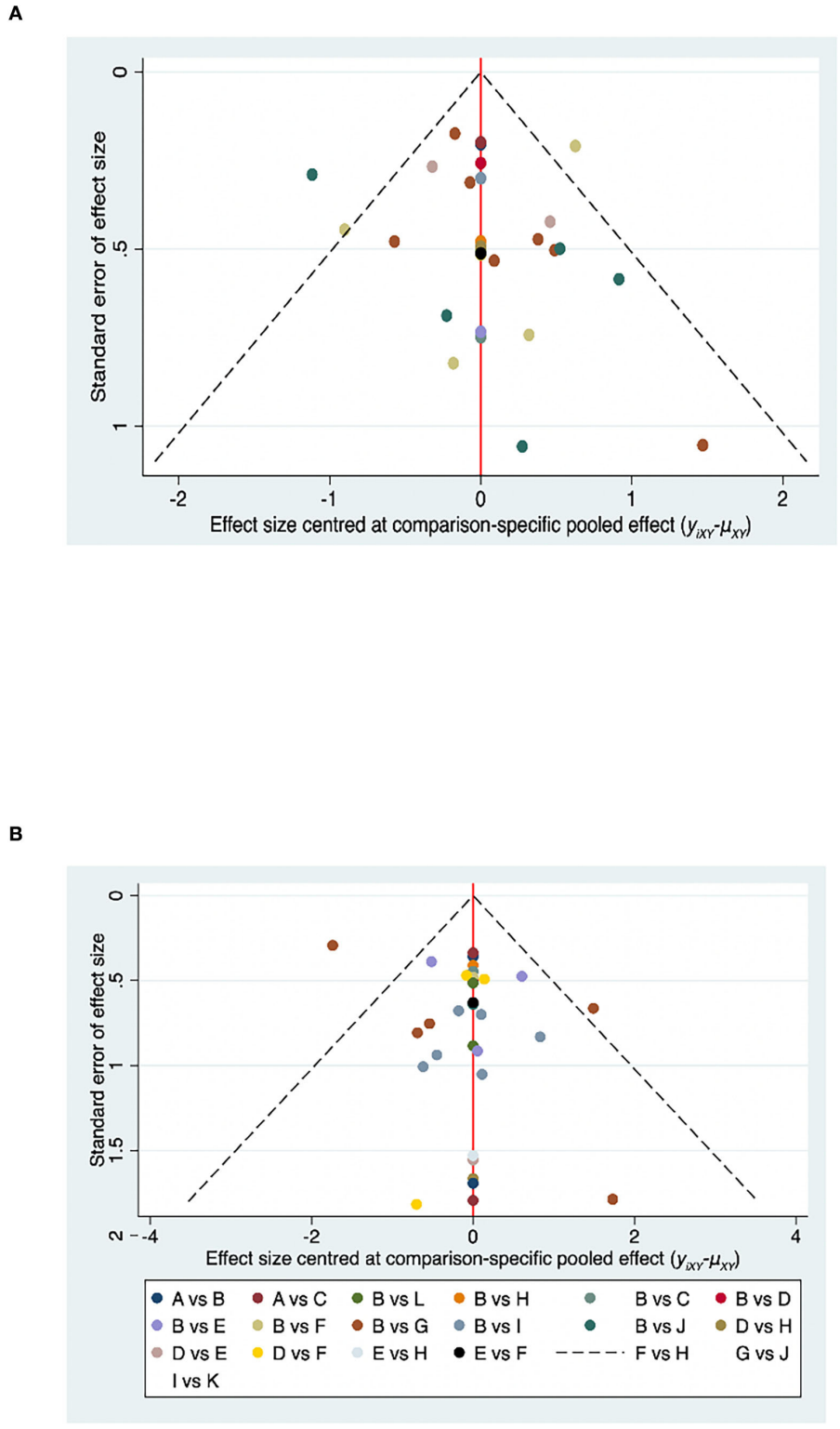

FIGURE 6
Funnel plot of MMSE and MoCA for the network meta-analysis. **(A)** Funnel plot of MMSE for the network meta-analysis. **(B)** Funnel plot of MoCA for the network meta-analysis.

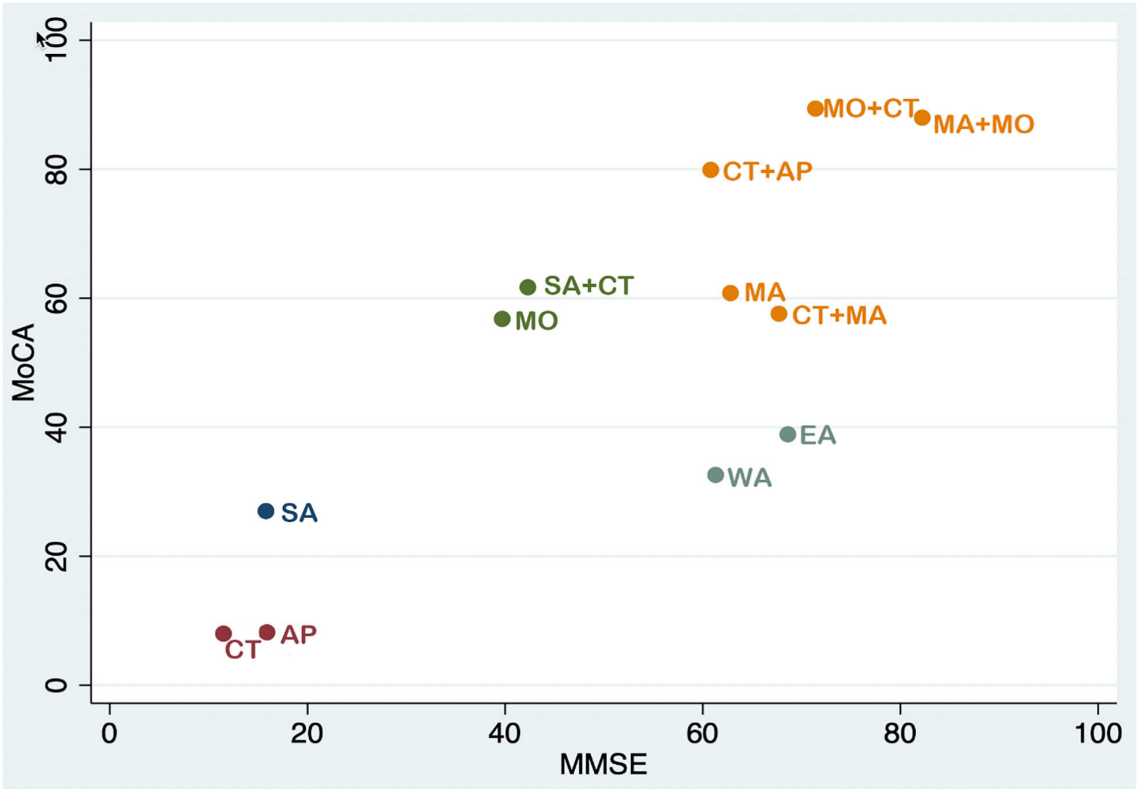

FIGURE 7
Cluster ranking plot in MMSE and MoCA scores. Each color represents a group of interventions that belong to the same cluster. Interventions lying in the upper right corner were more effective than the other interventions.

360 min, with 30 min being the most common ($n = 13$). The shortest treatment trial lasted 7 days, while the longest lasted 3 months. Despite the fact that treatment intervals ranged from 7 to 90 days, more than 96% of studies ($n = 26$) favored a long therapeutic course of at least 4 weeks.

Discussion

The study presented herein is, to the best of our knowledge, the first Bayesian NMA of acupuncture-related approaches for the treatment of MCI. Acupuncture has been demonstrated to be effective in the treatment of MCI, but there are also many different types of acupuncture. Low-curative-effect acupuncture methods worsen the condition of MCI patients and waste medical resources. As a result, we set out to find the best acupuncture therapy options for MCI in this Bayesian network to compare the effects of different acupuncture-related therapies. The study included 27 RCTs with a total of 2,210 subjects. MMSE in NMA indicated that of the 12 interventions evaluated, EA, MA combined with CT, MO combined with CT, and MO combined with MA had considerably more significant treatment effects than the other treatments. According to the results of MoCA in NMA, AP combined with CT, MA combined with CT, MO combined with CT, and MA also led to significantly increased beneficial effects. The node-splitting method revealed that the direct and indirect evidence supporting treatment efficacy was consistent. We were able to rate a large number of treatments by calculating similar probabilities and then ranking them from highest to lowest based on the method we employed. MO combined with MA ranked high in the MMSE, and MO combined with CT was shown to be the most effective treatment in MoCA. It is therefore noteworthy that the cumulative probability of MA combined with MO did not show a significant advantage over MO combined with CT in terms of MoCA. Due to individual variation, MoCA may not be the most suitable method for evaluating the clinical efficacy of TCM.

According to cumulative probability, the cluster ranking plot showed five categories of interventions (Figure 7). The following are a few key findings from the outcomes of the projects included in this study. The cluster ranking plot showed five categories of interventions that were based on cumulative probability. On the plot, the categories of SA combined with CT and MO are located in the left-middle, while the categories of EA and WA are situated near the right-middle. However, the impacts of these four acupuncture methods on MMSE and

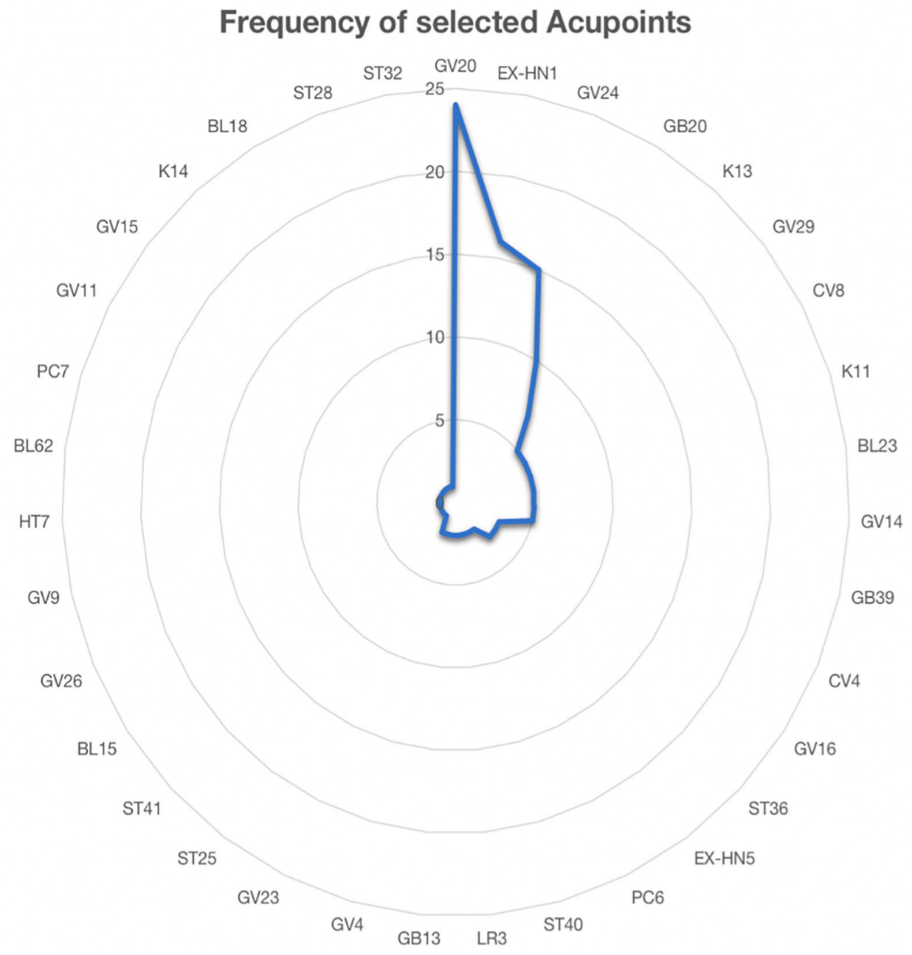

FIGURE 8
The frequency of selected acupoints for treatment.

MoCA scores were rather limited, and these methods may not contribute to satisfactory clinical benefits. Favorable MMSE and MoCA scoring results are in the last group, which is placed in the upper right corner: MA, MA combined with CT, CT combined with AP, MO combined with CT, and MA combined with MO. The most significant of the outcomes was that MO combined with MA may have superior therapeutic efficacy in the treatment of MCI. MMSE and MoCA scoring results are preferred in the final group, which is placed in the upper right corner and includes the following therapies: MA, MA combined with CT alone, CT combined with AP, MO, MO combined with CT, and MA combined with MO. Based on our findings, we propose that clinical acupuncturists choose one of these three approaches as the primary therapy option for MCI patients. MA combined with MO appears to be the most effective treatment for improving MMSE and MoCA scores in MCI patients.

In TCM, acupuncture is a crucial component for controlling health. Its therapeutic benefits may be induced by stimulating certain meridian acupoints. Numerous investigations have shown that acupuncture can help with brain tissue healing in both human tests and animal studies, with reliable and repeatable results. Acupuncture is increasingly being utilized in clinical studies to treat dementia and cognitive impairments brought on by MCI disease, especially because of its safety when compared to pharmaceutical treatments. Acupuncture stimulation has reportedly been shown to potentially stimulate nerve fibers, enhance local blood flow, and stabilize and speed up cerebral metabolic responses in a variety of brain systems. Acupuncture may also improve LTP deficiencies and boost cerebral blood flow to lessen dementia symptoms, according to animal studies (57). A previous systematic review found that MA improved MoCA and MMSE scores in elderly patients with MCI, indicating that MA may have some therapeutic benefits for senior patients with MCI (58). Additionally, a clinical investigation using MA to treat MCI demonstrated that manual acupuncture was beneficial in enhancing memory and cognitive function in MCI patients (59). Moxibustion is an external treatment method used in traditional Chinese medicine. It has

the effect of warming the meridians, dispersing cold, tonifying the deficient and consolidating the root, motivating Qi and blood, eliminating swelling and dispersing knots, and preventing diseases (60). Due to the deficiency of Qi in elderly MCI patients, Moxibustion has the effect of removing an obstruction from the meridians and collaterals. When the herb Artemisia vulgaris is burned over an acupoint, it produces a warm stimulation effect and is often regarded as an acupuncture treatment. It has proven to be fruitful when used in moxibustion intervention in MCI (61). Furthermore, MA and MO are frequently employed in research and therapeutic practice. Consequently, we recommend that clinical acupuncturists consider utilizing one of these approaches as the first therapy choice for MCI patients. Overall, MA combined with MO appears to be the most effective treatment for improving MMSE and MoCA scores in patients with MCI. Therefore, our study may provide an important clinical reference value for clinical investigations of acupuncture in the treatment of MCI and provide essential information to decision-makers.

The selection of acupuncture points is one of the essential factors for ensuring that acupuncture positively affects the patient. Despite the wide range of precise procedures in the included RCTs, a descriptive analysis of the data from the available studies showed the following acupuncture treatments to be effective for MCI. In our research, the most often used local points were Baihui (GV20), Si-shen-cong (EX-HN1), Shenting (GV24), and Feng-chi (GB20). The specific nature of acupuncture treatment makes it necessary to utilize studies that explore particular acupuncture manipulations. GV20 is a crucial point on the GV meridian, which receives all of the yang-qi transmitted by all of the body's meridians. It has been reported that GV20, EX-HN1, and GV24 are linked to the brain and play critical roles in influencing cerebral function, including cognition (62). It is believed in TCM that "the brain is the host of the mind," which explains why the primary acupoints in our study were mainly chosen in the craniofacial region, whereas the auxiliary acupoints that can lift the spirit, clear the mind, or promote resuscitation were selected to be dispersed throughout the body (63). This pattern of acupoint selection and the combination is highly consistent with the theory of Traditional Chinese Medicine. Given that MCI is a chronic neurodegenerative disease, most researchers recommended a longer retention time, more frequent sessions, and a longer therapy course to guarantee appropriate acupuncture stimulation. A needle retention time of 30 min is also advised.

In addition, we reviewed nine trials that had documented adverse events. The most often reported adverse effects were increased minor headaches, skin irritation, and other symptoms. According to the findings, the needle fainting effect was the primary source of a slight headache, whereas conventional medications induced stomachache and nausea. Furthermore, the rate of adverse events was relatively high for both moxibustion and warm acupuncture. However, because of the limited sample sizes in the studies of these two intervention modalities, it is difficult to draw definitive conclusions about adverse events.

Limitations

There were several limitations in this study. First and foremost, there was insufficient information on the effectiveness of acupuncture-related treatment for MCI due to the small sample sizes, the small number of patients in each trial, and the limited assessment of MMSE and MoCA data currently accessible. Second, a small number of randomized controlled trials (RCTs) revealed potential bias due to the small number of participants and the use of voluntary reporting. Fortunately, no apparent inconsistency or heterogeneity was found in this network meta-analysis. However, it is possible that some of the included articles overstated the efficiency of therapies, which could have had an impact on our findings if they had been excluded. Third, we have excluded several complementary and alternative therapy interventions due to our selection criteria for outcome measures, which may have impacted the quality of the evidence in this area. Furthermore, as for the use of Nimodipine and Donepezil in conventional therapy for MCI, some evidence from Chinese clinical articles shows that Donepezil and Nimodipine are used in the clinical treatment of MCI in some areas of China, but are rarely used in the USA and other parts of the world (52). Last, although the included studies were subjected to a full assessment using the Cochrane Collaboration's risk of bias methodology, the overall quality of the trials was not very good. This may be a result of using solitary blindness as a high-risk condition. Due to the particular nature of acupuncture research, single-blind designs are frequently used, which may have elevated the possibility of bias in the study findings.

Conclusion

This study has demonstrated that manual acupuncture combined with moxibustion is the most effective treatment for improving MMSE and MoCA scores in patients with mild cognitive impairment. However, more robust comparative evidence is needed to confirm this conclusion. We suggest that more high-quality, large-sample, multicenter randomized controlled trials (RCTs) be done to confirm these findings.

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

JZ and NX conceived and designed the study. XL and KD were involved in writing and draft preparation. LY and ZL were involved in literature inclusion and exclusion. XL was involved in writing, draft preparation, and supervision. All authors contributed to the manuscript and approved the submitted version.

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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.2022.942682/full#supplementary-material

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Acupuncture decreases amygdala functional connectivity in subjective tinnitus

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Introduction: Subjective tinnitus is a common and intractable ear disease. The effectiveness of acupuncture in the treatment of subjective tinnitus has been confirmed, but its mechanism of action is not clear. The structures of the amygdala (AMYG) are mainly closely related to emotion in the human brain. This study aimed to investigate the changes in functional connectivity (FC) of AMYG in subjective tinnitus to elucidate the neural mechanism of acupuncture.

Methods: Correlation scale scores of 26 patients with subjective tinnitus were collected, including Tinnitus Evaluation Questionnaire (TEQ), Tinnitus Handicap Inventory (THI) and Visual Analog Scale (VAS). Meanwhile, rs-fMRI data were collected before and after acupuncture treatment in the patients, and in healthy controls (HC) matching the patient's gender and age. Then, AMYG was selected as region of interest to perform FC analysis. Finally, FC patterns of AMYG were first compared between patients with subjective tinnitus and HC, and then within subjects pre-acupuncture and post-acupuncture. Simple linear regression models between correlation scale scores and FC-values were established as well.

Results: Acupuncture treatment relieved the severity of tinnitus. With the acupuncture treatment, the total THI score, TEQ score, and VSA score of patients were significantly lower than before ($p < 0.05$). Compared with HC, FC of tinnitus patients between AMYG and right inferior temporal gyrus and right precuneus significantly decreased before acupuncture (voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF), while FC of tinnitus patients between AMYG and left superior frontal gyrus and right superior temporal gyrus significantly decreased after acupuncture treatment (voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF). FC of tinnitus patients between the AMYG and right superior frontal gyrus and left paracingulate gyrus showed significant decrease after acupuncture treatment (voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF). Besides, the linear regression models of the effect of THI on FC and VAS on FC performed were statistically significant ($p < 0.05$).

Discussion: The findings demonstrate that acupuncture can decrease FC of AMYG, which could be positively correlated with the relief of tinnitus symptoms. This result suggests that acupuncture stimulation can effectively relieve the severity of tinnitus by decreasing FC of AMYG in subjective tinnitus patients.

KEYWORDS

acupuncture, subjective tinnitus, functional magnetic resonance imaging, functional connectivity, amygdala

Introduction

Subjective tinnitus refers to a type of auditory disease with abnormal sounds in the ear as clinical manifestations only and without any damage to the auditory structure and nervous system of the ear (1). The incidence of tinnitus in the population is relatively high. According to the European Multidisciplinary Tinnitus Guidelines, the prevalence of tinnitus in adults is 10–19%, and about 1/3 of senior citizens have long-term perception of tinnitus (2). The continuous annoying dull chirp will make patients easier angry, damage attention, anxiety and other negative effects. Tinnitus tends to cause emotional disorders, and mental factors affect tinnitus in turn, and the two enter a vicious circle (3). The psychological pressure generated by this vicious circle does serious harm to the physical and mental health of patients (4). Because the symptoms that patients complain about tinnitus are often subjective, and there are few methods for objective assessment, subjective tinnitus has become one of the difficult ontological diseases that need to be solved urgently in clinical practice.

With the development of functional magnetic resonance imaging (fMRI) technology, it is found that the abnormal activity of the auditory system may be caused by changes in functional connectivity (FC) between the auditory network and the non-auditory system (5). Some studies suggest that the central mechanism of subjective tinnitus involves auditory system and non-auditory system (6), tinnitus perception may be the result of auditory-limbic interaction, and structural abnormalities such as amygdala (AMYG) are related to the severity of tinnitus perception (7, 8). AMYG is a part of the limbic system (9), which is involved in a variety of emotional processes (10–12). Chen et al. found that the FC of AMYG to cortical regions was reduced in patients with tinnitus and mood disorders (13). Another study found that the volume of AMYG in tinnitus patients may be related to the distress of tinnitus patients to reduce the related emotions caused by tinnitus (14). On the basis of the above research, we concluded that the amygdala is closely related to tinnitus and speculate whether acupuncture affects AMYG to relieve tinnitus.

Acupuncture is considered to be an effective method for tinnitus and psychiatric diseases (15). At present, acupuncture research based on fMRI mainly includes the relevant research on acupoint specificity (16), acupuncture effect mechanism (17, 18), needling sensation of *deqi* (19, 20) and acupuncture analgesia (21, 22). These studies indicate that the mechanism of acupuncture and the central nervous system may be closely related (23). However, there are few studies on the neural mechanism of acupuncture for subjective tinnitus using fMRI technology. Therefore, this study aims to analyze the effects of acupuncture on AMYG of patients with subjective tinnitus based on fMRI technology, and to further explore the central mechanism of acupuncture in the treatment of subjective tinnitus, whether acupuncture changes the FC of AMYG in patients with subjective tinnitus and whether it is related to clinical symptoms.

Materials and methods

Participants

A sample size of twenty-six was decided according to the effective rate of our team treated subjective tinnitus with acupuncture, drop-out rate and other related factors. Twenty-six patients (fourteen females; mean age: 45.2 ± 11.45) with subjective tinnitus and twenty-six age- and gender-matched healthy controls (HC) (fourteen females; age 46.3 ± 12.82) were recruited through the Acupuncture and Rehabilitation Department and the Otolaryngology Department of the First Affiliated Hospital of Anhui University of Chinese Medicine. Exclusion criteria for all participants: (1) history of craniocerebral trauma; (2) those unsuitable for MRI (such as internal metal implants); (3) intracranial lesions such as tumors, hemorrhage and infarction detected after MRI.

This study is a case-control study and approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine (ethics number: 2021AH-29). Each subject signed a written informed consent form before participating in the study.

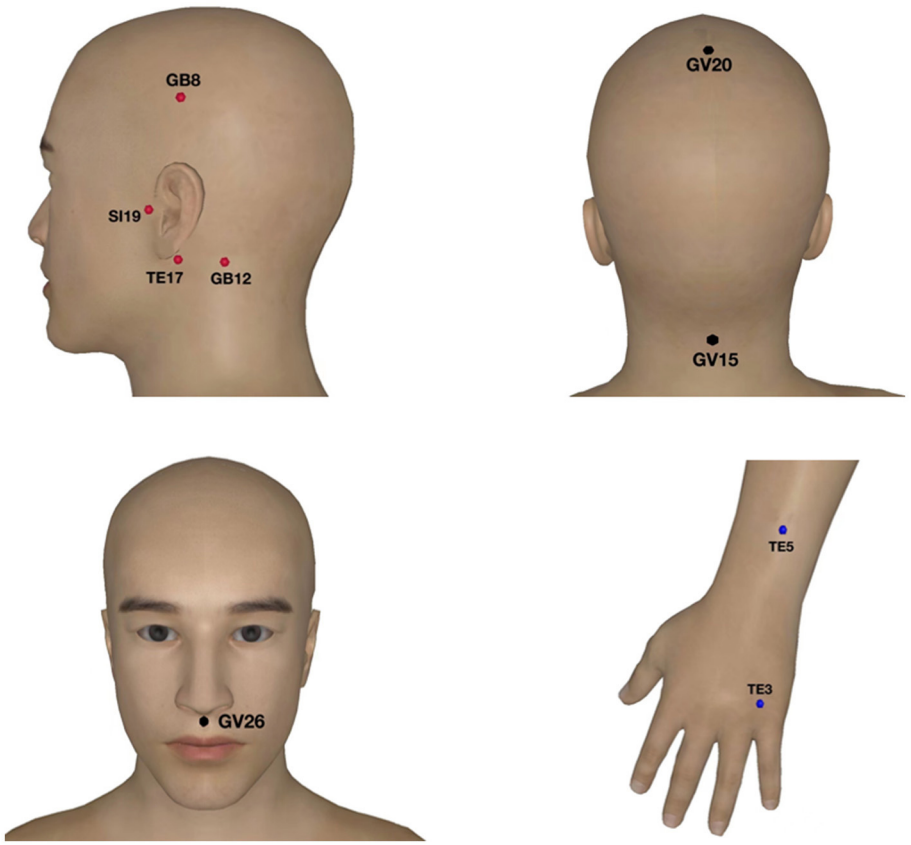

FIGURE 1
Acupoints selected for acupuncture treatment of subjective tinnitus. The red points are the ones on the affected side of tinnitus, the blue are the distal bilateral acupoints and the black are the Governor Vessel acupoints.

Evaluation of clinical symptoms

The scales used to assess the severity of tinnitus include Tinnitus Evaluation Questionnaire (TEQ) (24, 25), Tinnitus Handicap Inventory (THI) (26), Visual Analog Scale (VAS) (27). This study used the TEQ independently developed by the Chinese team to score. The TEQ divides the severity of tinnitus into five grades according to the total score of each index with grade one the least severe to grade five the most. The related scales (THI, TEQ, VAS) of subjective tinnitus patients were collected before and after the acupuncture course, respectively.

Acupuncture treatment

Acupuncture treatment was performed by Professor Yang Jun, the National Famous Doctor of Traditional Chinese Medicine, an honorary title for TCM expert in China. The acupoints on the affected side of tinnitus (SI19, TE17, GB12, GB8), distal bilateral acupoints (TE3, TE5) and the Governor Vessel acupoints (GV20, GV26, GV15) were selected (Figure 1). The acupuncturist inserted sterile and disposable needles (length 40 mm, width 0.35 mm) at the above acupoints. After disinfecting the skin with 75% alcohol, acupuncture a certain depth (1.5–3 cm), the acupuncturist manipulated the needle for obtaining the *deqi* sensation (acid, numbness, swelling and pain). All acupoints were routinely given acupuncture treatment, and SI19 was needle-inserted into with the mouth open. The needles were retained on the acupoints for 30 min, and the patients received 10 times acupuncture treatments (once every other day).

Data acquirement

The resting-state fMRI (rs-fMRI) scans of all subjects were performed on the same 3.0 T MRI scanner (Discovery MR750, GE, United States) in the Digital Imaging Technology Laboratory of the First Affiliated Hospital of Anhui University of Chinese Medicine, using an 8-channel high-resolution radio-frequency head coil. Data of rs-fMRI for all subjective tinnitus patients as well as HC were collected before and

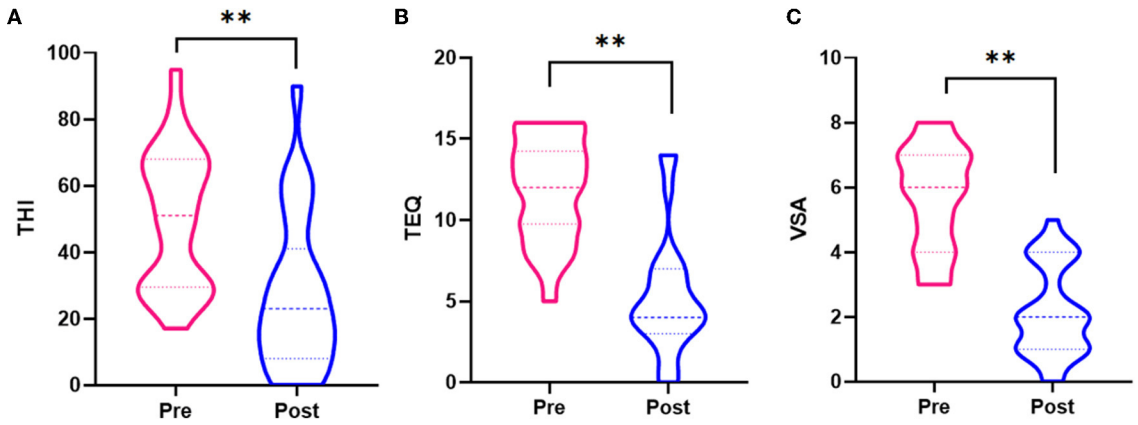

FIGURE 2
(A) Differences of THI scores between pre-acupuncture and post-acupuncture. **(B)** Differences of TEQ scores between pre-acupuncture and post-acupuncture. **(C)** Differences of VAS scores between pre-acupuncture and post-acupuncture. **Significant group difference with $p < 0.05$.

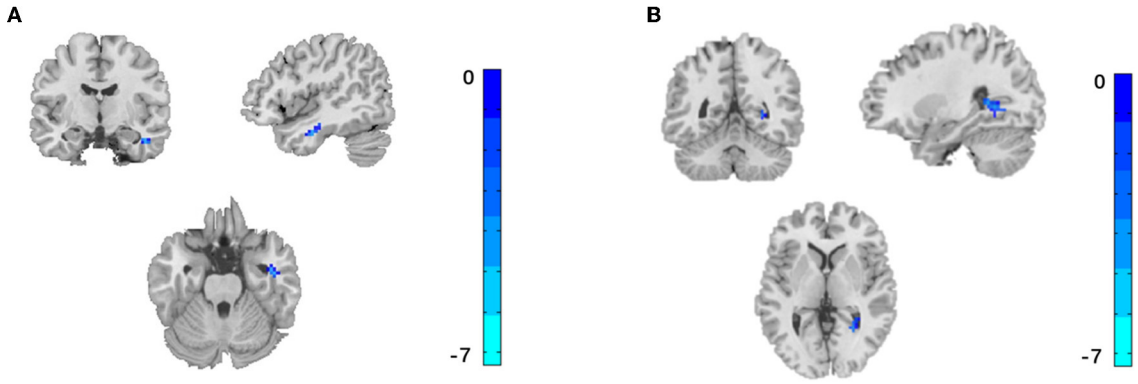

FIGURE 3
Significant difference for FC between pre-acupuncture in subjective tinnitus and healthy control. The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. **(A)** FC between AMYG and right inferior temporal gyrus. **(B)** FC between AMYG and right precuneus.

after acupuncture. The data of rs-fMRI after acupuncture was collected 2 days after 10 times of acupuncture treatment. Before scanning, the subjects were instructed to remove metal and magnetic objects from their bodies, and then entered the scanning room after the whole body was relaxed. Earplugs and foam pads were used to reduce noise, and foam pads were added to reduce head movement. During the scanning process, the subjects were instructed to stay awake, close their eyes, lie down quietly, and not to think about anything special.

Structure images were acquired with 3D T1 BRAVO sequence with the following settings: repetition time (TR) = 8.2 ms, echo time (TE) = 3.2 ms, inversion time = 450 ms, flip angle = 12°, field of view = 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm, voxel size =1 × 1 × 1 mm^3, slice number = 188. Resting-state fMRI data were acquired using a gradient-echo single-shot echo planar imaging sequence, which included 217 time points and took 8 min and 40 s. Specific scan parameters are as follows: TR = 2,400 mms, TE = 30 ms, flip angle = 90°, field of view = 256 × 256 mm^2, matrix size = 64 × 64, slice thickness = 3 mm, slice number = 46.

Data processing

Rs-fMRI data processing and analysis were performed with DPABI software (DPABI_V6.1_220101) (28) as follows. Firstly, the image collection data of the first 10 time points were removed to exclude the influence of the initial instability of the magnetic field signal, and at the same time to achieve the subject's adaptation to the magnetic field. Secondly, slice-timing and realignment for head motion correction were performed, and the data with head motion over 3 mm or 3° were excluded.

TABLE 1 Comparison of FC between pre-acupuncture in subjective tinnitus and healthy control.

Regions	Side	Voxels	MNI			*T*-value (Peak intensity)
			X	Y	Z	
Amygdala						
Inferior temporal gyrus	R	44	46	−9	−25	−5.599
Precuneus	R	35	27	−50	3	−4.818

The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. A positive *T*-value indicates an enhanced FC, and a negative *T*-value indicates a decreased FC.
MNI, Montreal Neurological Institute; Human brain coordinates proposed by the Montreal Neurological Institute.

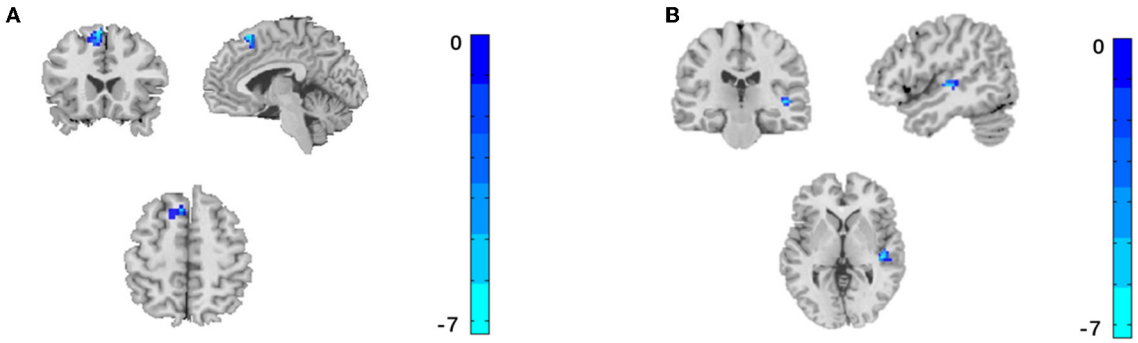

FIGURE 4
Significant difference for FC between post-acupuncture in subjective tinnitus and healthy control. The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. **(A)** FC between AMYG and left superior frontal gyrus. **(B)** FC between AMYG and right superior temporal gyrus.

Thirdly, data were co-registered with the structural images, spatial normalized to the Montreal Neurological Institute (MNI) template, and voxels were re-sampled to $3 \times 3 \times 3$ mm^3 resolution. Finally, data were spatially smoothed with a 6-mm full width at half-maximum (FWHM) Gaussian kernel, and detrended and filtered (0.01-0.08 Hz).

Using WFU_PickAtlas software (http://www.ansir.wfubmc.edu), the bilateral AMYG were used as region of interest (ROI). DPABI software was used to calculate FC between ROIs and the whole brain.

Statistical analysis

Two-sample *t*-tests were conducted at both pre-acupuncture and post-acupuncture to compare the FC changes between subjective tinnitus patients and HC, age and gender included as covariates. Paired Student's *t*-tests were used to compare the FC changes between pre-acupuncture and post-acupuncture. The results of group analysis were corrected using a Gaussian Random Field (GRF) of voxel $p < 0.001$, cluster $p < 0.05$.

The FC of brain regions with significant differences in subjective tinnitus patients was extracted. Then, simple linear regression models were established by using the clinical characteristics of tinnitus (THI, TEQ, VAS scores) as the independent variables and FC as dependent variable. With the data, six separate simple linear regressions were built which showed the effect of THI on FC, TEQ on FC, and VAS on FC before and after acupuncture, respectively. The significance value was set as $p < 0.05$.Residual normality, homoscedasticity and removal of outliers were checked by using visual inspection of their histograms, P-P plots and scatterplots.

Results

Clinical symptoms of tinnitus between pre-acupuncture and post-acupuncture

Compared with pre-acupuncture, THI, TEQ, and VAS scores were significantly decreased after acupuncture treatment (Figure 2), and the difference was statistically significant ($p < 0.05$).

Functional connectivity changes

Compared with HC, FC between AMYG and right inferior temporal gyrus and right precuneus were significantly decreased at pre-acupuncture (Figure 3 and Table 1, voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF), and FC between AMYG

TABLE 2 Comparison of FC between post-acupuncture in subjective tinnitus and healthy control.

Regions	Side	Voxels	MNI			*T*-value (Peak intensity)
			X	Y	Z	
Amygdala						
Superior frontal gyrus	L	47	−7	19	52	−5.255
Superior temporal gyrus	R	42	48	−23	1	−4.995

The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. A positive *T*-value indicates an enhanced FC, and a negative *T*-value indicates a decreased FC.
MNI, Montreal Neurological Institute; Human brain coordinates proposed by the Montreal Neurological Institute.

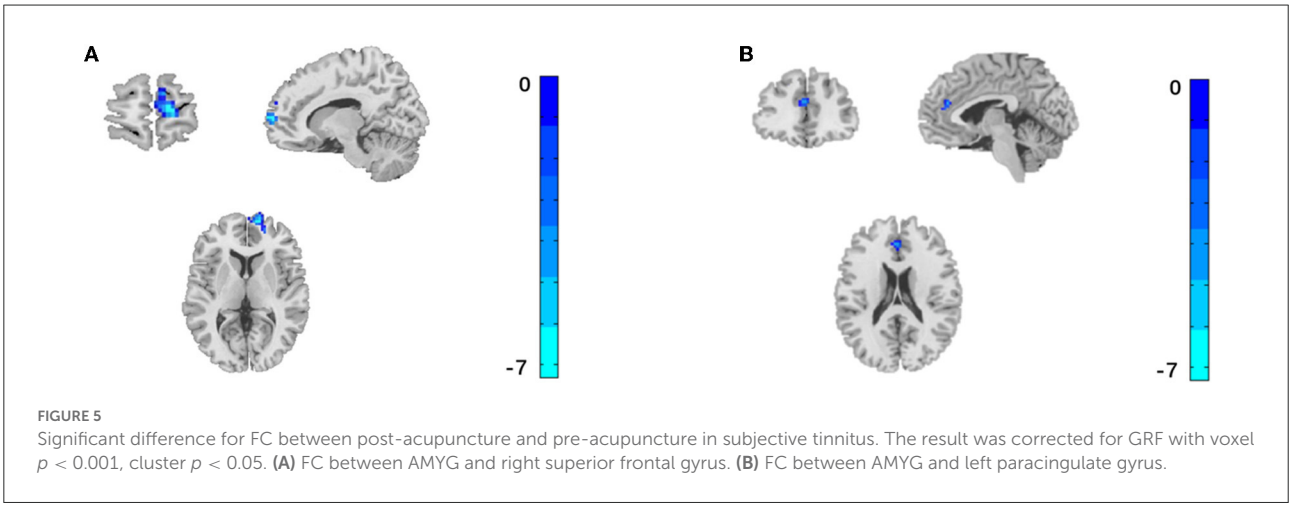

FIGURE 5
Significant difference for FC between post-acupuncture and pre-acupuncture in subjective tinnitus. The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. **(A)** FC between AMYG and right superior frontal gyrus. **(B)** FC between AMYG and left paracingulate gyrus.

TABLE 3 Comparison of FC between post -acupuncture and pre-acupuncture in subjective tinnitus.

Regions	Side	Voxels	MNI			*T*-value (Peak intensity)
			X	Y	Z	
Amygdala						
Superior frontal gyrus	R	99	12	63	12	−6.185
Paracingulate gyrus	L	30	−3	39	21	−4.976

The result was corrected for GRF with voxel $p < 0.001$, cluster $p < 0.05$. A positive *T*-value indicates an enhanced FC, and a negative *T*-value indicates a decreased FC.
MNI, Montreal Neurological Institute; Human brain coordinates proposed by the Montreal Neurological Institute.

and left superior frontal gyrus and right superior temporal gyrus were significantly decreased at post-acupuncture (Figure 4 and Table 2, voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF). Compared with pre-acupuncture, FC between the AMYG and right superior frontal gyrus and left paracingulate gyrus were significantly decreased at post-acupuncture (Figure 5 and Table 3, voxel $p < 0.001$, cluster $p < 0.05$, corrected with GRF).

Linear regression between clinical symptoms of tinnitus and FC

All linear regression models performed were statistically significantly (Table 4, $p < 0.05$), except the effect of THI on FC ($p > 0.05$). The linear regression with FC as dependent variable and TEQ as independent variable showed correlation (Figure 6), the determination coefficient (R^2) of TEQ correlated with the FC was weak and below 50%. The linear regression with FC as dependent variable and VAS as independent outcome showed a strong correlation (Figure 7).

Discussion

Acupuncture can effectively relieve the severity of tinnitus in patients with subjective tinnitus. This study explored the mechanism of acupuncture in the treatment of subjective tinnitus based on rs-fMRI. The results showed that there

are FC of subjective tinnitus patients between AMYG and right inferior temporal gyrus and right precuneus significantly decreased, and acupuncture can decrease FC between AMYG and right superior frontal gyrus and left paracingulate gyrus, which could be positively correlated with the relief of tinnitus symptoms.

TABLE 4 Linear regressions between clinical symptoms of tinnitus and FC.

	p-value	b	R^2	*F*-value
At pre-acupuncture				
TEQ vs. FC	0.006	0.022	0.271	8.917
VAS vs. FC	<0.0001	0.068	0.624	39.830
At post-acupuncture				
TEQ vs. FC	0.004	0.020	0.293	9.976
VAS vs. FC	0.001	0.055	0.346	12.680

b, regression coefficient; R^2, coefficient of determination.

This study selected AMYG as ROI and observed the effectiveness of acupuncture on the FC between it and related brain regions, based on the fact that AMYG is one of the most important brain regions involved in emotion recognition and regulation, and it is often studied in relation to emotional disorders (29–31). Our results suggested that compared with HC, FC between AMYG and right inferior temporal gyrus and right precuneus were significantly decreased at pre-acupuncture. It is basically consistent with previous studies that found abnormalities in AMYG (32), inferior temporal gyrus (33) and precuneus (34) in patients with subjective tinnitus. In addition, it is found that the more serious the tinnitus symptoms (TEQ, VAS scores) are, the more FC value of AMYG increases. Based on the above studies, the damaged pattern of AMYG in tinnitus is necessary, and it is speculated that AMYG may participate in the negative emotional regulation related to tinnitus. After acupuncture treatment, FC between the AMYG and right superior frontal gyrus and left paracingulate gyrus were significantly decreased, indicating that acupuncture might be involved in regulating the neuronal activities in

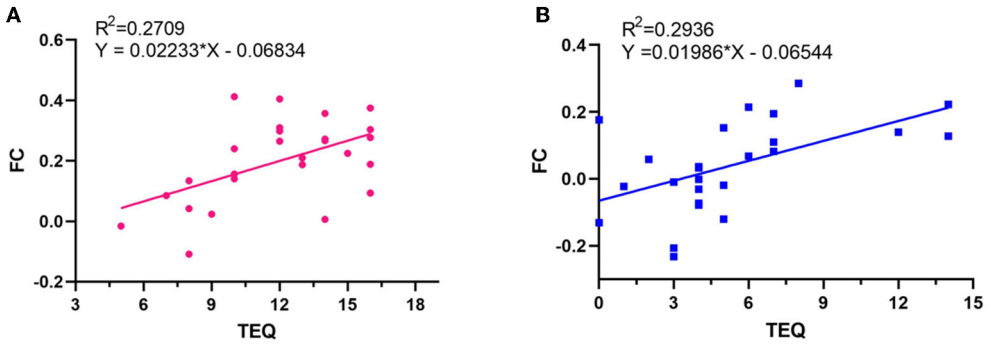

FIGURE 6
Relationships between FC and TEQ scores. **(A)** At pre-acupuncture. **(B)** At post-acupuncture.

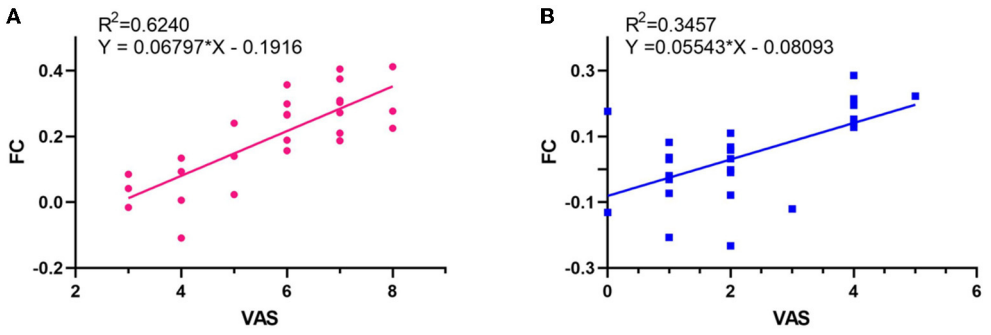

FIGURE 7
Relationships between FC and VAS scores. **(A)** At pre-acupuncture. **(B)** At post-acupuncture.

the above-mentioned brain regions of tinnitus patients, so as to relieve the perception of tinnitus in patients, but the specific regulation mode is still unclear. However, there are still differences in FC between post-acupuncture and HC, and these are mainly concentrated in the default mode network (precuneus, inferior temporal gyrus, superior temporal gyrus and superior frontal gyrus), which is involved in emotional processing and controls the brain's processing of internal and external environments (35). Therefore, we speculate that the decreased of FC in these brain regions may be the result of self-reactive compensation.

This study reveals part of the central mechanism of acupuncture intervention in tinnitus and provides scientific basis for acupuncture treatment of tinnitus. However, due to the limitation of sample size, it is impossible to grade patients with subjective tinnitus in more details and fully reveal the central mechanism of acupuncture treatment of subjective tinnitus. For further research, the sample size can be increased to score the emotion of patients with subjective tinnitus. The temporal cortex, frontal cortex and cingulate gyrus, which are closely related to subjective tinnitus, could be selected as seed points to analyze and compare the correlation between the spontaneous neural activities in different brain regions and cognition, language and hearing during tinnitus.

Conclusion

In conclusion, the study has demonstrated there may have decreased FC in the AMYG of patients with subjective tinnitus, and acupuncture may relieve the perception of subjective tinnitus by decreasing the FC of AMYG. Furthermore, this study might provide reference and new idea in clinical practice.

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 human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ and BZ wrote the first draft of the article, edited, and revised the article. YZ, NG, and WZ analyzed imaging data. ZR and WZ contributed to data acquisition. YF, ZJ, JY, and QZ helped perform the analysis with constructive discussions. LC revised the language. All authors contributed to and have approved the final version of the article.

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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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Comparison of the efficacy of acupuncture-related Therapies for post-stroke motor aphasia: A Bayesian network meta-analysis

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Background: Motor aphasia, which can affect the communication ability of patients and even triggers severe psychological disorders, is one of the most common sequelae after stroke. Acupuncture (a typical complementary alternative therapy) is frequently combined with speech training (ST) to treat post-stroke motor aphasia (PSMA) and presents significant efficacy. However, the most effective acupuncture intervention is still unknown. This study aims to analyze the efficacy of several acupuncture approaches combined with ST for PSMA to identify the best intervention for clinical decision-making by using network meta-analysis (NMA).

Methods: Eight major databases were searched from the time of their establishment to March 2022. Clinical efficacy rate (CER) was used as the primary outcome indicator. R software (version 4.13.0) and STATA software (version 16.0) were used to analyze the data.

Results: A total of 29 randomized controlled trials (RCTs) and six treatment regimens were included in this study. In the pair-wise meta-analysis, we found that the efficacy of scalp-tongue acupuncture (STA) combined with ST [OR = 8.30; 95% Credible interval (CrI): 3.87, 17.33], tongue acupuncture (TA) combined with ST (OR = 3.95; 95% CrI: 2.27, 6.89), scalp-body acupuncture (SBA) combined with ST (OR = 3.75; 95% CrI: 2.26, 6.22), scalp acupuncture (SA) combined with ST (OR = 2.95; 95% CrI: 1.74, 5.0), and body acupuncture (BA) combined with ST (OR = 2.30; 95% CrI: 1.26, 4.19) were significantly superior to that of ST. In addition, the efficacy of STA + ST was significantly superior to that of SA +ST (OR = 2. 82; 95% CrI: 1.24, 6.38) and BA + ST (OR = 3.61; 95% CrI: 1.40, 9.29). According to the surface under the cumulative ranking curve (SUCRA), STA + ST (SUCRA = 97.9%) may be the best treatment regimen to improve the clinical outcome in patients with PSMA.

Conclusion: The NMA showed that STA combined with ST may be the best treatment to improve CER, compared with other combination treatments. However, since the overall quality and number of studies are limited, further RCTs with a large sample and multicenter are needed for further validation.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=316081, identifier CRD42022316081.

KEYWORDS

stroke, motor aphasia, acupuncture, speech training, network meta-analysis

Introduction

Aphasia is a language impairment caused by damage to the brain's language centers (1). Stroke-induced cerebrovascular disease is the leading cause of aphasia, and it has an impact on one-third of stroke survivors. Among them, 30–43% of those affected still have language dysfunction after 6 months post-stroke (2–4). Motor aphasia, often known as Broca's aphasia, is the most common type of aphasia (5). The primary manifestation is impairment in oral expression, and even complete loss of speech, which inevitably affects the patient's ability to communicate and increases the risk of depression and other psychological disorders over time (6, 7).

Although most patients improve throughout the transition from the acute to chronic phase, persisting language impairment is still prevalent in patients (8). Currently, speech training (ST) remains the primary treatment for post-stroke aphasia. However, its effectiveness is inconsistent and restricted. A meta-analysis study of ST for post-stroke aphasia found that it is recommended that speech therapy must be provided for at least 5–10 h per week and should be started as soon as possible after a stroke. Moreover, intensive ST for over 2–3 months is essential to maximize patients' recovery from post-stroke aphasia, and failure to provide this training may affect the prognosis of patients (9). However, not all patients can bear this high intensity and frequency of training (10). Therefore, perhaps ST combined with other interventions may have a more desirable synergistic or complementary effect on the language recovery of patients (11).

As an essential part of Chinese medicine, acupuncture has a history of more than 3,000 years, and its efficacy has been widely recognized. The reconfiguration of the left brain language network has been found to be critical for language recovery in studies (12). An acupuncture study using magnetic resonance imaging (MRI) test showed that acupuncture could restore speech function by inducing activation in the most severely damaged part of the brain's left hemisphere (13). In addition, relevant clinical studies have shown that acupuncture at language-related acupoints can facilitate language recovery by promoting the reorganization of the functional cortex. All of these studies confirm the indispensable role of acupuncture in treating stroke aphasia (14). However, there are many types of acupuncture treatments for post-stroke motor aphasia (PSMA). Most clinical interventions are based on scalp, tongue, and body acupuncture (BA) and have also achieved significant efficacy. Scalp acupuncture (SA) is a method of treating the disease by stimulating acupoints or treatment areas of the cerebral cortex in the corresponding projection areas of the scalp (15). PSMA is located in the brain; thus, acupuncture of the corresponding acupoints in the head can dredge the meridians and can regulate the Qi and blood, which can promote the relative recovery of the patient's damaged speech (16). Tongue acupuncture (TA) is a newly created micro-needle therapy under the guidance of the Traditional Chinese Medicine (TCM) theory and modern biological holography. As the main vocal organ, the tongue is closely related to the internal organs and meridians. By acupuncture of specific points on the tongue body and the sublingual peripheral nerve, patients can promote their recovery of dysarthria and speech function (17). In addition, TCM theory emphasizes a holistic concept, and BA treatment is the integration of holistic and local regulation to regulate the whole body Qi activity of patients and help them restore healthy Qi and repel out pathogenic factors (18). However, it should be noted that there is a lack of guidelines to rank the efficacy of different acupuncture treatments for PSMA, which will confuse the clinical selection of appropriate treatment options for physicians. Combining direct and indirect evidence, network meta-analysis (NMA) draws on classically paired meta-analyses and summarizes the effects of many treatments for a single disease (19, 20). It can also evaluate the effectiveness of various therapies and estimate the relative efficacy of these interventions (21, 22). This study aims to examine the effectiveness of various acupuncture therapies combined with ST for treating PSMA by using NMA as the research tool, so as to provide a reference basis for selecting the best interventions for clinical application.

Abbreviations: PSMA, Post-stroke motor aphasia; RCTs, Randomized controlled trials; NMA, Network meta-analysis; TCM, Traditional Chinese medicine; CER, Clinical efficacy rate; ST, Speech training; BA, Body acupuncture; SA, Scalp acupuncture; TA, tongue acupuncture; SBA, Scalp-body acupuncture; STA, Scalp-tongue acupuncture.

Materials and methods

This NMA follows the NMA systematic review and meta-analysis preferred reporting project guidelines (23). The PROSPERO registration number for this NMA protocol is CRD42022316081.

Search strategy

We searched the Web of Science, PubMed, EMBASE, Cochrane Central Controlled Trials, China Knowledge Network (CNKI), WanFang database, VIP database, and China Biomedical Literature Database (CBM) for randomized controlled trials (RCTs) of acupuncture combined with ST for PSMA. In addition, relevant systematic evaluations and reference lists of included studies were searched manually to ensure the comprehensiveness of included studies. The search started with the establishment of the database on March 28, 2022. The search strategy was to combine subject terms with free words (from Mesh). The subject words included: "acupuncture", "scalp acupuncture", "tongue acupuncture",

"electro-acupuncture", "blood pricking therapy", "eye-acupuncture", "ear acupuncture", "speech training", "stroke", "cerebral infarction", "cerebral hemorrhage", "motor aphasia", "broca aphasia", and "randomized controlled trials." The search strategies such as PubMed are shown in Supplementary Table 1.

Selection and inclusion criteria

The inclusion criteria were as follows. (1) According to the clear diagnostic criteria, regardless of gender and age, patients were diagnosed with PSMA. However, the article should clearly describe that the baseline was comparable between the groups ($P > 0.5$). (2) RCTs. (3) The treatment group received ST combined with different acupuncture therapies [e.g., SA, TA, BA, scalp-tongue acupuncture (STA), and scalp-body acupuncture (SBA)]. There is no restriction on acupuncture point selection, stimulation intensity, or treatment mode. The control group was treated with ST alone or intercomparison between interventions. (4) The primary outcome was the clinical effective rate (CER). Based on the presence of clinical symptoms and objective indicators, efficacy was divided into valid and invalid categories. No improvement in clinical symptoms was considered invalid. CER = (total number − invalid number)/total number ×100% (24).

Exclusion criteria included: (1) The research subjects were non-clinical patients; (2) Participants did not meet the inclusion criteria, such as non-PSMA; (3) outcome indicators that failed to meet the inclusion criteria were included; (4) The treatment group received non-acupuncture therapy combined with ST; (5) repetitively published studies; and (6) Unavailability of full-text studies.

Study selection and data extraction

EndNote version 20 was used to exclude duplicate literature, and the first round of screening was performed by reading the titles and abstracts. Literature that did not meet the inclusion criteria was excluded by re-evaluating the whole text. The data were extracted by two researchers (MT and GH). In the event of a disagreement, the third researcher (SH) would make the final decision. Title, author, publication year, sample size, age, disease course, treatment group, control group interventions, duration of treatment, and outcome indicators were included in the data extraction contents.

Risk of bias assessment

Both JMW and YLL used the RCT risk of bias assessment tool of the Cochrane Handbook of Systematic Reviews version 5.1.0 (25) to assess the overall quality of the studies, and a third investigator (DL) assisted them in determining the degree of variation in their findings. The assessment consisted of seven items, and each item was rated as low, medium, or high risk of bias. Review Manager version 5.4 was used to generate the risk of bias data (Cochrane, London, UK).

Statistical analysis

Network meta-analysis was performed using R software version 4.13.0 based on the Bayesian framework of the Markov chain Monte Carlo (MCMC) consistency model. The initial value was set using four Markov chains. The number of iterations for the first update of the model was set to 50,000, and the number of iterations for continuous updates was set to 100,000. To eliminate the effect of the initial value, the first 50,000 anneals were discarded and the sampling was started from 50,001 iterations. Estimation and extrapolation assume that the density reaches a steady state under which the convergence of the results is evaluated using the potential scale reduction parameter (PSRF). Convergence is suggested to be complete when the PSRF is between 1 and 1.5, indicating that the model is stable enough for data analysis. Dichotomous variables were expressed as the ratio of odds ratios (ORs) and 95% confidence intervals (CIs).

Stata software version 16.0 (StataCorp, College Station, TX, USA) was used to draw a network evidence map to show the close relationship between interventions and each outcome indicator. The loop inconsistency test assessed the inconsistency between direct and indirect comparisons in the presence of closed loops. When the inconsistency factor (IF) was close to zero, 95% CI included zero. It indicated that the direct evidence was consistent with the indirect evidence and the results were reliable. The cumulative ranking curve [surface under the cumulative ranking curve (SUCRA)] was used to rank the probability of different interventions; the higher the scores of SUCRA, the better the efficacy or safety. Minor sample effects or publication bias were detected by comparing corrected funnel plots.

Results

Characteristics of the included studies

A total of 919 studies were searched. After several rounds of screening, 29 RCTs were finally included (26–54), and 2,082 patients were included in the total. Figure 1 depicts the process of screening the literature.

Of these, 28 trials (26–44, 46–54) were two-armed RCTs, and 1 trial (45) was three-armed. A total of six interventions were also included, such as ST, STA combined with ST, TA combined with ST, SBA combined with ST, SA combined with ST, and BA

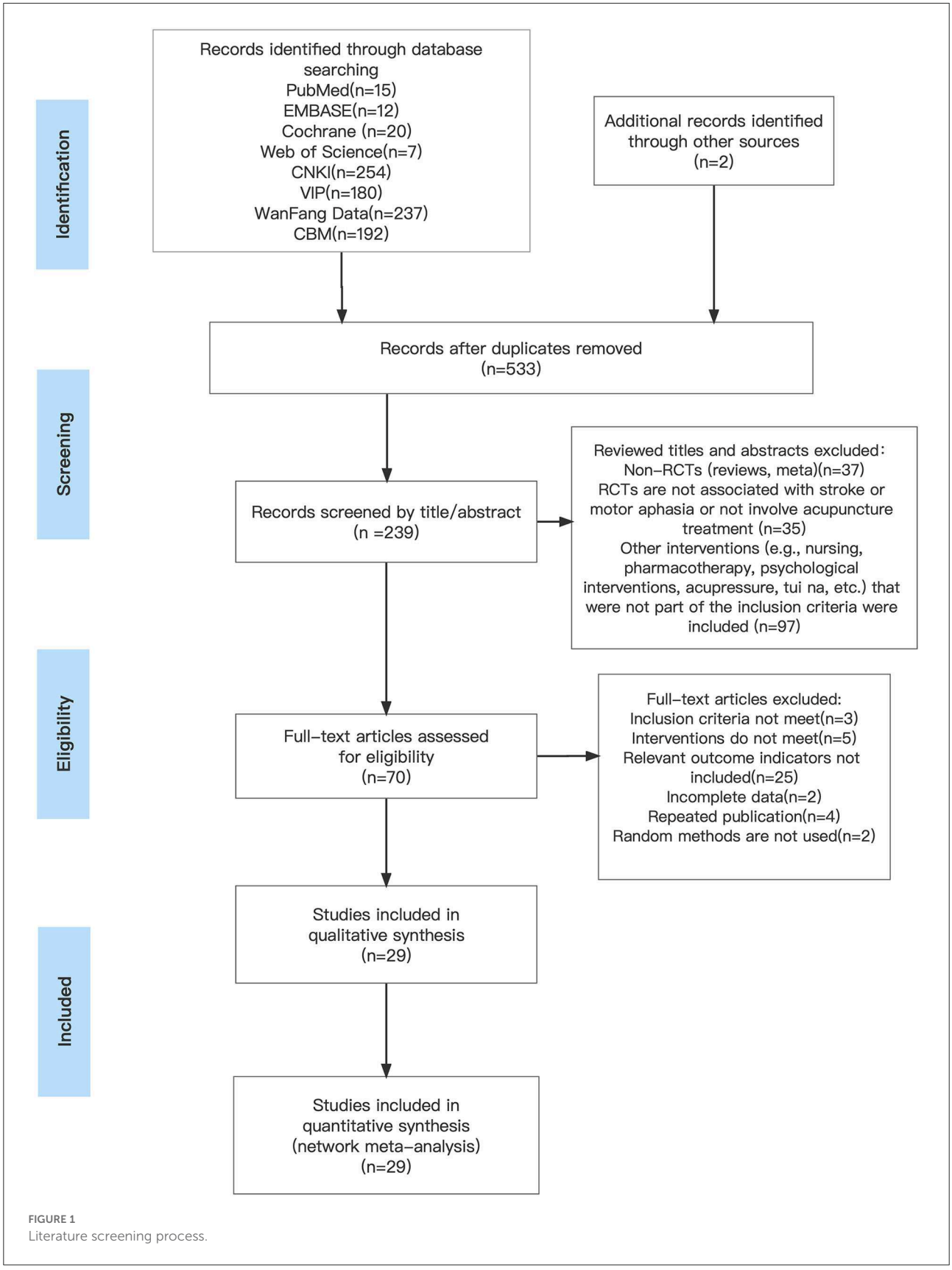

FIGURE 1
Literature screening process.

TABLE 1 Characteristics of included studies.

Study ID	Participant			Age	Gender (M/F)	Interventions			Course
	T	T1	C			T	T2	C	
Qin (26)	33		32	T: 60.52 ± 5.89	T: 23/10	BA + ST		ST	6w
				C: 58.44 ± 6.81	C: 28/ 4				
Fan (28)	34		34	T: 57.85 ± 8.85	T: 18/16	TA + ST		ST	2w
				C: 57.21 ± 9.08	C: 20/14				
Yu (27)	30		30	T: 62.80 ± 9.92	T: 17/13	SBA + ST		ST	8w
				C: 65.40 ± 9.45	C: 19/11				
Wang et al. (31)	35		35	T: 65.4 ± 4.6	T: 19/16	STA + ST		SA +ST	4w
				C: 64.5 ± 4.8	C: 20/15				
Ren et al. (33)	35		35	T: 53.0 ± 4.0	T: 19/16	TA + ST		ST	4w
				C: 55.0 ± 6.0	C: 15/20				
Li et al. (32)	51		51	T: 62.08 ± 7.11	T: 28/23	TA + ST		BA +ST	12w
				C: 63.42 ± 6.77	C: 24/27				
Xu (30)	25		25	T: 64.44 ± 9.7	T: 14/11	TA + ST		ST	8w
				C: 64.72 ± 7.87	C: 15/10				
Zhang (29)	25		24	T: 63.40 ± 8.28	T: 15/10	BA + ST		ST	4w
				C: 59.33 ± 8.13	C: 20/ 4				
Zhang and Sun (34)	38		38	T: 57.32 ± 7.43	T: 21/17	SA + ST		ST	8w
				C: 59.16 ± 7.9	C: 23/15				
Yin (35)	40		40	T: 59.70 ± 12.4	T: 27/13	SBA + ST		ST	4w
				C: 59.48 ± 10.9	C: 29/11				
Yang et al. (36)	30		30	T: 65 ± 9.66	T: 18/12	STA + ST		SBA + ST	3w
				C: 61.97 ± 13.2	C: 21/ 9				
Quan (37)	30		30	T: 56.77 ± 10.1	T: 18/12	SBA + ST		SA + ST	4w
				C: 57.73 ± 9.82	C: 17/13				
Jin et al. (37)	40		39	T: 53.98 ± 9.46	T: 23/17	SA + ST		BA + ST	4w
				C: 54.60 ± 7.65	C: 21/18				
Teng and Hong (39)	46		45	T: 56.30 ± 17.4	T: 24/22	SA + ST		ST	30d
				C: 57.60 ± 16.5	C: 25/20				
Xiong et al. (40)	32		32	T: 63.58 ± 7.44	T: 20/12	BA + ST		ST	5w
				C: 64.08 ± 7.67	C: 18/14				
Wang (41)	30		30	T: 58.24 ± 8.27	T: 18/12	SA + ST		ST	4w
				C: 59.10 ± 8.88	C: 16/14				
He et al. (42)	40		40	T: 53.86 ± 7.12	T: 26/14	STA + ST		ST	8w
				C: 54.18 ± 6.25	C: 25/15				
Hu (43)	30		30	T: 65.33 ± 9.33	T: 17/13	TA + ST		ST	30d
				C: 66.10 ± 6.70	C: 20/10				

(Continued)

TABLE 1 (Continued)

Study ID	Participant			Age	Gender (M/F)	Interventions			Course
	T	T1	C			T	T2	C	
Zhang (44)	30		30	T: -	T: 20/10	SA + ST		ST	3w
				C: -	C: 22/ 8				
Hou et al. (45)	30	30	30	T: 57.07 ± 10.9	T:16/14	SA + ST	SB +ST	ST	14d
				T2: 57.10 ± 11	T2:13/17				
				C: 56.70 ± 10.5	C:15/15				
Li and Yue (46)	36		31	T: 65.16 ± 8.09	T: 21/15	TA + ST		ST	15d
				C: 62.45 ± 7.92	C: 19/12				
Gu (47)	43		41	T: 62.80 ± 7.12	T: 23/15	TA + ST		ST	30d
				C: 63.69 ± 6.79	C: 22/14				
Huang and Huang (48)	42		42	T/C : 62 ± 5.0	T: 22/20	BA + ST		ST	2w
					C: 21/21				
Chen (50)	30		30	T: 61.38 ± 4.23	T: 17/13	STA + ST		ST	60d
				C: 61.25 ± 4.14	C: 16/14				
Huang (49)	58		57	T: 65.85 ± 3.02	T: 31/27	SBA + ST		ST	28d
				C: 64.86 ± 5.39	C: 29/28				
Liang (52)	39		39	T: 65.13 ± 11.32	T: 28/11	STA + ST		BA + ST	2w
				C: 66.44 ± 10.41	C: 29/10				
Shen and Shao (54)	20		20	T: 50.40 ± 11.87	T: 12/8	STA + ST		ST	8w
				C: 54.70 ± 8.63	C: 9/11				
Piao (53)	30		30	T: 58.20 ± 7.31	T: 15/15	SBA + ST		ST	30d
				C: 58.43 ± 6.85	C: 13/17				
Huang (49)	48		48	T: 60.96 ± 9.46	T: 24/24	SA + ST		ST	30d
				C: /	C: 26/22				

BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture; ST, speech training; C, control group; T, treatment group; m, month; d, day; w, week; CER, clinical effective rate.

combined with ST. Notably, all 29 studies reported CER. Specific baseline details are shown in Table 1.

Quality evaluation

Regarding random sequence generation, 17 studies (26, 28, 31, 33–37, 41, 42, 45, 47–49, 51, 53, 54) used random number tables, seven studies (29, 38, 43, 44, 46, 50, 52) used computer-generated random numbers, and 5 studies (27, 30, 32, 39, 40) mentioned randomness only. Regarding distribution concealment, five studies (33, 38, 44, 47, 52) used opaque envelopes, while the remaining 21 trials did not unclear it. Due to the limitations of the intervention, just two studies (29, 46) proposed the blinding of investigators. In four studies (29, 38, 46, 47), investigators were masked to the outcome indicators assessors. A total of 26 studies (26–54) reported prespecified outcome indicators. Moreover, five studies (26, 28, 29, 34, 44) mentioned safety. The results are shown in Supplementary Figures 1, 2.

Network meta-analysis

Clinical effectiveness rate

A total of 29 studies reported the CER (26–54), including 10 direct comparisons [ST vs. STA + ST ($n = 3$), ST vs. SBA + ST ($n = 4$), ST vs. TA ($n = 6$), ST vs. SA + ST ($n = 6$), ST vs. BA + ST ($n = 5$), BA + ST vs. SA + ST ($n = 2$), BA + ST vs. TA + ST ($n = 1$), SA + ST vs. SBA + ST ($n = 1$), SA + ST vs. STA +

ST ($n = 2$), SBA + ST vs. STA + ST ($n = 1$)]. Figure 2 shows the network evidence graph. The results of NMA of clinical efficacy are shown in Table 2. Compared with ST alone, STA + ST (OR = 3.80; 95% CrI: 3.87, 17.83), TA + ST (OR = 3.95; 95% CrI: 2.27, 6.89), SBA + ST (OR = 3.75; 95% CrI: 2.26, 6.22), SA + ST (OR = 2.95; 95% CrI: 1.74, 5.00), and BA + ST (OR = 2.30; 95% CrI: 1.26, 4.19) were all related to the improvement of CER. In addition, the efficacy of STA + ST was significantly superior to that of SA +ST (OR = 3.61; 95% CrI: 1.40, 9.29) and BA + ST (OR = 2.82; 95% CrI: 1.24, 6.38).

According to the results of the SUCRA probability ranking chart (Table 2 and Supplementary Figure 3), STA + ST was probably the most effective intervention to improve clinical efficacy (97.8%), followed by TA + ST (66.8%). The 6 interventions are ranked as follows: STA + ST (97.8%) > TA + ST (66.8%) > SBA + ST (62.6%) > SA + ST (44.3%) > BA + ST (28.3%) > ST (0.1%).

We plotted a comparison-adjusted funnel plot for the CER. As shown in Figure 3, studies were symmetrical in distribution on both sides of the inverted funnel; however, there was still a scattered point below the inverted funnel. Therefore, we further performed Egger's test, and the result showed $P = 0.327$ (>0.05), suggesting that the possibility of risk of bias in this study is low (Supplementary Table 2).

Model convergence and consistency test

Inconsistency can affect the accuracy of NMA and threaten the validity of the results. Thus, consistency testing is an essential part of the NMA process, and it provides specific assurance for the reliability of indirect evidence with the available statistical efficiency (55, 56). This study showed that the network analysis of the primary outcome was consistent with the consistency model ($P = 0.514$; >0.05). In the Brooks Gelman Rubin diagnostic plots, all of the shrinking factors were < 1.2 (Supplementary Figure 4). The IF values of each closed loop were distributed from 0.10 to 1.29 and the lower limit of 95% CI contained 0 (Supplementary Figure 5). Clearly, the results show no apparent signs of inconsistency in this NMA.

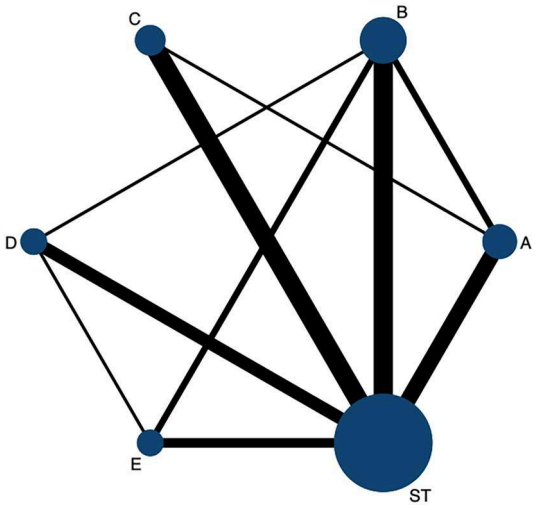

FIGURE 2
The network evidence graph for CER. ST, Speech training; BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture.

Discussion

To the best of our knowledge, this is the first Bayesian NMA study using different acupuncture techniques combined with ST for PSMA. From the 29 RCTs (26–54), we included five acupuncture therapies commonly used in the clinical treatment of PSMA combined with ST, BA + RT, SA + RT, TA + RT, SBA + RT, and STA+ RT, with significant efficacy compared with ST.

Post-stroke motor aphasia is a disease that severely affects the communication ability of patients and even triggers a range of psychological disorders. Thus, it is urgent to explore a safe and effective treatment option. As an alternative therapy for post-stroke aphasia rehabilitation, acupuncture has some typical advantages (57), such as no side effects, ease of operation, low cost, and high compliance. Also, it is more acceptable to most patients. A mechanistic study on acupoint stimulation pointed out that after nerve injury, long-term intense stimulation of acupoints will produce an inflammatory response, sensitize receptors and ion channels on local nerve fibers, and stimulate relevant receptors on acupoints to converge on spinal horn neurons so as to regulate body functions (58). Among the five different acupuncture techniques combined with ST interventions, STA combined with ST may be the most potential one for treating PSMA. This study showed that STA + ST (OR = 3.80; 95% CrI: 3.87, 17.83; SUCRA = 97.8%) was the optimal treatment option to improve the clinical efficiency rate in patients with PSMA.

According to Chinese medicine, the head is closely related to the five Zang organs. Precisely because the disease location of PSMA is in the brain, through the acupuncture of head acupoints, it can stimulate the meridians and internal organs that are connected to it, dredging the meridian, opening the orifice, and producing sound. Modern medical research on cerebral blood flow, EEG, and blood rheology pointed out that acupuncture of scalp points can improve cerebral blood circulation, increase blood flow, restore blood supply to diseased brain tissue, and improve cerebral electrical activity and cortical inhibition, thus activating brain speech function (59, 60). The clinical treatment of PSMA is based chiefly on acupuncture in the speech I region, namely, the projection of Broca's area on the scalp. Coincidentally, the speech I region coincides with

TABLE 2 Relative effect sizes of CER efficacy after the intervention.

SUCRA 97.8%					
E	SUCRA 66.8%				
2.10 (0.82, 5.37)	**C**	SUCRA 62.6%			
2.21 (0.94, 5.19)	1.05 (0.50, 2.22)	**D**	SUCRA 47.8%		
2.82 (1.24, 6.38)	1.34 (0.63, 2.84)	1.27 (0.66, 2.46)	**B**	SUCRA 26.1%	
3.61 (1.40, 9.29)	1.72 (0.83, 3.55)	1.63 (0.76, 3.52)	1.28 (0.63, 2.60)	**A**	SUCRA 0.1%
8.30 (3.87, 17.83)	**3.95 (2.27, 6.89)**	**3.75 (2.26, 6.22)**	**2.95 (1.74, 5.00)**	**2.30 (1.26, 4.19)**	**ST**

Treatments were ranked in order of their likelihood of being the best treatment. The above data represent the confidence interval. The bold font indicates that there was a statistically significant difference between the two treatments. BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture; ST, speech training; CER, clinical effective rate; SUCRA, The surface under the cumulative ranking curve.

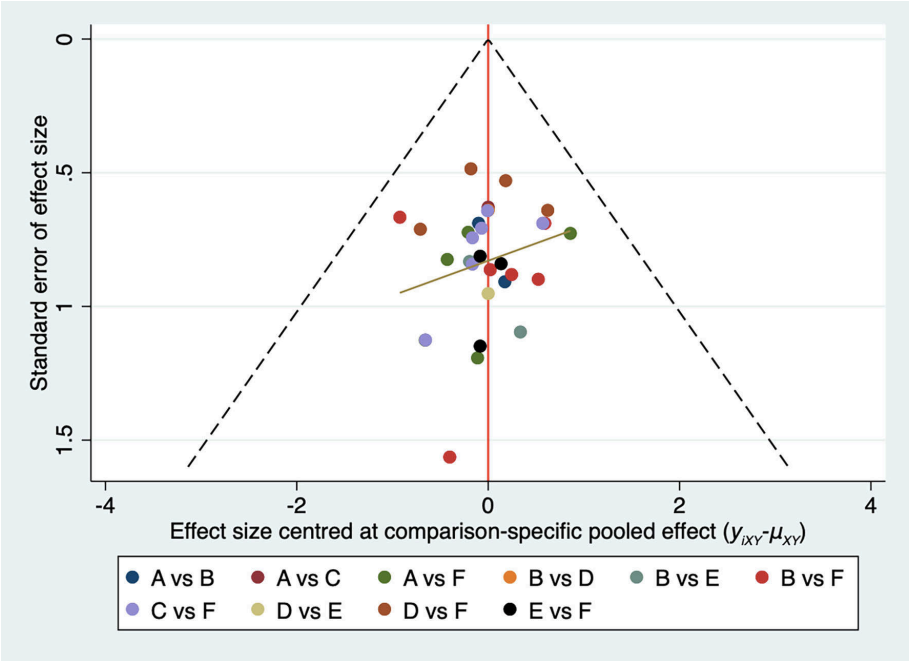

FIGURE 3
Comparison-adjusted funnel plots for the CER network. ST, Speech training; BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture.

the somatotopic projections of mirror neuron brain regions. Also, the activation of the mirror neuron system has an actual language support function, and it is involved in language processing and plays a significant role in activating language response mechanisms (61). Related studies have shown that stimulation of dominant hemispheric lesions and perifocal areas (Broca's area) along with the activation of nondominant hemispheric mirror areas (which coincide with language areas) leads to the strengthening of central reflex connections in language and contributes to the activation and neural remodeling of brain language networks (62, 63). However, SA + ST (SUCRA = 44.3%) ranked relatively weakly in our study results in terms of improved clinical effectiveness. Moreover, the efficacy of the combined treatment of STA + ST (OR = 3.61; 95% CrI: 1.40, 9.29) was significantly superior to that of SA + ST.

Thus, it is noteworthy that as an essential organ of phonation, the tongue plays an essential role in speech rehabilitation. It is closely related to the heart, spleen, kidney, and other visceral organs. Stimulating the acupuncture points on the tongue can dredge the blood stasis meridians on the tongue, improve the local blood supply, and increase the elasticity of the tongue. Also, it helps to regulate the Qi and blood to nourish the tongue's body, thus facilitating the recovery of speech function (43). Modern medicine believes that abundant nerve tissues are distributed on the tongue body, and the stimulation of acupuncture of tongue roots can reflexively enhance the excitability of the central nervous system. Balancing specific and nonspecific conduction systems through cortical-thalamo-cortical regulation can further reconstruct the neural circuit of speech activity and accelerate the recovery of speech function (64). Due to the inconvenience of leaving the needle in the tongue, blood pricking therapy, acupuncture of Jinjin (EX-HN12), Yuye (EX-HN13), and tongue points corresponding to the heart, spleen, and kidney are frequently adopted clinically (65). Studies on related mechanisms pointed out that the anatomical sites of the heart, spleen, kidney, EX-HN12, and EX-HN13 points are between the thyroid cartilage and the root of the tongue and have pharyngeal, vagus, sublingual, and hyoid muscle nerve distribution with the ability to innervate the pharyngeal muscles and vocal cords. Acupuncture of these points stimulates the lingual root nerve, activates reflex pathways, strengthens excitatory reflexes, and promotes recovery of damaged and deformed neurons, thus improving motor aphasia (66). Our study is generally consistent with the above findings that TA + ST (SUCRA = 66.8%) is the second most crucial intervention after STA + ST (SUCRA = 66.8%) for the treatment of PSMA. However, according to TCM, language production is a joint effort between the heart (brain) and the tongue. Although TA has advantages, interventions combined with STA can provide significantly better efficacy. Thus, it is more worthy of clinical application.

Notably, BA + ST (SUCRA = 28.3%) ranked the last among five acupuncture interventions. The concept of BA treatment is based on the holistic concept of Chinese medicine. TCM believes that language is a manifestation of consciousness, and BA treatment, based on the "Xingnao Kaiqiao" acupuncture method, achieves the purpose of opening the linguae orifices by means of inducing resuscitation and harmonizing the Qi and blood (67). The function mechanism in the treatment of PSMA may be related to the following: (1) improving blood rheology, increasing cerebral oxygen supply and blood flow, and significantly reducing brain tissue necrosis; (2) improving brain electrical activity and stimulating brain language function; and (3) improving the metabolism of ATPase in microvascular endothelial cells, thus promoting brain metabolism (40). However, two clinical studies on PSMA (68) pointed out that considering the specificity of post-stroke aphasia regarding disease location, "Xingnao Kaiqiao" acupuncture may lack targeting for language function improvement. This may explain why the efficacy of BA is not superior in treating PSMA compared to other acupuncture interventions. However, it still needs to be explored by including more direct evidence in the future.

Limitations

However, there are still some limitations to our study. First, all of the studies that were included were from China. No studies from other countries may make the results less accurate and convincing. Second, although no significant inconsistencies were found in this NMA, considering the small sample size of individual studies, the small number of included studies, and the lack of more direct comparisons between acupuncture treatments, it may lead to some potential bias and affect the reliability of the results. Finally, given the relatively small number of patients included, additional multicenter and high-quality RCTs are still needed to validate our findings in the future.

Conclusion

After a thorough comparison of the effectiveness indicators of six different treatments, the Bayesian NMA showed that scalp and TA combined with ST (STA + ST) may be the best acupuncture-related therapies to improve clinical outcomes in patients with motor aphasia after stroke. Since the current literature is limited and some reports are of average quality, more controlled trials with large samples and multicenter are necessary to validate the available evidence. However, our study still provides reliable information for PSMA treatment decision-making. Also, it is still recommended that physicians make reasonable choices in clinical practice based on the specific situation of their patients.

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

SF designed the study and wrote the manuscript. MT, GH, JW, and YL participated in the extraction and analysis of the data. LG, SH, and DL critically supervised, evaluated, and validated the article. All of the authors worked on the article and agreed with the submitted version.

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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.2022.992079/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Quality assessment percentage graph.

SUPPLEMENTARY FIGURE 2
Summary chart of quality assessment.

SUPPLEMENTARY FIGURE 3
Probability ranking results of CER of different interventions. ST, Speech training; BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture.

SUPPLEMENTARY FIGURE 4
PSRF diagnostic diagram for CER.

SUPPLEMENTARY FIGURE 5
Loop inconsistency tests. ST, Speech training; BA, body acupuncture; SA, scalp acupuncture; TA, tongue acupuncture; SBA, scalp-body acupuncture; STA, scalp-tongue acupuncture.

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Acupuncture treatment of a pregnant patient with Bell's palsy in the third trimester: Case report

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At present, the optimal treatment for Bell's palsy remains controversial, and the combination of corticosteroids and antiviral medication is usually recommended in the early stage. However, treatment is often delayed because the effects of these drugs on pregnant women and fetuses are still unclear. As a safe and effective complementary alternative therapy, acupuncture can alleviate Bell's palsy symptoms and improve the quality of life of the patient. Herein, we report the clinical presentation of a 27-year-old woman with Bell's palsy who was 26 weeks pregnant at the time of diagnosis. After five courses of treatment, the patient made a complete recovery.

KEYWORDS

acupuncture, Bell's palsy, pregnant patient, third trimester, case report

Background

Bell's palsy is the most common lower motor neuron facial palsy of the seventh cranial nerve, accounting for approximately 70% of all cases of facial nerve palsy. The annual incidence of Bell's palsy is 10–40 per 100,000 population. Pregnant women, especially in the third trimester and the first 2 weeks postpartum, are two to four times more likely to develop Bell's palsy than men and non-pregnant women. Moreover, the prognosis is more severe in pregnant women (1, 2).

The combination of corticosteroids and antiviral medication is usually recommended in the early stage of Bell's palsy. However, treatment is often delayed because the effects of these drugs on pregnant women and fetuses remain unknown (3). The use of steroids in pregnancy may affect the height, weight, and head circumference of newborns; lead to a cleft lip and palate; and worsen glucose control in patients with gestational diabetes (4–7). Therefore, effective drug therapy for Bell's palsy in pregnancy is limited.

As a vital part of traditional Chinese medicine, acupuncture is often used to treat Bell's palsy. While a number of studies (8–10) have certified the efficiency of acupuncture,

one study showed that more research investigating the efficacy of acupuncture for Bell's palsy was necessary (11). There is also a lack of sufficient evidence to support acupuncture treatment for Bell's palsy in pregnant women. A 2010 study reviewed six small-sample RCTs that suggested the efficacy of acupuncture in treating Bell's palsy, but pregnant patients were not included in any of the six RCTs (12). Furthermore, another study revealed that acupuncture can improve Bell's palsy sequelae, but the study excluded pregnant patients (13).

Acupuncture is a safe and acceptable therapy for pregnant women with Bell's palsy (14). In this case, the safety of acupuncture is manifested not only in the half-needling technique that can control the depth of the subcutaneous tissue but also in the acupoints located in the four limbs and face, which will not harm pregnant women or fetuses. Additionally, no reinforcing or reducing methods are used. Therefore, pregnant women with Bell's palsy can benefit from acupuncture because they feel less pain and are more receptive to it, which will lead to better treatment compliance. In this case study, we report a case of Bell's palsy in a 26-week pregnant patient who was successfully treated with acupuncture (Figure 1).

Case report

On 12 April 2022, a 27-year-old woman had chief complaints of asymmetrical grinning on the left side of the face, incomplete left eye closure, frequent tinnitus in the left ear, and insomnia for the preceding 2 weeks, commencing at 26 weeks of gestation. The patient had no medical history of hypertension, diabetes, stroke, or Bell's palsy. On 25 April, electromyography (EMG) of the left side of the face showed that her left facial nerve was severely damaged, the zygomatic branch was completely damaged, and the left blink reflex could not be elicited. Moreover, the symptoms of the patient had not improved by then. Hence, she visited our clinic on 27 April to receive acupuncture treatment. Subsequent examination revealed an inability to complete left eye closure (Figure 2A) and lift the left eyebrow (Figure 2B); furthermore, we noted the disappearance of creases on her forehead. The patient was unable to shrug her left nose, puff out her cheeks, and smile symmetrically (Figure 2C). In addition, her left nasolabial fold became shallow. Given that the clinical manifestation of the patient was consistent with Bell's palsy, the diagnosis was confirmed (15).

Further assessment of facial nerve function revealed that the patient had House–Brackmann grade IV Bell's palsy. The House–Brackmann Facial Nerve Grading System (HBS) is the gold standard for evaluating facial nerve function and is used to evaluate the severity of facial paralysis. According to the HBS, nerve function is graded from I to VI, reflecting normal to total paralysis, in which grades I–III indicate mild facial paralysis and grades IV–VI indicate severe facial paralysis.

Acupuncture treatment

The patient received five sessions of acupuncture treatment (one time a week for 5 consecutive weeks; all acupoints were retained for 30 min) without cointerventions. All sessions were performed by the same experienced acupuncturist registered in China. Each therapeutic session was consistent. A half-needling technique was used to stimulate the acupoints of the four limbs and the face, including BL 2 (Cuanzu), EXHN-5 (Taiyang), ST 2 (Sibai), ST 4 (Dicang), ST 6 (Jiache), ST7 (Xiaguan), EX-LE10 (Bafeng), EX-UE9 (Baxie), and KI 3 (TaiXi). The locations of the above acupoints are shown in Figure 3.

After selecting the acupoints and sanitizing the skin, needles (0.20 ×20 mm, Huanqiu Brand, China) were inserted at the acupoints. All needles were inserted to a depth of 5 mm, except for that inserted at the BL2 (Cuanzu) acupoint, which was pricked obliquely to the BL1 (Jingming) acupoint. Needles were inserted vertically at the other acupoints. All needles were stimulated to achieve De-Qi (characterized by soreness, heaviness, warmth, coolness, numbness, tingling, or distention around the acupoints) sensation and were retained for 30 min without the reinforcing and reducing methods. During treatment, she did not use any medication or other therapeutic aids except acupuncture.

Clinical outcome

After two sessions of acupuncture treatment, the patient felt that her facial palsy had improved. She could lift her eyebrow slightly and almost close her eyes completely. Slight movement could be seen at the left corner of the mouth, and the asymmetry of her smile also slightly improved. The severity of facial paralysis was determined as HBS grade III (Figure 4). After four sessions of acupuncture treatment, her facial palsy continued to improve. The patient could completely lift her eyebrow and close her eyes. Creases on the left forehead were almost similar to those on the right forehead. In addition, the nasolabial fold was more evident than before, and the smile was slightly symmetrical. The severity of facial paralysis was determined as HBS grade II (Figure 4). The similarities between grade III and grade II are the weakness of facial muscles and asymmetrical movement, which indicates that Bell's palsy is not cured. The difference is the degree of facial dyskinesia; grade III takes the form of obvious, non-disfiguring weakness with complete eye closure, and grade II shows slight weakness on close inspection and a slight asymmetry of the smile. The change in the grade reflects the improvement of facial movement, especially in the orbicularis oris muscle.

Because the patient was approaching her due date of delivery, she discontinued acupuncture treatment. After 1 week, the patient successfully gave birth to a healthy baby boy, and the postpartum recovery of the patient was satisfactory. Using

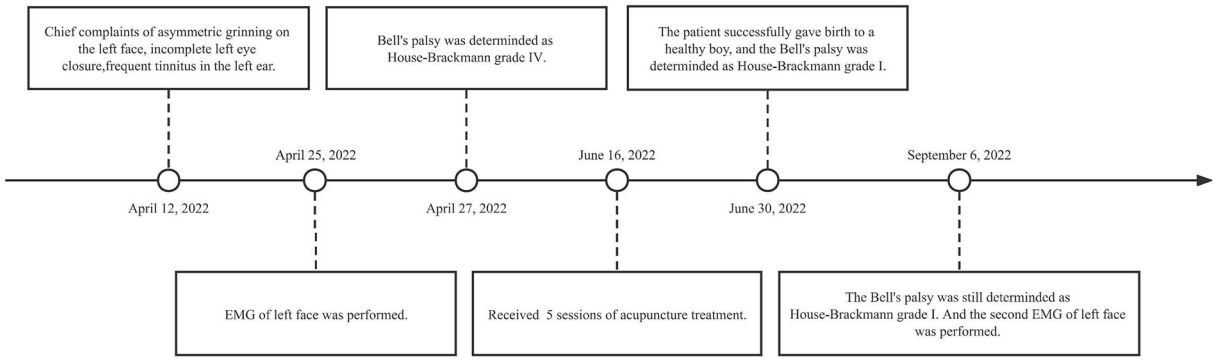


FIGURE 1
Timeline with relevant data from the episode of care.

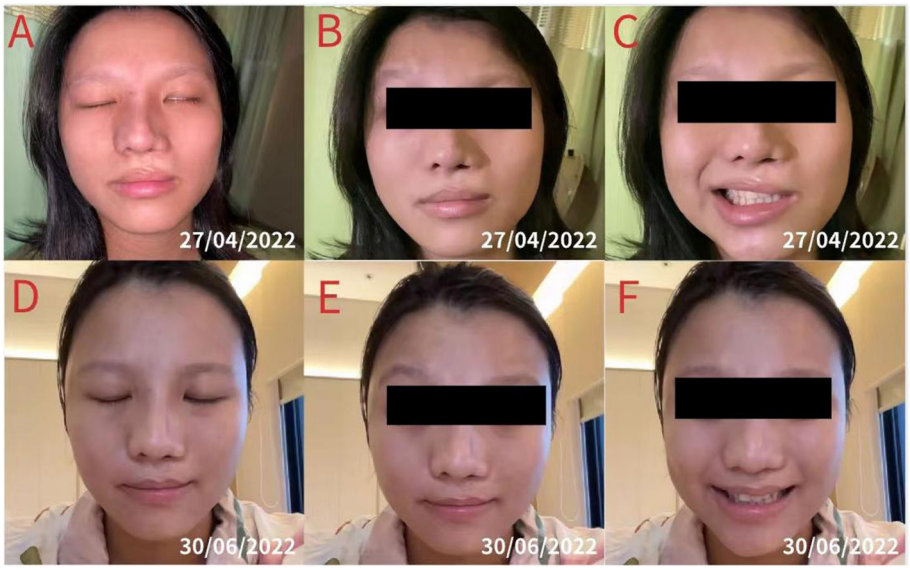


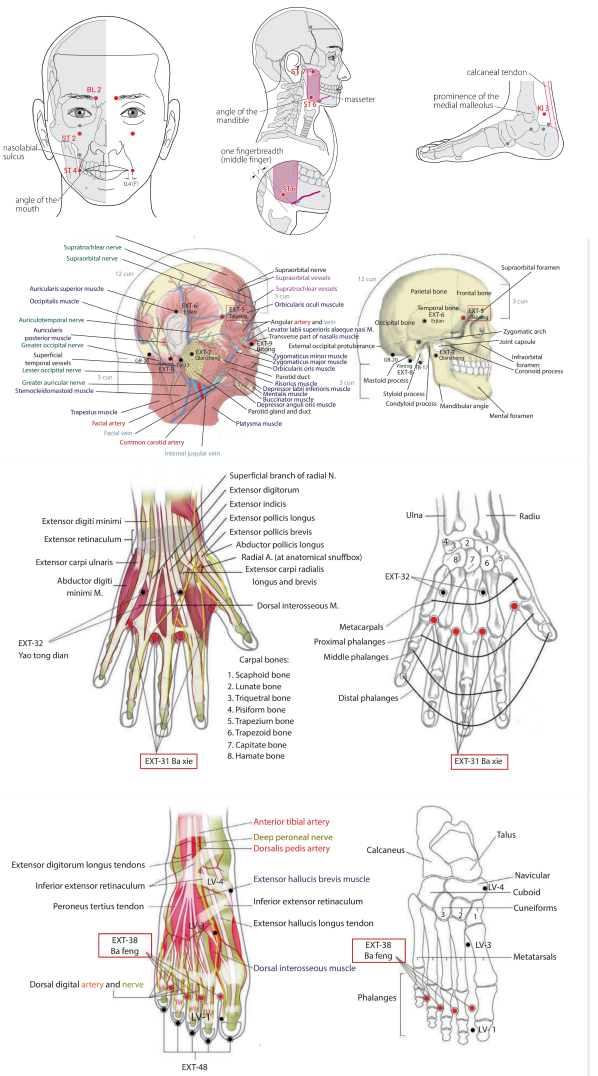
FIGURE 2
A patient with left-sided Bell's palsy. **(A)** Incomplete closure of the left eye and disappearance of creases on the forehead. **(B)** Inability to lift the left eyebrow. **(C)** Asymmetrical smiling and shallow left nasolabial fold. The patient received five sessions of acupuncture treatment. **(D)** Symmetrical closure of the eye. **(E)** Forceful raising of the left eyebrow and evident creases on the forehead. **(F)** Symmetrical smiling and an obvious left nasolabial fold.

an online video examination, we found that the patient could symmetrically close her eyes (Figure 2D), raise her eyebrows (Figure 2E), shrug the left nose, puff out her cheeks, and smile (Figure 2F) 1 week after delivery. In addition, she had symmetrical folds around her nose and eyes. The severity of facial paralysis was determined to be HBS I (Figure 4), indicating that the patient had recovered.

The patient had retained the symmetrical facial expression during the 2-month follow-up (Figure 4). During the follow-up, the baby showed good health. The EMG result of the left face on 6 September 2022 indicated that the partially damaged facial nerve had improved. An action potential could be seen in the left zygomatic branch of the facial nerve, and the mixed nerve action potential (MNAP) of the left buccal branch of the facial nerve increased. The blink reflex showed that the latency of the left R1 was slightly longer than that of the right R1 (13.8 vs. 10.1 m/s). The latency of the left R2 and R2' were 42.2 and 41.6 m/s, respectively, which was significantly longer than those of the right R2 and R2', which were 26.4 and 24.8 m/s, respectively.

Discussion

Our patient, who was 26 weeks pregnant, showed a significant decrease in HBS grade and an increase in the EMG data of the left facial nerve after five sessions of acupuncture.



Acupoints	Side	Angle	Locations
BL 2 (Cuanzu)	Both side	15°	On the head, in the depression at the medial end of the eyebrow.
ST 2 (Sibai)	Both side	90°	On the face, in the infraorbital foramen.
ST 4 (Dicang)	Both side	90°	On the face, 0.4 F-cun lateral to the angle of the mouth.
ST 6 (Jiache)	Both side	90°	On the face, one fingerbreadth (middle finger) anterosuperior to the angle of the mandible.
ST 7 (Xiaguan)	Both side	90°	On the face, in the depression between the midpoint of the inferior border of the zygomatic arch and the mandibular notch.
KI 3 (TaiXi)	Both side	90°	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon.
EXHN-5 (Taiyang)	Both side	90°	In the depression approximately 1 cun posterior to the midpoint between lateral extremity of eyebrow and outer canthus of eye lateral to the outer canthus.
EX-UE9 (Baxie)	Both side	90°	On the dorsum of the hand, at the junction of the red and white skin of the webs between each finger, comprising eight points total, four on each hand.
EX-LE10 (Bafeng)	Both side	90°	On the dorsum of the foot, at the junction of the red and white skin, proximal to the margins of the webs between the five toes. There are eight points in both feet combined.

FIGURE 3
The locations of acupoints (16, 17).

The etiology of Bell's palsy

The etiology of Bell's palsy remains unclear. Some studies suggested that the main cause of Bell's palsy is infection with reactivated viruses (18), such as the varicella-zoster virus (VZV) (19), herpes simplex virus type 1 (HSV-1) (20), human herpes virus 6 (21), and Usutu virus (22). HSV and VZV infections can be present throughout the life of the host (23). α-HVs enter the human body through the mucosa and localize in multiple ganglia of the neuroaxis *via* gene transcription, including in the autonomic and sensory ganglia of the head, the neck, and the cranium (24–27). In the case of immunodeficiency, HSV and VZV may get reactivated in the presence of circulating antibodies or an immunocompetent host (18). Some researchers proposed that immunosuppression in pregnant patients reduces the threshold for reactivation of the herpes virus in the geniculate ganglion, which increases the morbidity of Bell's palsy (28).

Possible mechanisms of acupuncture on Bell's palsy in pregnancy

Acupuncture, which has a long history of being part of traditional China therapies, is often used to treat facial palsy and can effectively improve facial nerve dysfunction and reduce the severity of paralysis (10). In the United States, acupuncture has been considered one of the main therapies for complementary and alternative medicine (CAM) (29). The use of BL2, EXHN5, ST2, ST4, ST6, and ST7 on both sides of the face can ameliorate local blood circulation and promote the recovery of facial nerve function. The use of EX-LE10, EX-UE9, and KI3 of the four limbs can contribute to dispersing Qi. In traditional Chinese medicine, defensive Qi can help to resist external pathogens and protect the body. Defensive Qi is similar to the superficial tissue fluid of the body, and the flow of defensive Qi benefits the formation of adaptive immunity, which can improve overall immunity and prevent the reactivation of the herpes virus (30).

The use of the half-needling technique can mobilize the defensive Qi and elevate the acceptance and safety of acupuncture among patients.

The mechanisms of acupuncture on Bell's palsy are still not clear. Several studies suggest that, in patients with Bell's palsy, lower motor neuron paralysis reduces the movement feedback and breaks the connectivity of the cortical facial motor network, which leads to cerebral cortical reorganization and increases abnormal functional connectivity. The functional connectivity modulation induced by acupuncture may be beneficial to the recovery of diseases (31, 32). In addition, some studies proposed that acupuncture

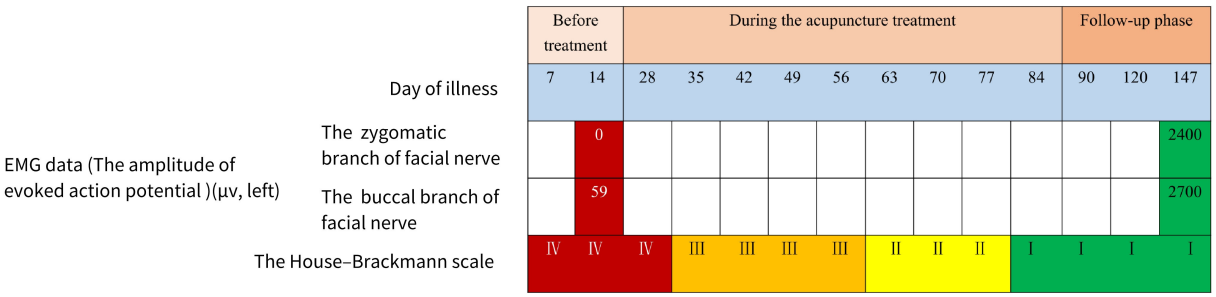


FIGURE 4
The EMG data and the House–Brackmann scale changed when the treatment progressed.

can promote the repair of facial nerve injury by altering the response of nerve fibers to electrical stimulation, accelerating the circulation of facial blood, relieving immunosuppression, and improving the expression of choline acetyltransferase (chAT) and neuritin (33–37).

Treatment of Bell's palsy in pregnancy

Thus far, the optimal treatment method for Bell's palsy in pregnancy remains controversial. At present, corticosteroids are the main treatment agents for Bell's palsy. Patients with severe facial nerve palsy are recommended to undergo combination therapy with steroids and antiviral drugs (15). The French Society of ENT (SFORL) guidelines recommend that corticosteroids such as prednisolone or methylprednisolone should be ideally administered within 72 h of the onset of Bell's palsy. A study reported that corticosteroids should be administered for 3–10 days, which is conducive to the prognosis of Bell's palsy (38). Additionally, that study showed that the concentration of prednisolone in fetal serum is one-tenth of that in the maternal blood. Therefore, prednisolone can be used to treat Bell's palsy in the early stage of pregnancy (39). Nonetheless, the use of steroids in pregnancy is considered unsafe, and adverse drug reactions may unpredictably injure pregnant women and fetuses. Furthermore, there is very low certainty of evidence on surgery for the early management of Bell's palsy. Consequently, the efficacy and safety of surgery remain to be determined (40). In addition, physiotherapy, including external eyelid weighting and taping techniques for the cheek and the eye, has clinically provided benefits for patients during the rehabilitation period and can balance the movement of the face (41). Apart from those, depression, anxiety, and stressful life events are significant cases for pregnancy or postpartum. Therefore, early intervention is critical for pregnant women with Bell's palsy (42).

Strengths and limitations

The clinical manifestation of the patient complied with the typical symptoms of Bell's palsy, which aided the prompt diagnosis. The clinical manifestation was paralysis of the unilateral facial muscle, resulting in the asymmetrical lifting of the eyebrows, forced closure of the eyes, shrugging nose, asymmetrical grinning, and disappearance of creases on the forehead and nasolabial fold. The disappearance of creases on the forehead could help differentiate it from central facial palsy.

Regarding diagnosis, a limitation of the study was the lack of magnetic resonance imaging (MRI). Hence, it was difficult to distinguish nuclear facial paralysis from lower sub-nuclear facial paralysis and rule out other diseases such as schwannoma, hemangioma, or a space-occupying lesion (43). One advantage of the evaluation used in this study lies in a variety of evaluation methods such as EMG and the HBS grading system to monitor the progress of facial nerve function over time. However, the follow-up period for this case was only 2 months, so it might be necessary to extend the follow-up period to evaluate the prognosis of Bell's palsy. Furthermore, the study showed that the main causes of neonatal Bell's palsy are congenital, developmental, and familial facial palsy (44, 45). Congenital palsy is related to perinatal trauma. Developmental palsy is related to an error in development (44). In addition, familial palsy occurs due to the inherited anatomical abnormality of the facial canal (46). According to the observation of the baby, perinatal trauma can be excluded. However, there needs to be a longer follow-up to observe the health of the baby to determine whether Bell's palsy can pass along to the baby and whether the acupuncture treatment can prevent it. Additionally, if the baby shows the symptoms of Bell's palsy, we will need to make a diagnosis by excluding the causes and performing an MRI. In addition, the EMG would need to be reevaluated after 6 months.

In this case study, the strengths of acupuncture treatment included the following: (1) All sessions were performed by

experienced acupuncturists; (2) in every session, acupoints and acupuncture methods were consistent, which showed the normality and repeatability of the operation; (3) the low frequency of treatment (one time a week) could provide sufficient rest time for the patient; (4) the acupoints located in the face and four limbs were safer than those on the trunk; and (5) the Medical Classic of the Yellow Emperor emphasized that needles can be used to invigorate Zhengqi by light insertion, mild thrust, lift, and long retention. Therefore, all needles were retained without the reinforcing and reducing methods and electroacupuncture, which ensured that the patient was comfortable and helped them return to normal mood status. Although this case study showed that acupuncture may be a safe and effective treatment for Bell's palsy in pregnancy, high-quality, randomized controlled trials should still be conducted to validate our findings.

Conclusion

Bell's palsy is an exclusionary diagnosis. The characteristic clinical manifestations are an important basis for diagnosis, and MRI is the best imaging modality to accurately exclude space-occupying lesions. EMG can evaluate the standard of facial nerve injury and determine the outcome of Bell's palsy. According to this case study, acupuncture can be used as soon as possible when the vital signs of pregnant women and fetuses are stable. The acupoints of the bladder meridian and stomach meridian on the face can ameliorate local blood circulation, and the combination with EX-LE10, EX-UE9, and KI3 can stimulate defensive Qi, which can warm the face, resist external pathogens, and improve the overall immunity. The half-needling technique is shallower in depth and safer and less uncomfortable, which can reduce the psychological burden of acupuncture. This case report demonstrated the feasibility, safety, and validity of acupuncture for treating Bell's palsy in pregnancy.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Foshan Hospital of Traditional Chinese Medicine (KY2022-255). The patients/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

ZL performed the treatment and prepared the initial draft. KH, QL, and XP collected and analyzed the data. DL and WD were responsible for manuscript editing. JL was responsible for the review and overall supervision of the entire study. All the authors reviewed the final draft of the case report and accepted it for publication.

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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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A protocol for the integration of multi-omics bioinformatics: Mechanism of acupuncture as an adjunctive therapy for alcohol use disorder

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Background: Alcohol use disorder (AUD) has become a significant global factor in various diseases. As a non-pharmacological therapy, certain therapeutic potential has been found in acupuncture; however, in-depth mechanistic studies related to acupuncture for patients with AUD are still insufficient.

Methods: Based on a randomized control design and a multi-omics analysis plan, this protocol details the recruitment (42 AUD patients), group allocation (21 in acupuncture group vs. 21 in sham acupuncture group), intervention and follow-up (replacement drugs as a normal treatment, 2 weeks acupuncture duration, and 3 month follow-up), and data collection and analytical processes. For the clinical outcomes, in addition to the time required for alcohol withdrawal symptoms to subside as the primary outcome, changes in the alcohol withdrawal symptoms, alcohol craving, mood dysfunction, sleep disorder, fatigue, self-efficacy, gastrointestinal symptoms, the quality of life, and the relapse outcomes will be compared between the groups to confirm the acupuncture clinical effectiveness on alcohol withdraw. The gut microbiome and the fecal metabolomics will also be assessed to explore the association of the structure and the function of gut microflora and the mediation of acupuncture effect on AUD fully utilizing gut microflora multi-modal data and clinical information, via the combination of multi-omics methods, feature screening algorithms and appropriate models.

Discussion: The results of this study may help to strengthen clinical evidence of the mechanism of acupuncture intervention in patients with AUD, through

understanding of the regulatory mechanism of acupuncture in the gut microbiome and its metabolism as well as AUD-related clinical manifestations.

Trial registration: Chinese Clinical Trial Registry ChiCTR2200058120. Registered on 24 Mar 2022.

KEYWORDS

alcohol use disorder, Jin's three-needle technique, acupuncture, microbiome, metabolomics, multi-omics, multi-modal bioinfomation

1. Introduction

Alcohol use disorder has become a significant global factor in various diseases (1–4). In recent years, the health benefits in many developing countries and regions have been impaired by increased alcohol consumption (3–6). Alcohol use disorder (AUD) is one of the most prevalent chronic relapsing substance use disorders (SUDs), with widespread negative impacts on global public health (7).

As a systematic mechanism of bidirectional information exchange between the brain and the gut microbiota (8), the microbiota-gut-brain axis has received significant attention, with an increasing number of findings suggesting that the gut microbiota and drinking-related behavioral factors can interact with each other (9–11). It has been clinically observed that many patients with AUDs (especially alcohol-dependent patients) often present obvious gastrointestinal symptoms in the early stages of abstinence, as well as alcohol-related psychiatric symptoms. Gastrointestinal symptoms are some of the most common somatic symptoms in alcohol withdrawal syndrome (AWS), often gradually relieved with the decline of psychiatric symptoms. On the one hand, alcoholism may lead to a decrease in the protective gut microbiome or an increase in the pathogenic gut microbiome, as well as bacterial translocation. A recent systematic review (12) showed that alcoholism leads to a disease-specific alteration in the gut microbiota, with a lower relative abundance of phylum bacteroidetes, most firmicutes, and actinobacteria (especially the genus Bilobacteria) in alcoholic individuals, but a higher relative abundance of enterobacteriaceae and the genus streptococcus, characterized by reduced obligate anaerobic bacteria and increased facultative anaerobic bacteria. Such alterations may involve potential mechanisms or hypotheses such as down-regulation of antimicrobial peptides, ethanol-induced oxidative stress, alterations in bile salt concentrations (13), bacterial overgrowth due to slowing of bowel motility, increased fecal pH (14), and interference in bacteriocin secretion by some enterobacteria which affect other bacteria (15). On the other hand, alterations in gut microbiota and its metabolism fundamentally influence brain function through many potential pathways such as the nervous and immune systems (16–19), involving many types of signaling such as enteroendocrine, neurotransmitters (20–22), branched-chain amino acids, and short-chain fatty acids (23). Previous studies have suggested that alterations of gut microbes can generate effects on specific brain regions, involving myelin plasticity (24, 25), neuroinflammatory response (26, 27), and neurotransmitter function (28, 29) which mediate related behavioral changes. However, microbiome-gut-brain interactions are still not clear in patients with AUD, and the microorganisms and their metabolites that are sensitive to AUD-specific interventions remain unexplored.

The efficacy of acupuncture on patients with SUDs has been verified by long-term clinical observations; acupuncture helps to alleviate pathological cravings, promote regression of acute withdrawal syndrome, reduce protracted discomfort of withdrawal, decrease relapse, and improve social function and quality of life (30, 31). A previous study with a sample size of 503 patients revealed that nearly half of the subjects reported a decrease in alcohol desire after acupuncture intervention (32). As previous laboratory studies have also confirmed, acupuncture stimulation can alleviate stress and alcohol-related anxiety (33), relieve pain during alcohol withdrawal (34), decrease alcohol dependence (35), enhance self-control (36), and improve learning and memory functions (33, 37–40). Previous molecular-level studies have shown that acupuncture can rebalance AUD-induced maladaptation of neurotransmitters and hormones in related brain regions, inhibit the inflammatory response of the central nervous system (CNS), and protect the function of important brain regions (35, 39, 41–45).

Many studies have indicated that acupuncture can improve brain function and behavior through regulation of the microbiome state. For example, acupuncture can alleviate behavioral deficits by modulating gut microbiota, neuroinflammation, and brain-gut peptide expression in mice suffering from Parkinson's disease (46, 47). Acupuncture can also exert antidepressant effects by modulating the gut microbiota and neurotransmitters in depressive rats (48). At present, studies have shown that acupuncture not only restores the relative abundance of gut microbial genera in mice, but also restores physiological functions such as glutathione metabolism, methane metabolism, and Parkinson's disease

(PD) pathways, and improves their motor function and comorbid anxiety (49). In addition, studies have shown that acupuncture inhibits the inflammatory response of CNS by balancing the gut microbial structure, reducing inflammatory factors (such as lipopolysaccharide, interleukin-1β (IL-1β), and IL-6), and inhibiting inflammatory pathways (50). Thus, acupuncture can mediate the improvement of gut microbial structure and function, regulating psychiatric symptoms. In other words, gut microbial information may provide improved efficacy and prognostic indications for the clinical application of acupuncture in patients with AUD. However, previous studies on acupuncture in patients with AUD mainly evaluated the efficacy, but seldom explored the mechanism; a number of articles have introduced laboratory indicators; however, most of these indicators were used to assess alcohol-related psychiatric symptoms as their biomarker (e.g., serum homocysteine (Hcy) for cognitive function) or their objective reflection (e.g., event-related potentials (ERPs) and exploratory eye movement (EEM) for cognitive function) (51). Thus, acupuncture has a co-regulatory effect on the brain and the gut, but still requires further observation in patients with AUD.

In summary, pre-evidence based (49, 52) acupuncture may help improve AUD by regulating the gut microbiome and its metabolism. Moreover, the fact that the fecal metabolome can be used as a functional readout of the gut microbiome (53) supports a combination of these omics tools to obtain multimodal information on the gut microbial communities. Therefore, the gut microbiome and the fecal metabolomics of patients with AUD, and their role in the effect of acupuncture on the psychopathology of patients with AUD will be explored in this study.

2. Study aims

The purpose of this study is to report a protocol for the integration of multi-omics bioinformatics and the mechanism of acupuncture as adjunctive therapy for AUD, including three sub-studies:

(1) The clinical psychiatric symptom sub-study aims to evaluate the clinical symptom response to acupuncture in patients with AUD.

(2) The intestinal microbiome and metabolomics sub-study aims to compare changes in the biodiversity and metabolites between pre- and the post-intervention in both groups of patients.

(3) The joint analysis sub-study aims to demonstrate associations between the gut microbiome and the clinical changes of patients with AUD after acupuncture intervention, identifying important factors affecting the response to acupuncture and assessing their contribution to the impact.

3. Design and methodology

3.1. Design

The trial is a randomized, placebo-controlled, 2-arm parallel-group clinical trial, with participants randomized to receive acupuncture or sham acupuncture over 2 weeks. The study was ethically approved by the Institutional Review Board of the Affiliated Brain Hospital of Guangzhou Medical University (ABHGMU, project number 2022/007). The trial has been registered with the Chinese Clinical Trial Registry (ChiCTR2200058120). This study protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Section 1, Supplementary Table S1 in Appendix 1) (54) and the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) checklist (see Section 2, Supplementary Table S2 in Appendix 1) (55). The flowchart of the study is shown in Figure 1.

3.2. Center

This trial was designed by the Clinical Research and Big Data Laboratory, South China Research Center for Acupuncture and Moxibustion, Medical College of Acu-Moxi and Rehabilitation, Guangzhou University of Chinese Medicine (GZUCM). Clinical data collection is currently being conducted at ABHGMU, Guangzhou, China.

3.3. Participants

Enrollment for the study began on April 1 2022, with an expected completion date of March 31 2023. It is expected that 42 participants from the overall sample will be recruited into the patient group. Based on cultural factors and features of the population of China, the target population of this study is male patients with AUD. The inclusion and exclusion criteria for eligibility are as follows:

3.4. Inclusion

(1) In line with the diagnosis of AUD in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (see Section 4, Supplementary Table S3 in Appendix 1) (56).
(2) Male patients.
(3) Aged between 18–70 years old.

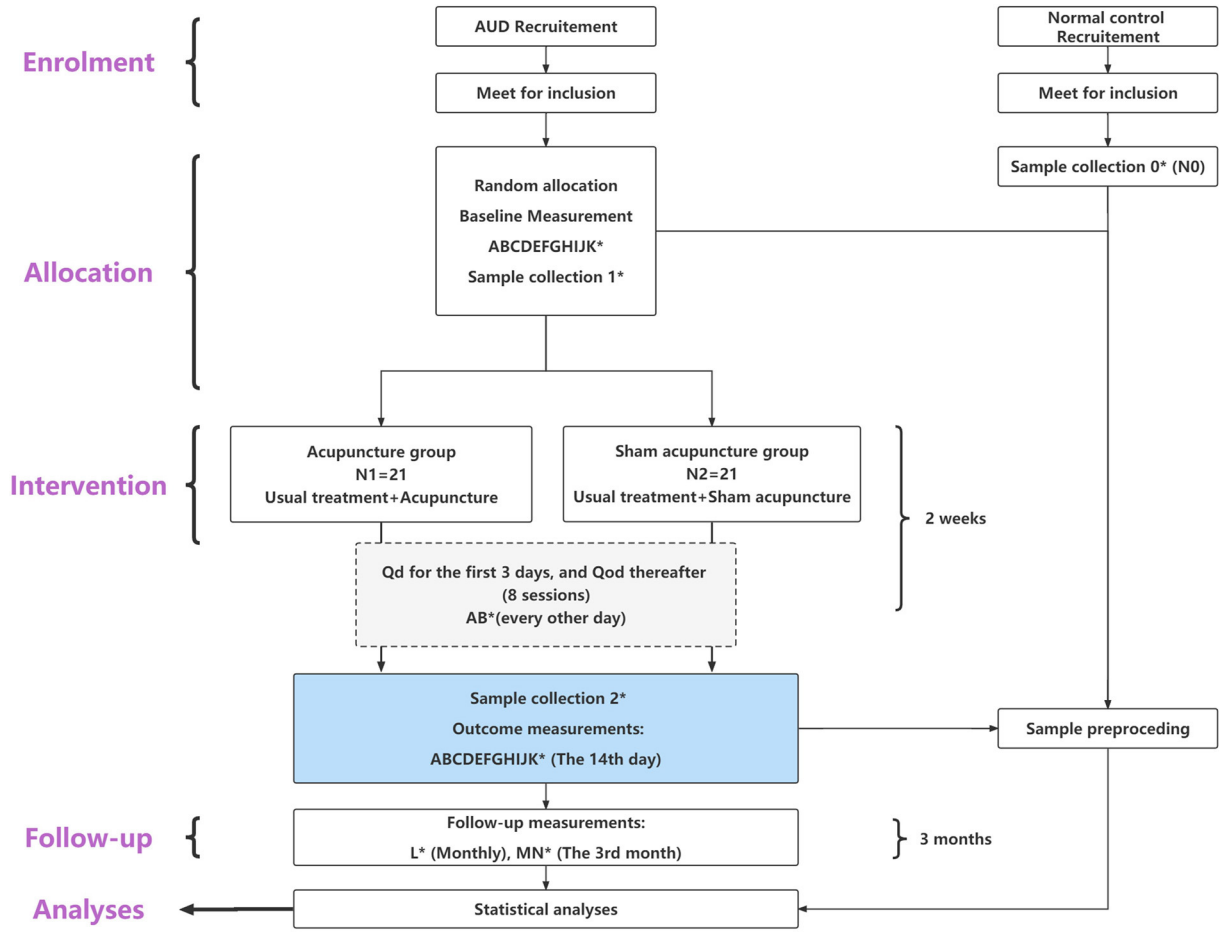

FIGURE 1
Flow diagram of the study process. *Sample collection 0, 1, 2 means to collect 10 fecal samples from each patient group (N1 and N2) at baseline and at the end of the last intervention; additionally, to collect 10 fecal samples from the health control group (N0). (A–N) means the 14 measurement tools applied in this study, distributed in specific study phases. (A) CIWA-Ar, Clinical institute alcohol withdrawal syndrome scale. (B) abs-VAS, Abstinence visual analog-rating scale. (C) AUQ, Alcohol urge questionnaire. (D) cue-VAS, Cue-related visual analog-rating scale. (E) BDI-II, Beck depression inventory II. (F) BAI, Beck anxiety inventory. (G) PSQI, Pittsburgh sleep quality index. (H) MFS, Mental fatigue scale. (I) GSES, General self-efficacy scale. (J) Gastrointestinal symptom rating scale. (K) QOL-DA, Quality of life scale for patients with drug addiction/dependence. (L) TLFB, Timeline followback. (M) AUDIT, Alcohol use disorder identification test. (N) MAST, Michigan alcohol screening test.

(4) Proposed or ongoing systematic management of alcohol withdrawal.
(5) Understand the study and sign the informed consent.

3.5. Exclusion

Subjects will be excluded if they meet any of the following criteria:

(1) Patients with any serious neurological or psychiatric diseases caused by diseases other than alcohol dependence (including brain tissue damage caused by traumatic brain injury).
(2) Use of other psychoactive substances apart from alcohol, including traditional drugs and new psychoactive substances, or smoking over 30 cigarettes per day.
(3) Patients with severe disease of the heart, liver, spleen, lung, or kidney.
(4) Patients with syphilis or acquired immunodeficiency syndrome (AIDS).
(5) Those with severe digestive system diseases or severe malnutrition.
(6) Patients with severe primary diseases of the hematopoietic system.
(7) Patients with abnormal coagulation function.
(8) Those with inflammation, scars, or trauma at the operation site, or those with severe systemic infection.

(9) Those with cognitive dysfunction, those unable to cooperate, or receiving other treatments that may affect assessment.
(10) Those who have received any acupuncture treatment in the past 6 months.

3.6. Sample size calculation

As the primary outcome of this study, the time required for the alcohol withdrawal reaction to subside is 11 ± 5 days in the routine intervention group and 5 ± 3 days in the acupuncture adjunct intervention group, with a minimal clinically important difference (MCID) of 1.5, based on our previous clinical professional experience. Under the one-sided condition $\alpha = 0.025$ and test power $1-\beta = 0.90$, at least 19 cases are required in each group, based on estimation using the superiority assumption in PASS 11. Given that all subjects will be recruited from inpatients, and two of the most common reasons for dropout are early discharge and transfer to different departments, taking a dropout rate of 10% into consideration, the sample size in each group is: 19/(1–10%) = 21 cases, giving a total of 42 cases. Considering that there has not been relevant research on acupuncture intervention in patients with AUD, and assessment of the intestinal microbiome, this study is a preliminary exploration. Referring to a number of similar studies (57–61), data collection of intestinal microbiome and metabolomics will be performed for at least 10 cases in each patient group. Additionally, 10 fecal samples from both healthy controls [teetotalers or light social drinkers, with an Alcohol Use Disorder Identification Test (AUDIT) score ≤ 7, and normal cognition and memory function assessed using the Mini-mental State Examination (MMSE)] and AUD participants will be collected to determine differences in gut microbiomes and metabolomics between AUD and normal groups.

3.7. Randomization procedure

Before randomization, all eligible participants will be asked to sign an informed consent (the index in Section 5 in Appendix 1, and the operative document in Appendix 2). A random sequence in a block size of four will be generated by the central random allocation system developed by the Clinical Research and Big Data Laboratory of GZUCM. Participants will be informed that they have an equal chance of being assigned to the acupuncture or control group. Eligible patients ($N = 42$) will be assigned a random number by an independent researcher who is not involved in the outcome assessment, and will be randomly allocated to the acupuncture group ($N = 21$) or the sham acupuncture group ($N = 21$) in a 1:1 ratio.

3.8. Blinding

Patients, assessors, and data analysts will be blinded. Acupuncture providers will not.

3.9. Usual care

Participants will routinely enter into an abstinence procedure, and will be given replacement drugs according to their conditions at initiation in order to control acute withdrawal symptoms such as tremors and irritation (diazepam, for example, at a total dose of 15–100 mg/day, will be administered several times according to the degree of alcohol addiction). According to the conditions, the dose may be tapered every 1–2 days until discontinuation (62). Symptomatic and supportive treatment will also be provided (instead of interventions regarding intestinal flora regulation such as taking probiotics, gavage, etc.).

3.10. Intervention

According to traditional acupuncture theory and previous RCTs, the acupuncture study interventions were developed by a consensus of corresponding experts. The interventions will be performed by licensed acupuncturists with over 3 years of clinical experience, who will obtain a total understanding of the treatment based on special training and who will receive a brochure showing the acupuncture manipulation, with detailed information provided before initiation. Subjects who will be randomized to the acupuncture group will receive usual care and JTN treatment for 30 min per session. Meanwhile, those in the control group will receive usual care and sham JTN treatment. From the day after hospital admission for abstinence, acupuncture intervention will be performed once a day for the first 3 days (if the patient is sober) and once every other day thereafter for a total of 2 weeks (8 sessions). This will be followed by a follow-up period lasting until the end of the third month. If the patient presents severe delirium during the last acute withdrawal or has a delirium episode during admission, taking safety into account, the initial acupuncture intervention will not be performed until the delirium recedes and consciousness becomes clear.

3.10.1. Acupoints

Based on JTN theory, each acupoint group has a special name and contains three or four points. A previous study on acupuncture detoxification Wen et al., (63) showed an effective reduction of opioid craving, and improvement of protracted withdrawal symptoms if three acupoint JTN groups (Sishen-zhen, Dingshen-zhen, and Shouzhi-zhen) were added

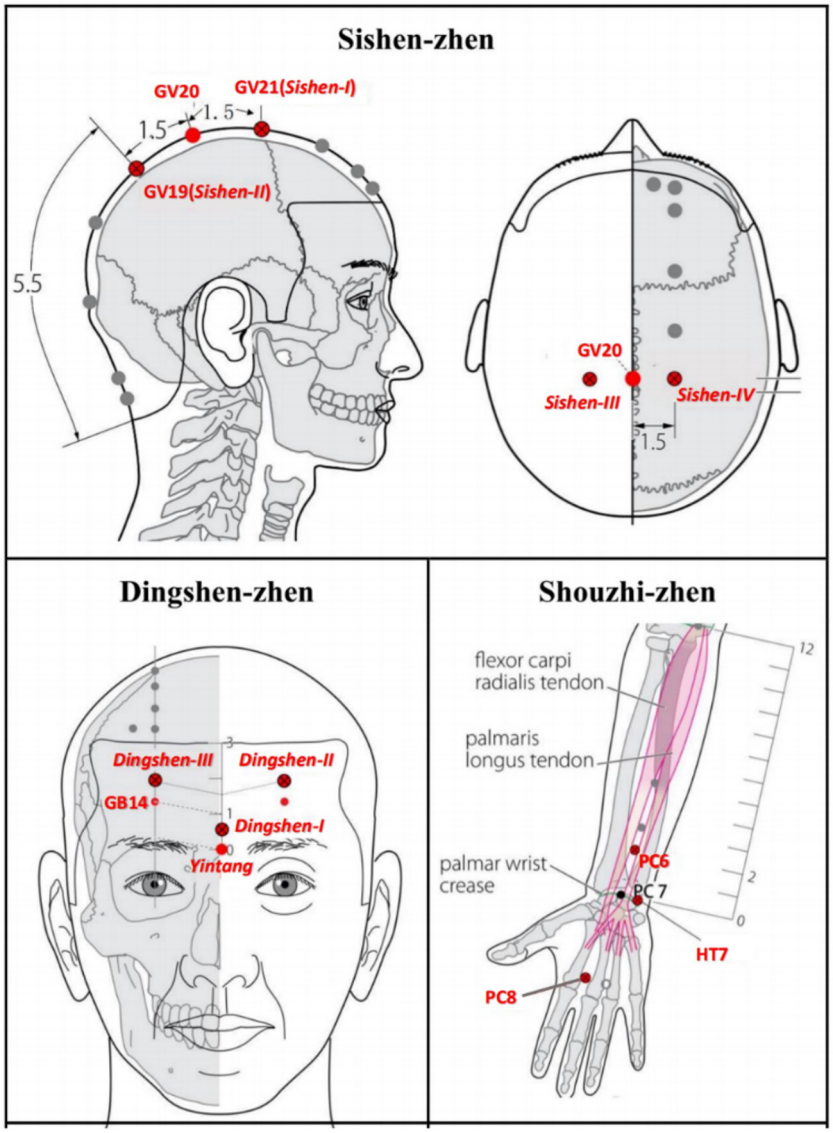

FIGURE 2
JTN acupoint groups (Sishen-zhen, Dingshen-zhen, and Shouzhi-zhen).

to methadone replacement therapy (63, 64). Therefore, this set of acupoints will also be chosen in this study (see Figure 2 and Section 6, Supplementary Table S4 in Appendix 1).

3.10.2. Acupuncture device

Acupuncture needle: sterile stainless-steel disposable acupuncture needles (Huatuo, Suzhou, China; diameters and lengths of 0.3 mm × 40 mm or 0.25 mm × 25 mm) will be used in the acupuncture group. Blunt acupuncture needles (0.3 mm × 25 mm) will be used in the sham acupuncture group.

Placebo device: a real needle device will be applied in the acupuncture group; a disposable placebo needle device (material: acrylonitrile butadiene styrene plastic, ABS) with a hollow patch on the bottom (material: foam substrate, double-sided, coated with acrylic glue). A sham needle device will be applied in the sham group; a disposable placebo needle device with a mouthless patch on the bottom, made from the same material as the acupuncture group device. The device appearance for both groups is exactly the same. The device has been granted a patent (ZL202121352221.7) by the State Intellectual Property Administration of China (see Figure 3 and Section 6.2 in Appendix 1) (65).

FIGURE 3
Different types of appliance (left: non-hollow patch for sham acupuncture; right: hollow patch for real acupuncture).

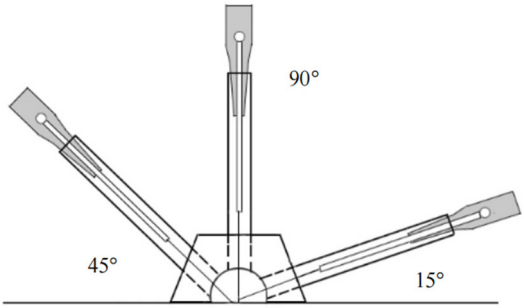

FIGURE 4
Acupuncture insertion angles.

3.10.3. Acupuncture group

The corresponding real needle devices will be inserted at Shouzhi-zhen at an angle of 45–90° to the participant's skin, while at Dingshen-zhen and Sishen-zhen, will be inserted at 15° (Figure 4). The needles will be inserted at depths of 5–30 mm. Subsequently, stimulation to achieve the typical acupuncture sensation of "de qi," characterized by soreness, numbness, and heaviness will be manually performed. During each session, the acupuncture needles will be retained in the skin for 30 min and twirled every 10 min. The intervention will be discontinued if the patient suffers from any adverse events, and the acupuncturists can decide on termination (63).

3.10.4. Sham acupuncture group

Sham acupuncture at the same acupoints will be added to the usual care as a control. Each blunt needle will be inserted into the mouthless patch of the sham needle device, slightly touching the skin, and causing a pinprick-like sensation, without actually penetrating the skin. The needling directions will be the same as those of the acupuncture group. During needle retention, needle handles will be only touched, without any stimulation by acupuncture manipulation, once every 10 min for a total of 3 touches. The setting of the treatment environment, posture, treatment session, frequency, and treatment duration will be equivalent to the acupuncture group; the assessment and the follow-up times for the control group will match those of the experimental group.

3.11. Assessment and analyses

The severity of withdrawal symptom assessments and abstinence craving assessments will be conducted every other day, with other indicators assessed at baseline and at the end of the second week of intervention.

4. Clinical psychiatric symptom sub-study

4.1. Overview of outcome collection

Demographic characteristics will be collected at baseline, and will include age, gender, ethnicity, height, weight, marital status, education level, education duration, occupation, long-term residence, alcohol use (history, common types of drinks, drinking rhythm, frequency, amount, times of treatment for abstinence, etc.), cognitive function, alcohol craving, withdrawal symptoms, accompanying symptoms (mood dysfunction, sleeping disturbance, and fatigue), self-efficacy, and quality of life; replacement drug use will be recorded daily, alcohol craving and the degree of withdrawal symptoms will be recorded every other day for the duration of treatment; alcohol craving, withdrawal symptoms, accompanying symptoms, self-efficacy, and quality of life will be recorded at the end of the last intervention; and drinking self-management and relapse will be recorded at the 3 month follow-up (see Section 7.1, Supplementary Table S5 in Appendix 1). Outcomes are listed in Section 7.2, Supplementary Table S6 in Appendix 1 and their measurements are described in Section 7.3 in Appendix 1, with the measurement tool (scales) index in Section 8 in Appendix 1 and the operative document in Appendix 3. Safety will also be recorded.

4.2. Outcomes and measurements

4.2.1. Primary outcome

As an indicator of how quickly alcohol withdrawal symptoms subside, the time required for the symptoms to subside will be assessed according to the **Clinical Institute Alcohol Withdrawal Syndrome Scale** (CIWA-Ar) (66). CIWA-Ar is a 10-point scale for diagnosis, assessment, and guidance for intervention, with the highest score of 67 points possible. According to the ABHGMU model, levels are defined as follows: a total score of 7–9 for mild, 10–18 for moderate, and >18

for severe. The primary outcome is the time required for the CIWA-Ar score to change from ≥ 7 to < 7.

4.2.2. Key secondary outcomes

(1) Change of the alcohol withdrawal symptoms: the change in CIWA-Ar scores after intervention (ΔCIWA-Ar).

(2) Change of the withdrawal craving: visual analog-rating scale (VAS) (67), with the range 0–100 mm used to evaluate the craving derived from alcohol abstinence (abs-VAS) (68). A change of the withdrawal craving is indicated by the change of abs-VAS after intervention (Δabs-VAS).

4.2.3. Secondary outcomes

(1) Change of the alcohol urge: the alcohol urge questionnaire (AUQ) is an 8-item, 7-level self-evaluation questionnaire covering three fields of craving (cue-induced craving, expectation for positive effect from drinking, and compulsion) (69). Since VAS is an abstract and unidimensional psychological scale, in order to more comprehensively take into account changes in the patients' positive and compulsive cravings, the change in AUQ (ΔAUQ) on day 14, relative to the baseline, will be used for supplementary measurement of Δabs-VAS.

(2) Change of cue-induced craving: VAS, with a 0–100 mm range, will also be used to evaluate the craving derived from alcohol-related cues (cue-VAS) (68, 70, 71). A change of the cue-induced craving is indicated by the change of cue-VAS after the last intervention, relative to the baseline (Δcue-VAS).

(3) Change of alcohol-related mood dysfunction: ① depression: the beck depression inventory II (BDI-II) (72) is a 21-question measurement with four-level scoring, from 0 (normality) to 3 (extreme deterioration). A higher score indicates more severe depression: 0–13 = no depression, 14–19 = mild, 20–28 = moderate, and 29–63 = serious. ② Anxiety: the beck anxiety inventory (BAI) (73) is a 21-question measurement with four-level scoring, from 1 (normality) to 4 (extreme deterioration). A total score of 15–25 = mild, 26–35 = moderate, and > 36 = serious. A change of the alcohol-related mood dysfunction is indicated by the change of BDI-II and BAI after the last intervention, relative to the baseline (ΔBDI-II and ΔBAI).

(4) Improvement of sleep disorder and the sense of fatigue: ① the Pittsburgh sleep quality index (PSQI) (74) is an 18-item and 7-component measurement of the sleep status, with each component scored according to grade 0–3; the cumulative score is the total PSQI score, with a full score of 21 points possible. The higher the score of each item, the worse the sleep: 0–5, 6–10, 11–15, and 16–21 points indicate good, general, barely acceptable, and poor sleep quality, respectively. ② The mental fatigue scale (MFS) (75) is mainly used to evaluate the mental fatigue of people with neuropsychiatric disorders, and includes 15 items and four options (0, 1, 2, and 3 for no problem, problem existing, with a significant problem, and with a severe problem, respectively) per item for a the total score of 42 (≥ 10.5 is considered as mental fatigue), except for the last item (the change of 24 h fatigue). The higher the score, the more serious the mental fatigue. An improvement of sleep disorder and the sense of fatigue is indicated by the change of PSQI and MFS after the last intervention, relative to the baseline (ΔPSQI and ΔMFS).

(5) Other secondary outcomes: other secondary outcomes include changes in the self-efficacy, quality of life, and digestive system dysfunction, the measurement of which are described in Section 7.3 of Appendix 1. The relative scales are presented in Appendix 3.

4.2.4. Follow-up outcomes

(1) Percentage of heavy drinking days (PHDD), percentage of days abstinent (PDA), drinks per drinking day (DDD), drinks per heavy drinking day (DHDD): these are indicators of drinking self-management. With monthly timeline followback (TLFB) (76) applied, patients will be asked to review their drinking days for the prior month, and the amount drunk per drinking day, which will be calculated to measure their level of abstinence and their ability to control alcohol intake.

(2) Relapse or not: this study will focus on the somatic relapse (re-exposure to alcohol and return to obsession and compulsive desire) (77, 78); relapse will be defined by an AUDIT score ≥ 20 (79) or a Michigan alcohol screening test (MAST) score ≥4 (weighting method) (80) to evaluate whether patients are trapped in relapse, which may require further forced withdrawal treatment during the 3 month follow-up. AUDIT (79) is a questionnaire containing a total of 10 questions and is used to screen for risky and harmful drinking and alcohol dependence. According to the 8-point grading scale, 0–7 points indicates no or mild drinking problems (risk level zone I), 8–15 points indicates moderate drinking problems (zone II), 16–19 points indicates high drinking problems (zone III), and ≥ 20 points may indicate alcohol dependence (zone IV). MAST is a 25-item self-evaluation questionnaire, compiled by referring to the Li version (80). According to the weighting method, a MAST score ≤ 3 can be regarded as having no clinical significance, 4 points indicates possible or suspected alcohol dependence, 5–6 points indicates mild dependence, 7–25 points indicates moderate dependence, 26–39 points indicates serious dependence, and 40–53 points indicates severe dependence. These scales will be used at baseline and at the end of the third follow-up month.

4.3. Statistical analysis plan

In this study, the primary outcome and key secondary outcomes will be analyzed using intention to treat (ITT); other outcomes will be analyzed using the PP set. Suspicious results in the analysis process will be discussed using sensitivity analysis. Imputation of missing data will be performed according to the characteristics of the data.

Descriptive statistics will be presented as mean change ± SD (95% confidence intervals) or as a percentage for each group. When normally distributed, and with homogeneous variances, the continuous outcomes will be compared between the groups by independent sample *t*-test, with significance if the *P*-value is < 0.05 (two-sided). Tests will be adjusted if variance is heterogeneous; non-parametric tests will be used for between-group comparisons for abnormal distributions. The Chi-square (χ^2) test or Fisher's exact test will be used to compare unordered categorical variables between the groups; the rank sum test will be used to compare ordered variables between the groups. Repeated measures analysis of variance or survival time analysis will be used if necessary for outcomes with multiple observation points. For more exploratory analyses, within group comparison may be utilized. SPSS statistical software version 23 (IBM SPSS Statistics, New York, USA) will be used.

5. Gut microbiome and fecal metabolomics sub-study

5.1. Data preprocessing

Gut microbiome: paired-end reads of the raw sequencing data will be preprocessed using cutadapt software to detect and cut off the adapter. After trimmed and low quality sequences filtered, paired-end reads will be denoised, merged, and detected, and the chimera reads will be cut off. Finally, the software will output the representative reads and the ASV abundance table. The representative read of each ASV will be selected using the QIIME2 package. All representative reads will be annotated and blasted against Silva database Version 138 (or Unite) (16s/18s/ITS rDNA) using a q2-feature-classifier with default parameter (81, 82).

Fecal metabolomics: a data-independent acquisition (DIA) approach will be applied to simultaneously acquire all fragmented ions of all precursors, thereby increasing the coverage of observable molecules and reducing false negative identification. A series of processing on imported data will be performed, such as peak detection, peak identification, MS2Dec deconvolution (83), characterization, peak alignment, filtering, and missing value imputation.

5.2. Data analyses

Fecal microbiome: (1) analysis of community structure (differences in the abundance of microorganisms at each taxonomic level): this will mainly involve annotation and abundance summary at each taxonomic level. (2) Biodiversity analysis: ① alpha diversity analysis will be used to learn about the diversity of gut microbiome in each group; ② beta diversity analysis will be used to learn about the diversity of biological environments. (3) Differential microorganism analysis: microbial multivariate statistical analysis will be used to determine and compare significantly different microorganisms between the groups.

Fecal metabolomics: (1) multivariate statistical analysis will first use unsupervised principal component analysis (PCA) to observe the overall distributions between samples and the stability of the entire analysis process, then, supervised partial least squares analysis (PLS-DA) and orthogonal partial least squares analysis (OPLS-DA) will be utilized to distinguish overall differences in metabolic profiles between the groups and to determine differential metabolites (84). (2) Univariate analysis will mainly involve interval estimation and statistical hypothesis testing. *T*-test (student's *t*-test) and fold change analysis will be used to compare metabolites between the two groups. (3) Metabolic pathway enrichment analysis of differential metabolites will be based on the KEGG database (85, 86).

The details were provided in Section 9 of Appendix 1.

6. Joint analysis sub-study

6.1. Omics conjoint analysis

(1) Expression correlation analysis: the Pearson correlation algorithm will be used to calculate the correlation between fecal 16s rRNA and metabolites; (2) pathway mapping: for differential microbiome and metabolites, simultaneous mapping to the pathway database will be performed to obtain common pathway information. (3) Other exploratory analyses will be considered.

6.2. Feature screening and predictive model construction

To determine the factors affecting the response to acupuncture, factors such as baseline demographic characteristics, alcohol use, relevant gut microbial and metabolomic indicators obtained using the above steps, and intervention methods (acupuncture/sham acupuncture) will be used as representative feature variables; the outcomes will be used as dependent variables (response variables) to construct corresponding datasets. Feature screening algorithms

(based on five rules: missing value, single value, correlation, zero importance, and low importance), combined with the tree model, will be used to integrate and evaluate the critical independent variables and their weights affecting each clinical variable in response to acupuncture.

Considering the small sample size, the transfer learning method will be employed to adapt the predictive model from the source domain to the target domain. First, a general model will be built using the existing public omics data (source domain), and then the model will be fine-tuned using backpropagation on the target domain data in order to adapt the model to the characteristics of the target domain, and, finally, the model will be cross-validated.

The details were provided in Section 10 of Appendix 1.

7. Discussion

7.1. Protocol overview

The effect of acupuncture on patients with SUDs was well-supported by much previous empirical evidence; however, to the best of our knowledge, no clinical study applying gut microbiome and fecal metabolomics has been performed for acupuncture treatment in the AUD population. This study describes a prospective, randomized, controlled design, utilizing clinical and multi-omics biological information for integrated analysis of microbiome-gut-brain/behavioral mechanisms to explore the gut microbiome and its metabolism mechanisms upon acupuncture adjunctive intervention in patients with AUD.

7.2. Comparison with similar previous studies

Although potential positive results have been presented for acupuncture in clinical practice, limitations include acupoint selection is either too simple (87) or not systematic enough (88). As a well-known acupuncture technique, JTN refined acupoints into many concise acupoint groups to target corresponding diseases, regulating the body and spirit together. A study by Wen et al. showed that this three-JTN-group setting imparts the synergistic and detoxifying effects of acupuncture to substance-dependent patients' detoxification intervention (64). Therefore, this study will continue this acupoint setting strategy. Additionally, in contrast to previous studies (89), the sense of "de qi" instead of aversion, will be the target of the needling stimulus manipulation.

Similar to most previous studies, sham acupuncture along with usual care will be applied (51, 89, 90). In contrast, considering the population (familiar with acupuncture) and the specificity of the acupoint effect, a placebo acupuncture device will be used, which has been verified to maintain a suitable blinding effect. This study will carry out rigorous clinical research, conduct an in-depth and systematic analysis of the clinical mechanism of acupuncture for alcohol withdrawal, and apply artificial intelligence algorithms to analyze multi-dimensional data, different from previous studies.

Moreover, the application of combinatorial analysis of the fecal metabolomics and the gut microbiome to obtain multimodal information on the gut microbial community (53) is also scarce in similar studies. This will facilitate understanding of the links between the characteristics of the microbial community structure and the metabolic function, as well as the microbial-host (91).

7.3. Implications for clinical practice

Important variables affecting the clinical response of patients with AUD to acupuncture are expected to be found, and their contributions to the response are expected to be shown, which may act as important and non-invasive biomarkers in predictable AUD management in the future. The microbiome-gut-host mechanism of the response of patients with AUD to acupuncture is expected to be discovered in this study, through the fusion of multi-omics and clinical bio-information analyses.

7.4. Advantages of this study

A combination of omics techniques and artificial intelligence will be applied to the analysis of the clinical mechanism of acupuncture for alcohol withdrawal, with the efficient use of multi-dimensional clinical data and biological information. Moreover, in this study, the clinical mechanism of acupuncture in patients with AUD will be discussed from the perspective of the relationship between gut microbes and the host.

8. Conclusions

A protocol is described above for the integrative analysis of the clinical and multi-omics bioinformatics of acupuncture used as an adjunctive intervention in patients with AUD, which may help to strengthen clinical evidence of the mechanisms related to acupuncture intervention in patients with AUD, through understanding of the regulatory mechanism of acupuncture in the gut microbiota and its metabolism as well as clinical psychopathological manifestations in patients with AUD.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of The Affiliated

Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CT, LL, and NF proposed the concept for this trial and designed the study. PZ and XLa contributed equally to the conception, design, and manuscript writing. BF, YC, and XW helped search the literature and assisted in the recruitment of patients. BF, YC, and XLi participated in the revision and editing of this manuscript. All authors approved the final version of the manuscript.

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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.2022.977487/full#supplementary-material

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Acupuncture for the treatment of overactive bladder: A systematic review and meta-analysis

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Background: Acupuncture (AT) successfully regulates overactive bladder (OAB) symptoms. However, previous systematic reviews and meta-analyses have not provided sufficient evidence. This review presents the current evidence of the efficacy of AT in the management of OAB symptoms.

Methods and analyses: A total of 12 databases were searched from their inception: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and AMED databases; five Korean medical databases; and three Chinese medical databases. Study selection, data extraction, and assessment were independently performed by two researchers. The risk of bias was assessed using the Cochrane risk of bias assessment tool. RevMan 5.4.1 software was used for data aggregation, and the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) assessment was used to evaluate the quality of the study outcomes.

Results: A total of 30 studies were included in this review. Compared with the sham AT group, the AT group exhibited significant effects in reducing overactive bladder symptom scores (OABSS) [mean difference (MD): −1.13, 95% confidence interval (CI): −2.01 to −0.26, $p = 0.01$ $I^2 = 67\%$] and urinary frequency [standardized mean difference (SMD): −0.35, 95% CI: −0.62 to −0.08, $I^2 = 0\%$]. The AT group showed an equivalent effect as drug therapy in reducing OABSS (MD: −0.39, 95% CI: − 1.92 to 1.13, $p = 0.61$, $I^2 = 94\%$) and urinary frequency (MD: 0.74, 95% CI: −0.00 to 1.48, $p = 0.05$, $I^2 = 71\%$) with fewer adverse events [risk ratio (RR): 0.38, 95% CI: 0.16–0.92, $p = 0.03$, $I^2 = 58\%$]. The AT plus drug therapy group had a more favorable effect than drug therapy alone for reducing OABSS (MD: −2.28, 95% CI: −3.25 to −1.31, $p < 0.00001$, $I^2 = 84\%$) and urinary frequency (MD: −2.34, 95% CI: −3.29 to −1.38, $p < 0.00001$, $I^2 = 88\%$). The GRADE assessment demonstrated that the level of evidence was mostly low or very low given the high risk of bias and small sample sizes.

Conclusion: AT had more favorable effects than sham AT in reducing OAB symptoms. AT improved OAB symptoms as effectively as conventional drug

therapy, and the combination of AT and drug therapy had more favorable effects than drug therapy alone. However, more rigorous studies are needed to enhance the level of evidence.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42014010377, identifier: PROSPERO [CRD42014010377].

KEYWORDS

acupuncture, overactive bladder, systematic review, meta-analysis, grade

Introduction

Overactive bladder (OAB) refers to urinary urgency that is accompanied by increased frequency and nocturia with or without urgency urinary incontinence in the absence of urinary tract infection (UTI) or other obvious pathology (1). The symptoms of OAB are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle, so-called detrusor overactivity (1). However, only 64% of patients with OAB have uro-dynamically proven detrusor overactivity. Therefore, OAB is a syndrome characterized as a "symptom-based diagnosis" (2).

Once a diagnosis of OAB has been made, most patients progress through a stepwise treatment path from conservative options to medical treatments and finally surgical treatments. As a first step, conservative management includes modifying behaviors and interventions, such as pelvic muscle exercises (3). The second step, pharmacotherapy, employs antimuscarinic agents, which have an antagonistic action on muscarinic receptors throughout the body, therefore affecting both involuntary detrusor contraction and increased sensory afferent signaling. However, despite these effects, antimuscarinic agents have several uncomfortable side effects resulting in an overall poor adherence profile with 17–35% of patients still taking their prescribed drug after 1 year (4). Dry mouth is the most common side effect, and other symptoms, such as blurred vision, constipation, erythema, fatigue, increased sweating, nausea, and vomiting, have also been reported (5). The third step, which includes surgical treatments, such as neuromodulation or botulinum toxin injection, is more invasive; therefore, patients with those conditions may seek other treatment options (6).

The mechanisms underlying acupuncture (AT) for neuromodulation of the bladder are not precisely understood. However, urodynamic evidence of detrusor overactivity suggests that AT suppresses uninhibited bladder contractions (7). Furthermore, AT stimulation seems to pass information *via* sensory ganglia to the spinal cord and *via* interneurons to modulate the activity of motor neurons in the brainstem that controls autonomic function, including urogenital activity, such as detrusor and sphincter muscle activity (8). These findings suggest that AT may help to improve OAB symptoms.

This review aims to systematically evaluate the evidence for the safety and effectiveness of AT for patients with OAB from randomized controlled trials (RCTs).

Methods

This protocol was registered with The International Prospective Register of Systematic Reviews (PROSPERO) (CRD42014010377). The reporting of this review adheres to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9).

Search strategy

Electronic databases, including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, five Korean databases [KoreaMed, the Korean Traditional Knowledge Portal (KTKP), DBpia, the Research Information Service System (RISS), and the Korean Studies Information Service System (KISS)], and three Chinese databases [China National Knowledge Infrastructure (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database], were searched from their inception to February 2022. Our search strategy included keywords, such as "acupuncture," "overactive bladder," "detrusor instability," and "urinary urgency," in English, Chinese, and Korean. The search terms for each database are listed in Supplementary material 1.

Inclusion and exclusion criteria

Types of studies

Only RCTs were included in this systematic review. We excluded trials, case studies, case series, qualitative studies, and uncontrolled trials. Trials that failed to provide detailed results were also excluded. RCTs published in the form of abstracts were included. No language restrictions were imposed.

Types of participants

We included studies that involved patients with OAB regardless of age, sex, and race. We excluded OAB studies that involved patients with neurological disease, for example, OAB in Parkinson's disease or stroke.

Types of interventions and controls

Studies evaluating all types of AT with and without electrical stimulation were included. Studies were included if AT was used as the only intervention. We also included trials in which the control group received general conventional care, such as a behavioral approach, conventional drug treatments, and sham AT (interventions mimicking "true" AT/true treatment). The acceptability of sham AT as a valid control is highly controversial (10, 11), and we planned to analyze the results using subgroup analysis. Pragmatic trials that compared AT with any other treatments (e.g., conventional drugs/exercise and education) were included. Studies were excluded if the AT was a part of a complex intervention. We excluded warm needle AT and fire AT. Studies investigating other methods of AT point stimulation without needle insertion [e.g., acupressure, transcutaneous electrical nerve stimulation (TENS), pressed studs, and laser stimulation] were excluded. Trials were excluded if the study design did not allow for the evaluation of the effectiveness of AT (e.g., use of a treatment with unproven efficacy in the control group or a comparison between two different forms of AT) or if the study adopted comparisons between treatments or groups that were expected to have similar effects to AT (e.g., moxibustion).

Types of outcome measures

Primary outcome measures

- OABSS: overactive bladder symptom scores.
- Frequency: number of daily urinary events.

Secondary outcome measures

- Incontinence: number of daily incontinence events.
- Response rate: number of patients whose OAB symptoms improved/total participants.
- Adverse events (AEs).

Data collection, extraction, and assessment

Study selection

Two reviewers (J-JL and J-WH) independently screened the titles and abstracts of the studies identified in the search, assessed the criteria for study selection, and recorded their decisions based on predefined criteria. Another reviewer (J-IK) resolved any disagreements in the study selection. The study selection process was documented and summarized in a PRISMA flow diagram. The process is presented in Figure 1.

Data extraction

All articles were read by two independent reviewers (J-JL and J-WH), who extracted data from the articles according to predefined criteria. The extracted data included the author's name(s), year of publication, sample size, age, sex, OAB duration, AT intervention, control intervention, main outcomes, adverse effects, and authors' conclusion. For the extraction of intervention-related information, the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) items were used to describe the details of AT treatments used in each study (12). When the reported data were insufficient or unclear, the author contacted the first author or corresponding authors by e-mail or telephone to request missing data or clarify data.

Assessment of risk of bias

Two authors (J-JL and J-WH) independently extracted the data from the included trials. The Cochrane risk of bias tool (13) was used to assess the internal validity of each study. The following characteristics were assessed: (1) random sequence generation, (2) allocation concealment, (3) the blinding of participants and personnel, (4) the blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias (we evaluated baseline imbalance). This review uses "L, U, and H" as keys for these evaluations, where "L" (low) indicates a low risk of bias, "U" (unclear) indicates that the risk of bias is unclear, and "H" (high) indicates a high risk of bias. Disagreements were resolved by discussion among all authors. Information regarding the risk of bias assessment for the included studies is presented in a table, and the results and implications are critically discussed.

Grades of recommendation, assessment, development and evaluation evaluation

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to evaluate the level of evidence (14). We initially gave four points to each outcome in each RCT and then lowered the total scores for defects in bias risks, inconsistency, indirectness, inaccuracy, and publication bias. Bias risks included erroneous randomization methods, absence of allocation concealment, insufficient blinding, and excessive data loss to follow-up. The inconsistencies mainly involved different interventions or evaluation techniques. Indirectness principally included two categories: (1) lack of direct comparison between the two groups

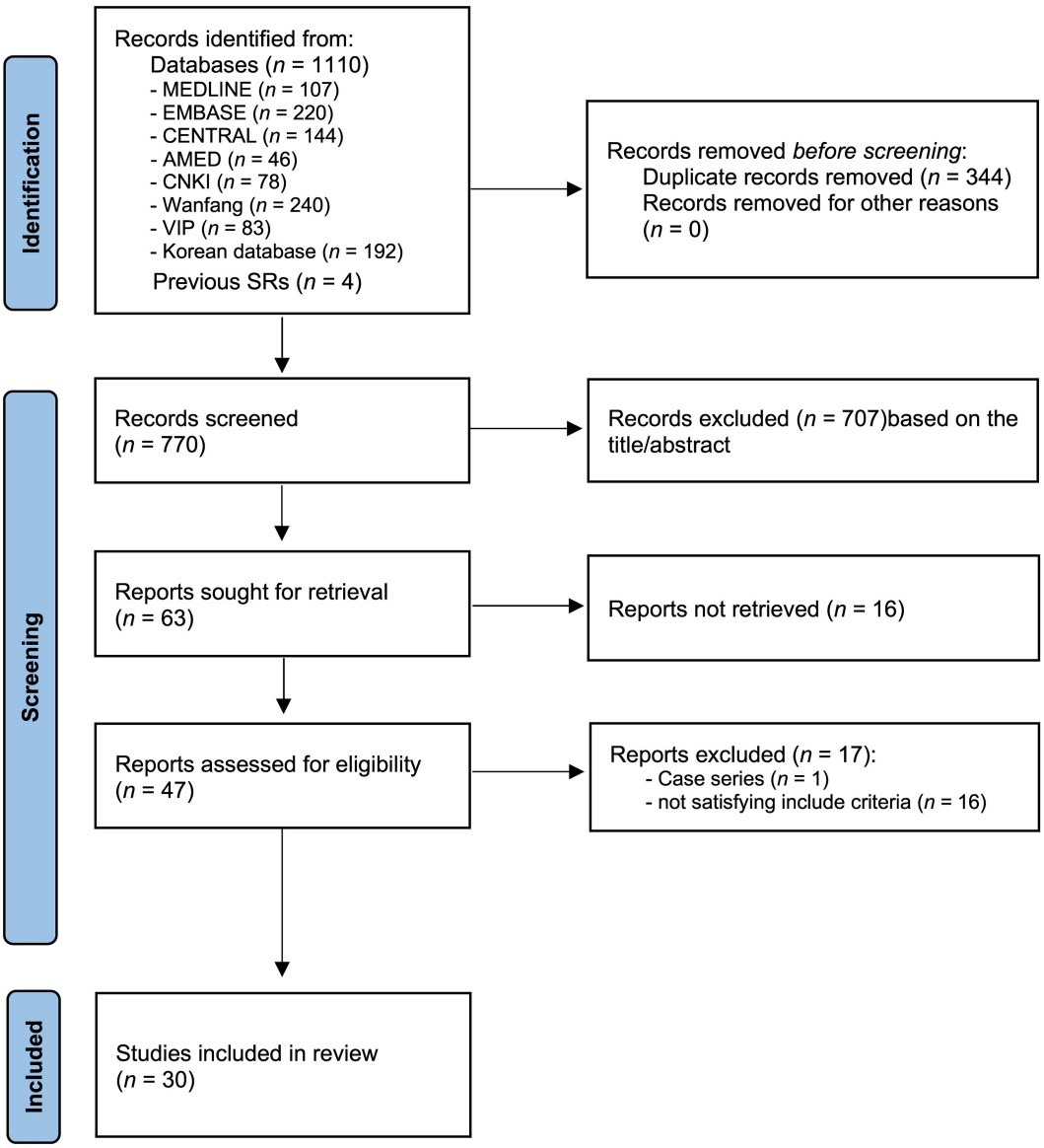

FIGURE 1
PRISMA 2020 flow diagram for the included studies.

and (2) outcome measure sensitivity to direct evaluation of efficacy. Inaccuracy was mainly evaluated based on the width of the confidence interval (CI). Publication bias was related to an unpublished study (usually containing negative results) by the investigator. The quality of evidence was categorized as high, moderate, low, or very low quality.

Data analysis

All statistical analyses were conducted by the Cochrane Collaboration's software Review Manager (RevMan) v.5.4.1 for Windows (The Nordic Cochrane Center, Copenhagen, Denmark). Differences between the intervention and control groups were assessed. In the analysis of clinical efficacy, dichotomous data were assessed in terms of risk ratios (RRs), and continuous data were assessed in terms of mean differences (MDs). Dichotomous and continuous variables were expressed as efficacy values with 95% confidence intervals (CIs). In cases of outcome variables assessed using different scales, the standardized MD (SMD) was used instead of the weighted MD (WMD). If heterogeneity was detected (defined by heterogeneity tests with a chi-square test of $p < 0.1$ and Higgins of $I^2 \geq 50\%$), subgroup analyses were performed to determine the

TABLE 1 Summary of the characteristics of the included studies.

References	Sample size (randomized/analyzed) Sex (M/F) OAB duration (years) Age (years)	Intervention group (regimen)	Comparison group (regimen)	Outcome measures	Main results	Authors conclusion	Adverse effects
Emmons and Otto (16)	85/74 (0/85) n.r. A: 53; B: 51	(A) MA (20 min, once weekly for 4 weeks, $n = 38$)	(B) Sham MA (penetrating, not related acupuncture points, 20 min, once weekly for 4 weeks, $n = 36$)	1) Frequency[y] 2) Incontinence[yy]	1) SMD −0.55 (−1.02, −0.09), $p < 0.05$ 2) SMD −0.57 (−1.04, −0.11), $p < 0.05$	"… MA … significant improvements..."	Bleeding or bruising (n.r.: 23%), discomfort with needle (n.r.: 25%)
Lin et al. (17)	100/96 (45/55) n.r. A: 69.0; B: 67.9	(A) MA (30 min, twice weekly for 8 weeks, $n = 49$)	(B) Sham MA (non-penetrating, same acupuncture points, 30 min, twice weekly for 8 weeks, $n = 48$)	1) OABSS[y] 2) Frequency[y] 3) Incontinence[y]	1) MD −0.20 (−1.24, 0.84), NS 2) SMD −0.11 (−0.52, 0.29), NS 3) SMD 0.26 (−0.14, 0.66), NS	"… beneficial effect of MA…"	None
Aydogmus et al. (18)	90/82 (0/90) n.r. 38	(A) MA (20 min, twice weekly for 4 weeks, $n = 28$)	(B) Sham MA (non-penetrating, same acupuncture points, 20 min, twice weekly for 4 weeks, $n = 24$) (C) Drug therapy (Solifenacin, oral, 5 mg, once daily for 4 weeks, $n = 30$)	1) OABSS[y] 2) AEs[y]	1) A vs. B: $P < 0.001$, A vs. C: NS 2) A vs. C: RR 0.03 (0.00, 0.43), $P < 0.0001$	"…MA may be considered another treatment option."	Dry mouth (C: 19)
Tang et al. (19)	64/64 (0/64) A: 3.2; B: 3.2 A: 41.88; B: 46.19	(A) EA (20 min, 3 times weekly for 1week, $n = 33$)	(B) Sham EA (5 mm penetrating, same acupuncture points, current, 20 min, 3 times weekly for 1week, $n = 31$)	1) OABSS[y] 2) Response rate[yy]	1) MD −1.16 (−1.38, −0.94), $p < 0.00001$ 2) RR 3.76 (1.78, 7.94), $p < 0.00001$	"EA can effectively improve … with OAB"	n.r.
Yang (20)	37/33 (10/27) n.r. A: 60.5; B: 62.8; C: 49.4	(A) EA (30 min, 3 times weekly for 8 weeks, $n = 12$)	(B) Sham EA (non-penetrating, same acupuncture points, 30 min, 3 times weekly for 8 weeks ($n = 13$) (C) Drug therapy (Solifenacin, oral, 5 mg, once daily for 8 weeks, $n = 8$)	1) Frequency[y] 2) Incontinence[y] 3) AEs	1) A vs. B: SMD −0.48 (−1.28, 0.32), NS, A vs. C: MD 2.20 (−0.45, 4.85), NS 2) A vs. B: SMD −0.37 (−1.16, 0.42), NS A vs. C: MD −0.33 (−2.75, 2.09), NS 3) A vs. C: RR not estimable	"EA …may be a good way to solve OAB"	None
Zhang et al. (21)	50/45 (0/50) A: 2.1; B: 1.9 A: 39.0; B: 43.5	(A) EA (30 min, 5 times weekly for 6 weeks, $n = 23$)	(B) Sham EA (superficial penetrating, non-acupuncture points, no-current, 30 min, 5 times weekly for 6 weeks, $n = 22$)	OABSS[y]	MD −2.40 (−3.88, −0.92), $p < 0.01$	"EA … effective, safe …"	Pain at needling sites (A: 3, B: 2)
Yu (22)	22/22 (7/15) A: 3.0; B: 5.0 A: 68.0; B: 62.6	(A) EA (30 min, 3 times weekly for 4 weeks, $n = 13$)	(B) Sham EA (penetrating, acupuncture points, no current, 30 min, 3 times weekly for 4 weeks, $n = 9$)	1) Frequency[y] 2) Incontinence[y]	1) SMD −0.61 (−1.49, 0.26), NS 2) SMD 0.00 (−0.85, 0.85), NS	"EA… has specific effect, … safe…"	Thumb-sized crape myrtle (n.r.: 1)

(Continued)

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TABLE 1 (Continued)

References	Sample size (randomized/analyzed) Sex (M/F) OAB duration (years) Age (years)	Intervention group (regimen)	Comparison group (regimen)	Outcome measures	Main results	Authors conclusion	Adverse effects
Wang et al. (23)	60/60 (0/60) ≥0.5 35–60	(A) MA (30 min, once daily for 4 weeks, $n = 30$)	(B) Drug therapy (solifenacin, oral, 5 mg, once daily for 4 weeks, $n = 30$)	1) OABSS[y] 2) Frequency[y] 3) Response rate[yy]	1) MD −0.20 (−1.14, 0.74), NS 2) MD −0.40 (−2.76, 1.96), NS 3) RR 1.04 (0.86, 1.25), NS	"MA can safely and effectively improve . . ."	n.r.
Wang and Lin (24)	60/60 (52/8) n.r. 61	(A) MA (30 min, 6 times weekly for 4 weeks, $n = 30$)	(B) Drug therapy (solifenacin, oral, 5 mg, once daily for 4 weeks, $n = 30$)	1) Frequency[y] 2) Incontinence[y] 3) Response rate[yy]	1) MD 0.80 (−0.27, 1.87), NS 2) MD 0.00 (−0.35, 0.35), NS 3) RR 0.93 (0.76, 1.13), NS	"MA . . . improve . . ."	n.r.
Hou et al. (25)	90/90 (26/64) 0.6 51.5	(A) MA (30 min, once daily for 10 days and rest 3 days, total 36 days, $n = 30$) (B) MA(30 min, once daily for 10 days and rest 3 days, total 36 days, $n = 30$), plus C	(C) Drug therapy (solifenacin, oral, 5 mg, once daily for 36 days, $n = 30$)	1) OABSS[y] 2) Frequency[y] 3) Response rate[yy]	1) A vs. C: MD 1.07 (−0.05, 2.19), NS, B vs. C: MD −2.21 (−3.64, −0.78), $p < 0.01$ 2) A vs. C: MD 1.87 (1.25, 2.49), $p < 0.00001$, B vs. C: MD −1.68 (−2.60, −0.76), $p < 0.001$ 3) A vs. C: RR 0.95 (0.67, 1.34), NS, B vs. C: RR 1.24 (0.94, 1.63), NS	". . . combined use of acupuncture and M receptor antagonists is significantly better . . ."	n.r.
Yuan et al. (26)	272/240 (0/272) n.r. A: 57.5; B: 58.2	(A) MA (20 min, once weekly for 4 weeks, $n = 118$)	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily for 4 weeks, $n = 122$)	1) Frequency[y] 2) Incontinence[y] 3) AEs[y]	1) MD 0.10 (−0.51, 0.71), NS 2) MD 0.20 (−0.01, 0.41), NS 3) RR 0.85 (0.36, 1.97), NS	"...MA is safe with significant improvements...".	Needling pain (A: 9), dry mouth (B: 11)
Wang and Shi (27)	40/40 (0/40) n.r. 51–79	(A) MA (20 min, once daily for 4 weeks, $n = 20$)	(B) Drug therapy (tolterodine oral, 2 mg, twice daily for 4 weeks, $n = 20$)	1) Frequency[y] 2) Response rate[yy] 3) AEs[y]	1) MD −1.20 (−4.24, 1.84), NS 2) RR 1.29 (0.93, 1.77), NS 3) RR 0.20 (0.01, 3.92), NS	"...the total effective rate in the treatment group was better . . ."	Dry mouth (B: 2)
Yu and Wang (28)	44/44 (22/22) A: 0.5–5; B: 0.3–4 A: 35.2; B: 37.1	(A) MA (n.r. twice daily for 2 weeks, $n = 24$)	(B) Drug therapy (tolterodine oral, 2 mg, twice daily for 2 weeks, $n = 20$)	Response rate[yy]	RR 1.52 (0.98, 2.34), $p < 0.05$	"MA.. is better. . ."	n.r.

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TABLE 1 (Continued)

References	Sample size (randomized/analyzed) Sex (M/F) OAB duration (years) Age (years)	Intervention group (regimen)	Comparison group (regimen)	Outcome measures	Main results	Authors conclusion	Adverse effects
Kelleher et al. (29)	39/36 (0/39) A: 5.2; B: 4.9 A: 51.2; B: 48.1	(A) MA (10 min, once weekly for 6 weeks, $n = 20$)	(B) Drug therapy (oxybutynin, oral, 5 mg, twice daily for 6 weeks, $n = 16$)	1) Frequency[y] 2) AEs[y]	1) NS 2) RR 0.27 (0.13, 0.56), $P < 0.0001$	"AT is … effective.. with few adverse effect…"	Discomfort (A: 2), headache (A: 3), dry mouth (B: 21), headaches, dizziness, GI upset, transient visual impairment (B: >10), unacceptable side effect (n.r. in detail, B: 3)
Zhu et al. (30)	60/57 (30/30) A: 1.6; B:1.7 A: 51.6; B: 49.4	(A) EA (45 min, 3 times weekly for 28 days, $n = 28$)	(B) Drug therapy (solifenacin, oral, 5 mg, once daily for 28 days, $n = 29$)	1) OABSS[y] 2) Frequency[y]	1) MD 0.50 (0.23, 0.77), $p < 0.001$ 2) MD 0.60 (−0.03, 1.23), NS	EA is effective and safe	Dry mouth (B: 1), constipation (B: 1)
Zhu and Bi (31)	90/90 (32/58) A: 4.3; B: 4.6 A: 63.4; B: 63.6	(A) EA (30 min, once daily for 2 weeks, $n = 45$)	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily) or (solifenacin, oral, 5 mg, once daily) for 2 weeks, $n = 45$)	Response rate[yy]	RR 1.42 (1.03, 1.95), $p < 0.05$	"EA …can significantly improve …"	n.r.
Zhang et al. (32)	104/97 (62/44) A: 2.4; B: 2.6 A: 66.5; B: 68.2	(A) EA (20 min, 6 times weekly for 2 weeks, $n = 48$)	(B) Drug therapy (tolterodine, oral, 4 mg, once daily for 3 weeks, $n = 49$)	1) OABSS[y] 2) Response rate[yy] 3) AEs	1) MD −3.00 (−4.00, −2.00), $p < 0.00001$ 2) RR 1.07 (0.94, 1.21), NS 3) RR 0.68 (0.20, 2.26), NS	"EA … can improve … better than the tolterodine tartrate…"	10 minor adverse (A: 4); (B: 6)
Chen et al. (33)	48/48 (48/0) 1–32 51	(A) EA (30 min, once daily for 14 days, $n = 24$)	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily for 14 days, $n = 24$)	Response rate[yy]	RR 1.11 (0.86, 1.43), NS	"EA is an effective…"	n.r.
Su et al. (34)	67/67 (25/42) A: 2.4; B: 2.2 A: 50.3; B: 51.6	(A) MA (20 min, 3 times weekly for 12 weeks, $n = 34$), plus B	(B) Drug therapy (tolterodine, oral, 4 mg, once daily for 12 weeks, $n = 33$)	1) OABSS[y] 2) Response rate[yy]	1) MD −1.94 (−2.59, −1.29), $p < 0.00001$ 2) RR 1.14 (0.98, 1.34), NS	"…MA with tolterodine… can significantly improve..."	Dry mouth (A: 3, B: 5), constipation (A: 2, B: 4), dry eyes (A: 3, B: 2)
Mao (35)	60/58 (26/64) 0.4–1.7 51.5	(A) MA (30 min, once daily for 10 days and rest 3 days, total 36 days, $n = 30$), plus B	(B) Drug therapy (solina, oral, 5 mg, once daily for 36 days, $n = 28$)	1) OABSS[y] 2) Response rate[yy]	1) MD −2.21 (−3.65, −0.77), $p < 0.01$ 2) RR 1.28 (0.95, 1.71), NS	"MA…is safe and effective…"	None
Li et al. (36)	60/60 (60/0) A: 11.8; B: 10.5 A: 61.5; B: 60.9	(A) MA (40 min, manipulate at 20 min, once daily for 12 weeks, $n = 30$), plus B	(B) Drug therapy (Finasteride, oral, 5 mg, twice daily for 12 weeks, $n = 30$)	Response rate[yy]	RR 1.29 (0.99, 1.67), $p < 0.05$	"MA …significantly improve the symptoms...."	n.r.

(Continued)

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TABLE 1 (Continued)

References	Sample size (randomized/analyzed) Sex (M/F) OAB duration (years) Age (years)	Intervention group (regimen)	Comparison group (regimen)	Outcome measures	Main results	Authors conclusion	Adverse effects
Xiong et al. (37)	40/40 (0/40) A: 4.1; B: 4.2 A: 45.8; B: 46.2	(A) EA (30 min, once per 2 days for 12 weeks, $n = 20$), plus B	(B) Drug therapy (SOLIFENACIN, oral, 5 mg, once daily daily for 12 weeks, $n = 20$)	1) OABSS[y] 2) Frequency[y]	1) MD −3.76 (−4.52, −3.00), $p < 0.00001$ 2) MD −3.62 (−5.61, −1.63), $p < 0.01$	"… EA… significantly improve …"	n.r.
Chen et al. (38)	74/74 (0/74) A: 1.4; B: 1.3 A: 58; B: 60	(A) EA (30 min, 5 times weekly for 4 weeks, $n = 37$), plus B	(B) Drug therapy (Solifenacin, oral, 5 mg, once daily daily for 4 weeks, $n = 37$)	1) OABSS[y] 2) Frequency[y] 3) Incontinence[y] 4) Response rate[yy]	1) MD −1.30 (−1.92, −0.68), P < 0.001 2) MD −1.93 (−2.27, −1.59), $p < 0.00001$ 3) MD −0.44 (−0.59, −0.29), p < 0.00001 4) RR 1.21 (1.00, 1.45), $p < 0.05$	"EA plus Solifenacin … effective and safe … OAB"	n.r.
Zhao (39)	68/68 (30/38) A: 1.2; B: 1.3 A: 33.9; B: 35.0	(A) EA (20 min, once daily for 30days, $n = 34$), plus B	(B) Drug therapy (solifenacin, oral, 5 mg, once daily daily for 30 days, $n = 34$)	Frequency[y]	MD −3.35 (−4.96, −1.74), $p < 0.001$	"EA combined with solifenacin … improve…"	Dry mouth (B: 1)
Chen et al. (40)	96/96 (0/96) 3.8 44	(A) EA (30 min, once daily for 14 days, $n = 48$), plus B	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily for 14 days, $n = 48$)	1) Frequency[y] 2) Incontinence[y] 3) Response rate[yy]	1) MD −2.50 (−3.18, −1.82), $p < 0.00001$ 2) MD −0.60 (−0.97, −0.23), p < 0.01 3) RR 1.26 (1.04, 1.52), $p < 0.05$	"EA combined with tolterodine… is better…"	None
Wang et al. (41)	120/120 (n.r.) n.r. n.r	(A) EA (30 min, once daily for 3 months, $n = 60$), plus B	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily for 3 months, $n = 60$)	Frequency[y]	MD −0.13 (−0.75, 0.49), NS	"EA... have significant clinical effect"	n.r.
Liao et al. (42)	67/67 (27/40) A: 2.7; B: 2.5 A: n.r.; B: 43	(A) EA (30 min, once daily for 4 weeks, $n = 35$), plus B	(B) Drug therapy (tolterodine, oral, 2 mg, twice daily for 4 weeks, $n = 32$)	Frequency[y]	MD −8.00 (−11.62, −4.38), $p < 0.00001$	"EA … can significantly improve…"	n.r.
Hargreaves et al. (43)	30/29 (0/30) Not clearly reported A: 57.2; B: 54.5	(A) MA (30 min, 6 sessions for 8 weeks, $n = 16$), plus B	(B) Usual care (fluid intake, caffeine modification, bladder health advice, pelvic floor exercises, weight reduction, smoking cessation advice, 8 weeks, $n = 13$)	1) Frequency[y] 2) Incontinence[y]	1) MD 0.12 (−1.73, 1.97), NS 2) MD 0.88 (−1.09, 2.85), NS	"may be benefits … MA"	11 minor adverse Bleeding (A: 4); bruising (A: 6); vomiting (A: 1)

(Continued)

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TABLE 1 (Continued)

References	Sample size (randomized/analyzed) Sex (M/F) OAB duration (years) Age (years)	Intervention group (regimen)	Comparison group (regimen)	Outcome measures	Main results	Authors conclusion	Adverse effects
Xie and Yang (44)	71/71 (0/71) n.r. A: 45.9; B: 46.3	(A) MA (30 min, once daily for 2 months, n = 36), plus B	(B) Usual care (urination training, bladder training, pelvic floor muscle exercise, health education, 2 months, n = 35)	1) Frequency[y] 2) Incontinence[y] 3) Response rate[yy]	1) MD −2.10 (−2.82, −1.38), $p < 0.00001$ 2) MD −0.40 (−0.68, −0.12), $p < 0.01$ 3) RR 1.30 (1.01, 1.67), $p < 0.05$	"MA combined with behavioral intervention… effective."	n.r.
Li et al. (45)	60/60 (0/60) 3.5 36.3	(A) MA (10 min, 6 times weekly for 5 weeks, n = 30), plus B	(B) Usual care (bladder training, biofeedback therapy, pelvic floor muscle training, 5 weeks, n = 30)	1) Frequency[y] 2) Incontinence[y]	1) RR 0.50 (0.22, 1.16), NS 2) RR 0.44 (0.10, 1.97), NS	"MA and nursing intervention … effectively improve…"	n.r.

MA, manual acupuncture; EA, electroacupuncture; n.r., not reported; MD, mean difference; SD, standard deviation; OABSS, over active bladder symptom score; RR, response rate.

[y]A lower score indicates a better condition.

[yy]A higher score indicates a better condition.

cause of clinical heterogeneity. A random-effects model was used to assess combined effect sizes from efficacy variables, and substantial clinical heterogeneity was expected across the included studies based on diversity among the interventions, study designs, and other conditions. An albatross plot showing the effects of direction and size range by p-value and the given sample size was generated for each included study. Publication bias was assessed using funnel plots if more than 10 studies were available (15).

Results

A total of 1,110 studies were identified in the search of 12 databases. A total of four studies were added based on other identified sources. A total of 344 articles were eliminated due to duplication. A total of 770 studies were screened by reading the titles and abstracts, and 63 articles remained. Notably, 33 articles were excluded due to the reasons described in Figure 1 after the full texts of the 63 articles were read. Finally, 30 studies (16–45) met the inclusion criteria, and a meta-analysis was conducted. The PRISMA flowchart of the search process is shown in Figure 1.

Characteristics of included studies

A total of 25 studies were conducted in China (19–28, 30–42, 44, 45), two in the United Kingdom (29, 43), one in the United States (16), one in Turkey (18), and one in Hong Kong (17). The main characteristics of the 30 included studies are presented in Table 1. Seven studies compared AT with sham AT (16–22), and 13 studies compared AT with drug therapy (18, 20, 23–33). Two of the studies had two control groups: sham AT and drug therapy (18, 20). One study had two intervention groups: AT and AT plus drug therapy (25). Ten studies used AT plus drug therapy as an intervention and drug therapy alone as a control (25, 34–42). Three studies compared AT plus standard care with standard care alone (43–45).

Rationales for using AT were reported in 97% of studies. These studies were mainly based on traditional Chinese medicine (TCM) theory (16–29, 31, 33–36, 38–45).

All studies reported acupoints, and the more frequently used acupoints included SP6 (17 studies) (16–19, 24–29, 31, 34, 35, 39, 41, 43, 44), BL23 (17 studies) (17, 19, 23–25, 27–29, 31, 35, 38–42, 44, 45), BL28 (15 studies) (16, 17, 23–25, 27–29, 31, 35, 38, 39, 42, 44, 45), CV4 (15 studies) (16–18, 23, 25–27, 29, 31, 34, 35, 39, 40, 43, 44), BL32 (15 studies) (17, 19, 21, 23–25, 27, 31–33, 35, 39, 41, 44, 45), and CV3 (11 studies) (19, 23, 25, 27, 29, 31, 34, 35, 39, 43, 44).

In total, 19 studies selected the "de qi" response (16, 18, 21, 22, 26, 31, 33–36, 38–40, 42, 43). All studies reported needle stimulation methods. The most frequently used retention time

was 30 min (17 studies) (17, 21–24, 31, 33, 35, 37, 38, 40–44). The treatment period varied from 1 to 12 weeks, and the largest number of studies was conducted over 4 weeks (16, 18, 22–24, 26, 27, 30, 38, 42). The details of the STRICTA domains are shown in Supplementary material 2.

Risk of bias in the included studies

The risk of bias in these studies is presented in Figure 2. A total of 14 studies had a low risk of bias regarding random sequence generation (16–21, 26, 29, 30, 34, 37, 39, 40, 43), whereas 16 studies did not provide detailed information about their random generation method (22–25, 27, 28, 31–33, 35, 36, 38, 41, 42, 44, 45). Notably, five studies reported the allocation concealment method (16, 17, 20, 26, 43), whereas the other 25 studies did not mention the allocation concealment method (18, 19, 21–25, 27–42, 44, 45). A total of seven studies had a low risk of performance bias given that these studies selected AT as the intervention and sham AT as the control (16–22). The remaining 23 studies had a high risk of performance bias. Given the distinct differences between the intervention and control groups, patients or clinicians could not be blinded (18, 23–45). In five studies, blinding was performed by the investigators (16, 17, 21, 26, 29). In one study, blinding was not performed, but it was judged to not affect the evaluation of results given that every participant wrote their symptom scores by themselves (34). In one study, the practitioner and outcome investigators were the same people given the lack of resources (43). The other 23 studies did not report the blinding of the outcome assessor (18–20, 22–25, 27, 28, 30–33, 35–42, 44, 45). Twenty-six studies had a low risk of attrition bias given that 19 of these studies had no dropout rate (19, 22–25, 27, 28, 31, 33, 34, 36–42, 44, 45); six had a low dropout rate, which is small enough to not affect the results (17, 20, 21, 30, 32, 35); and one had moderate dropout, but the reasons were similar in both the intervention and control groups (16). Four studies had high dropout rates (18, 26, 29, 43). Two studies were conducted in accordance with their protocols (17, 26), whereas the other 28 studies did not report the protocol or disclose all prespecified and expected results (16, 18–25, 27–45). Three studies reported adequate details to eliminate various biases (16, 17, 26), whereas the other 27 studies did not report sufficient information (18–25, 27–45).

Effects of interventions

AT vs. sham AT

OABSS

Seven RCTs compared the effects of AT with sham AT (16–22). Three RCTs reported OABSS. In one study, AT exhibited an effect equivalent to sham AT (17), whereas the other two studies showed favorable effects of AT on reducing OABSS compared with sham AT (19, 21). Meta-analysis revealed that AT showed a more favorable effect than sham AT, and heterogeneity was high (MD: −1.13, 95% CI: −2.01 to −0.26, $p = 0.01$, $I^2 = 67$, Figure 3A).

Frequency

Four RCTs reported urinary frequency, and one of these studies showed a favorable effect of AT compared with sham AT (16). The other three RCTs showed equivalent effects (17, 20, 22). Meta-analysis revealed that AT had more favorable effects than sham AT on reducing urinary frequency (SMD: −0.35, 95% CI: −0.62 to −0.08, $p = 0.01$, $I^2 = 0\%$, Figure 3B).

Incontinence

Four RCTs reported urinary incontinence. One showed a favorable effect of AT compared with sham AT (16), but three showed equivalent effects (17, 20, 22). Meta-analysis revealed that AT exhibited effects equivalent to sham AT on reducing urinary incontinence (SMD: −0.16, 95% CI: −0.62 to 0.30, $p = 0.50$, $I^2 = 60\%$, Figure 3C).

Response rate

One RCT reported the response rate and showed a favorable effect of AT compared with sham AT (RR: 3.76, 95% CI: 1.78 to 7.94, $p = 0.0005$) (19).

AT vs. drug therapy

OABSS

Thirteen RCTs used anticholinergic conventional drug therapy as a control (18, 20, 23–33). Four RCTs reported OABSS. Two showed equivalent effects of AT (23, 25), and one showed a favorable effect of AT (32). In contrast, the other study reported a favorable effect of drug therapy (30). A meta-analysis demonstrated equivalent effects of AT with drug therapy on reducing OABSS (MD: −0.39, 95% CI: −1.92 to 1.13, $p = 0.61$, $I^2 = 94\%$, Figure 4A).

Frequency

Seven RCTs reported urinary frequency, and six of these studies showed equivalent effects of AT with drug therapy on reducing urinary frequency (20, 23, 24, 26, 27, 30). The other reported a favorable effect of drug therapy (25). Meta-analysis revealed that AT exhibited effects equivalent to drug therapy on reducing urinary frequency (MD: 0.74, 95% CI: −0.00 to 1.48, $p = 0.05$, $I^2 = 71\%$, Figure 4B).

Incontinence

Three RCTs reported the number of daily incontinence episodes, and all of them showed that AT had equivalent effects to drug therapy (20, 24, 26). Through the meta-analysis, AT had equivalent effects with drug therapy on reducing urinary incontinence (MD: 0.15, 95% CI: −0.03 to 0.32, $p = 0.11$, $I^2 = 0\%$, Figure 4C).

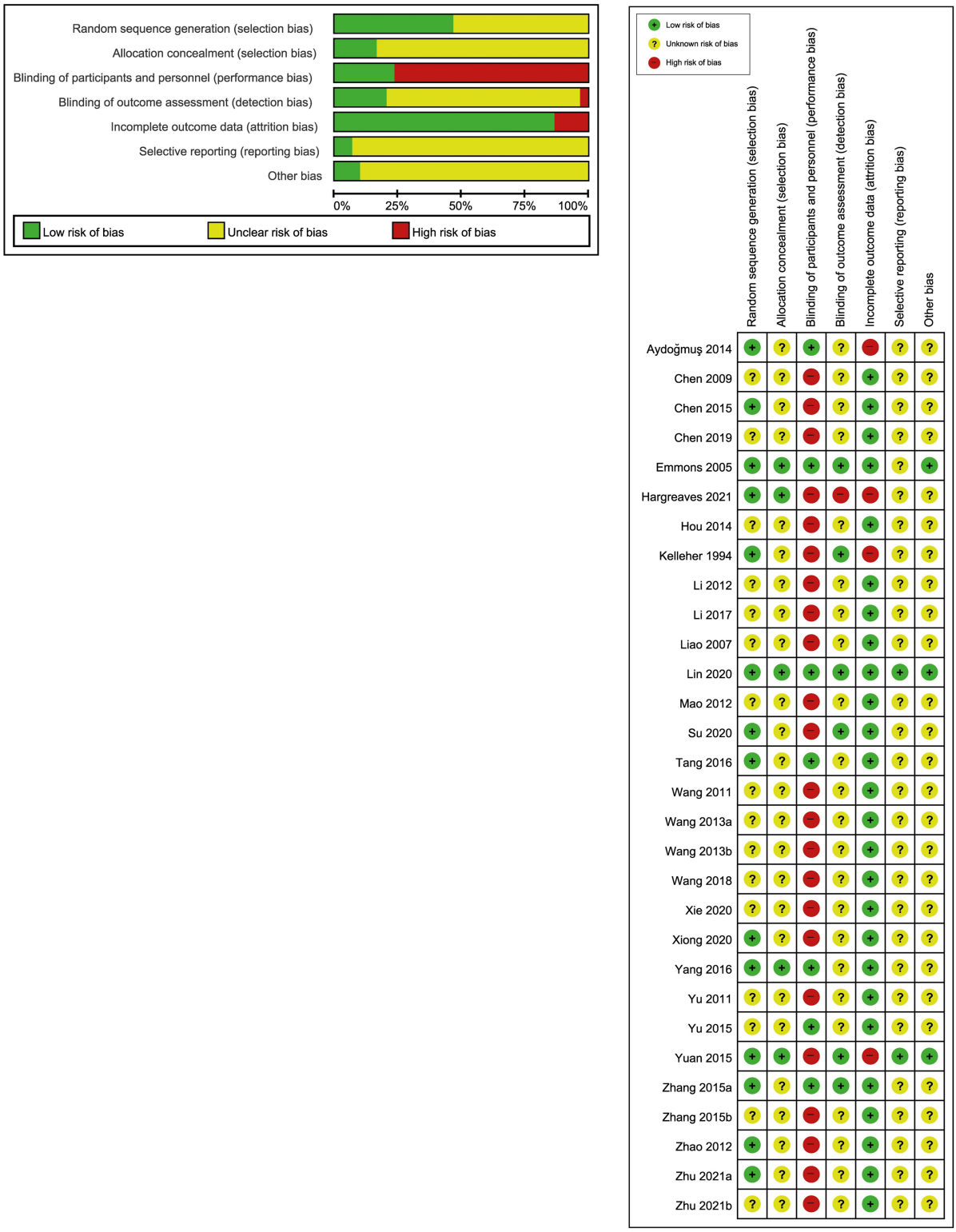


FIGURE 2
Risk of bias. **(A)** Risk-of-bias graph and **(B)** risk-of-bias summary: The present authors' judgments regarding the risk of each form of bias in all included studies.

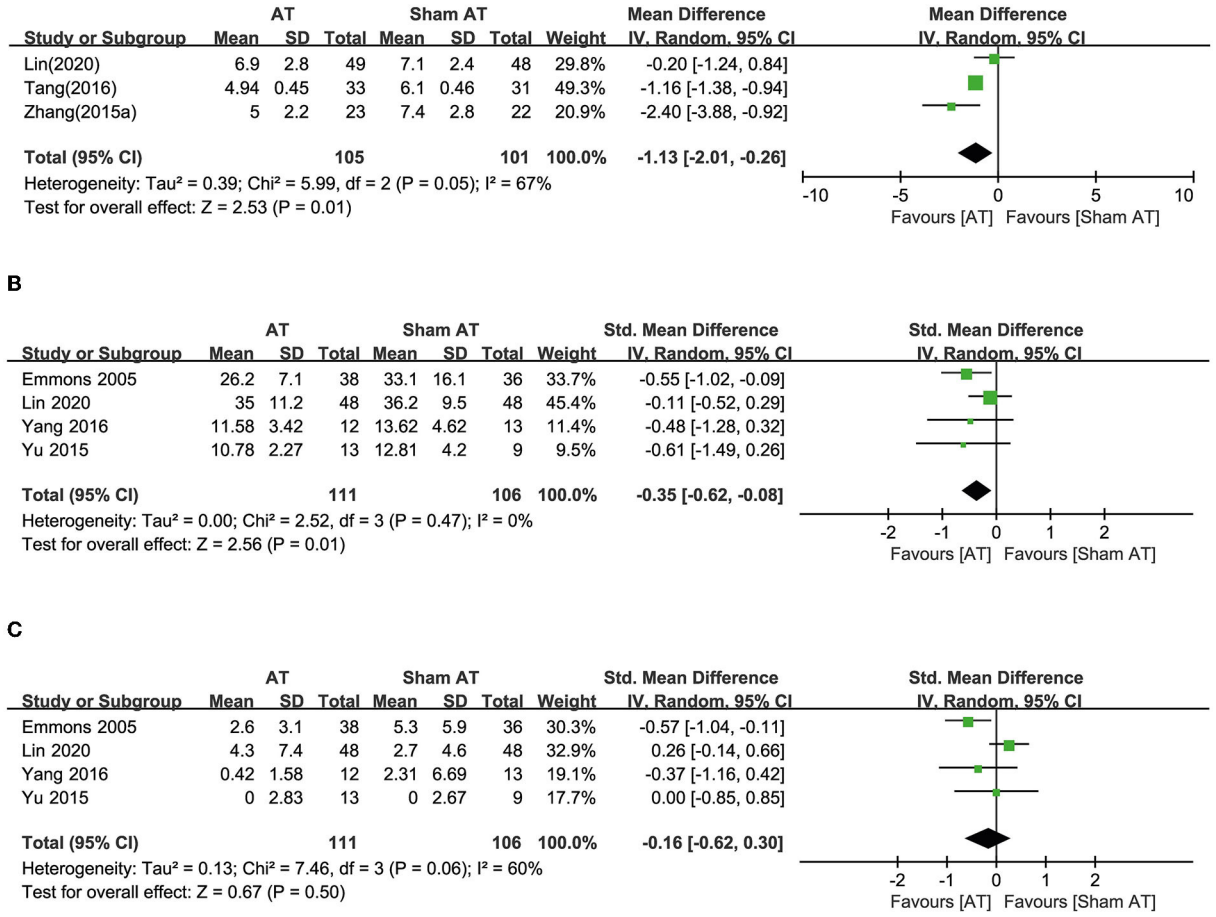


FIGURE 3
Forest plot of **(A)** OABSS, **(B)** frequency, and **(C)** incontinence according to the comparison of AT vs. sham AT.

Response rate

Eight RCTs reported the response rate, and seven of them showed equivalent effects of AT and drug therapy (23–25, 27, 28, 32, 33). One RCT showed a favorable effect of AT compared with drug therapy (31). Through the meta-analysis, AT showed equivalent effects as drug therapy on the response rate (RR: 1.09, 95% CI: 0.99 to 1.21, $p = 0.09$, $I^2 = 32\%$, Figure 4D).

AEs

Six studies reported the AEs of participants, and three of the studies showed an incidence of AT equivalent to that of drug therapy (26, 27, 32). Two RCTs reported a significantly lower incidence of side effects with AT compared with drug therapy (18, 29). AEs could not be estimated in one RCT because it reported that both groups experienced no AEs (20). Meta-analysis revealed that AT showed a significantly lower incidence of AEs compared with drug therapy (RR: 0.39, 95% CI: 0.16 to 0.93, $p = 0.03$, $I^2 = 57\%$, Figure 4E).

AT plus drug therapy vs. drug therapy

OABSS

A total of 10 RCTs used the combination of AT and drug therapy as an intervention, and the same anticholinergic conventional drug therapies served as a control (25, 34–42). Five RCTs reported OABSS, and all of them showed favorable effects of AT plus drug therapy for reducing OABSS compared with drug therapy alone (25, 34, 35, 37, 38). The meta-analysis revealed that the combination of AT and drug therapy showed favorable effects compared with drug therapy alone (MD: −2.28, 95% CI: −3.25 to −1.31, $p < 0.00001$, $I^2 = 84\%$, Figure 5A).

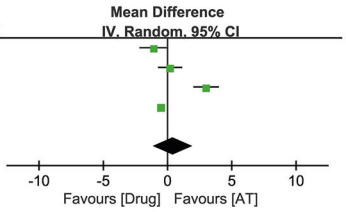
Frequency

Seven RCTs reported urinary frequency, and six of them showed favorable effects of AT plus drug therapy for reducing urinary frequency compared with drug therapy alone (25, 37–40, 42). In one RCT, the combination of AT and drug therapy

A

Study or Subgroup	AT Mean	AT SD	AT Total	Drug Mean	Drug SD	Drug Total	Weight	Mean Difference IV, Random, 95% CI
Hou 2014	-8.88	2.21	30	-7.81	2.23	30	23.8%	-1.07 [-2.19, 0.05]
Wang 2013a	-3.9	2.1	30	-4.1	1.6	30	24.7%	0.20 [-0.74, 1.14]
Zhang 2015b	-6.32	2.09	48	-9.32	2.87	49	24.4%	3.00 [2.00, 4.00]
Zhu 2021a	-3.6	0.7	28	-3.1	0.2	29	27.1%	-0.50 [-0.77, -0.23]
Total (95% CI)			**136**			**138**	**100.0%**	**0.39 [-1.13, 1.92]**

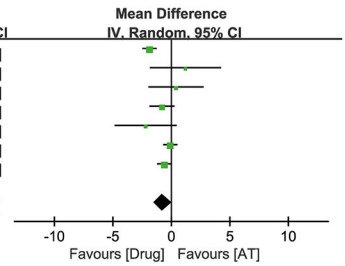
Heterogeneity: Tau² = 2.22; Chi² = 46.97, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.50 (P = 0.61)



B

Study or Subgroup	AT Mean	AT SD	AT Total	Drug Mean	Drug SD	Drug Total	Weight	Mean Difference IV, Random, 95% CI
Hou 2014	-8.88	1.24	30	-7.01	1.21	30	21.8%	-1.87 [-2.49, -1.25]
Wang 2011	-7.9	4.568	20	-9.1	5.223	20	4.8%	1.20 [-1.84, 4.24]
Wang 2013a	-8.3	4.2	30	-8.7	5.1	30	7.1%	0.40 [-1.96, 2.76]
Wang 2018	-8	2.4	30	-7.2	1.8	30	16.7%	-0.80 [-1.87, 0.27]
Yang 2016	-11.58	3.42	12	-9.38	2.62	8	6.0%	-2.20 [-4.85, 0.45]
Yuan 2015	4.2	2.1	118	4.3	2.7	122	21.9%	-0.10 [-0.71, 0.51]
Zhu 2021a	-6.9	1.3	28	-6.3	1.1	29	21.7%	-0.60 [-1.23, 0.03]
Total (95% CI)			**268**			**269**	**100.0%**	**-0.74 [-1.48, 0.00]**

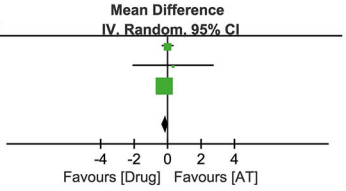
Heterogeneity: Tau² = 0.56; Chi² = 20.59, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 1.95 (P = 0.05)



C

Study or Subgroup	AT Mean	AT SD	AT Total	Drug Mean	Drug SD	Drug Total	Weight	Mean Difference IV, Random, 95% CI
Wang 2018	-0.2	0.7	30	-0.2	0.7	30	25.5%	0.00 [-0.35, 0.35]
Yang 2016	-0.42	1.58	12	-0.75	3.25	8	0.5%	0.33 [-2.09, 2.75]
Yuan 2015	1	0.6	118	1.2	1	122	74.0%	-0.20 [-0.41, 0.01]
Total (95% CI)			**160**			**160**	**100.0%**	**-0.15 [-0.32, 0.03]**

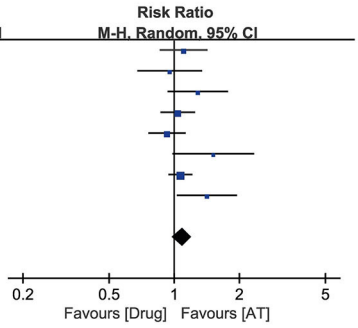
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)



D

Study or Subgroup	AT Events	AT Total	Drug Events	Drug Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen(2009)	21	24	19	24	11.7%	1.11 [0.86, 1.43]
Hou(2014)	20	30	21	30	7.4%	0.95 [0.67, 1.34]
Wang(2011)	18	20	14	20	8.2%	1.29 [0.93, 1.77]
Wang (2013a)	27	30	26	30	17.8%	1.04 [0.86, 1.25]
Wang(2018)	25	30	27	30	16.2%	0.93 [0.76, 1.13]
Yu(2011)	20	24	11	20	5.0%	1.52 [0.98, 2.34]
Zhang(2015b)	45	48	43	49	25.3%	1.07 [0.94, 1.21]
Zhu (2021b)	34	45	24	45	8.3%	1.42 [1.03, 1.95]
Total (95% CI)		**251**		**248**	**100.0%**	**1.09 [0.99, 1.21]**
Total events	210		185			

Heterogeneity: Tau² = 0.01; Chi² = 10.36, df = 7 (P = 0.17); I² = 32%
Test for overall effect: Z = 1.70 (P = 0.09)



E

Study or Subgroup	AT Events	AT Total	drug Events	drug Total	Weight	Risk Ratio M-H, Random, 95% CI
Aydoğmuş(2014)	0	28	19	30	8.0%	0.03 [0.00, 0.43]
Kelleher(1994)	5	19	16	16	32.1%	0.28 [0.14, 0.58]
Wang(2011)	0	20	2	20	7.1%	0.20 [0.01, 3.92]
Yang(2016)	0	12	0	8		Not estimable
Yuan(2015)	9	118	11	122	29.7%	0.85 [0.36, 1.97]
Zhang(2015b)	4	48	6	49	23.1%	0.68 [0.20, 2.26]
Total (95% CI)		**245**		**245**	**100.0%**	**0.39 [0.16, 0.93]**
Total events	18		54			

Heterogeneity: Tau² = 0.48; Chi² = 9.24, df = 4 (P = 0.06); I² = 57%
Test for overall effect: Z = 2.13 (P = 0.03)

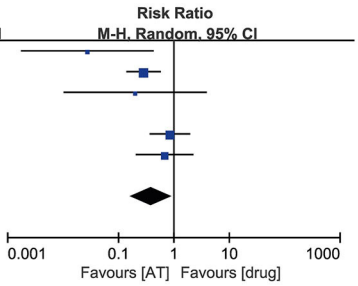


FIGURE 4
Forest plot of **(A)** OABSS, **(B)** frequency, **(C)** incontinence, **(D)** response rate, and **(E)** adverse effects according to the comparison of AT vs. drug therapy.

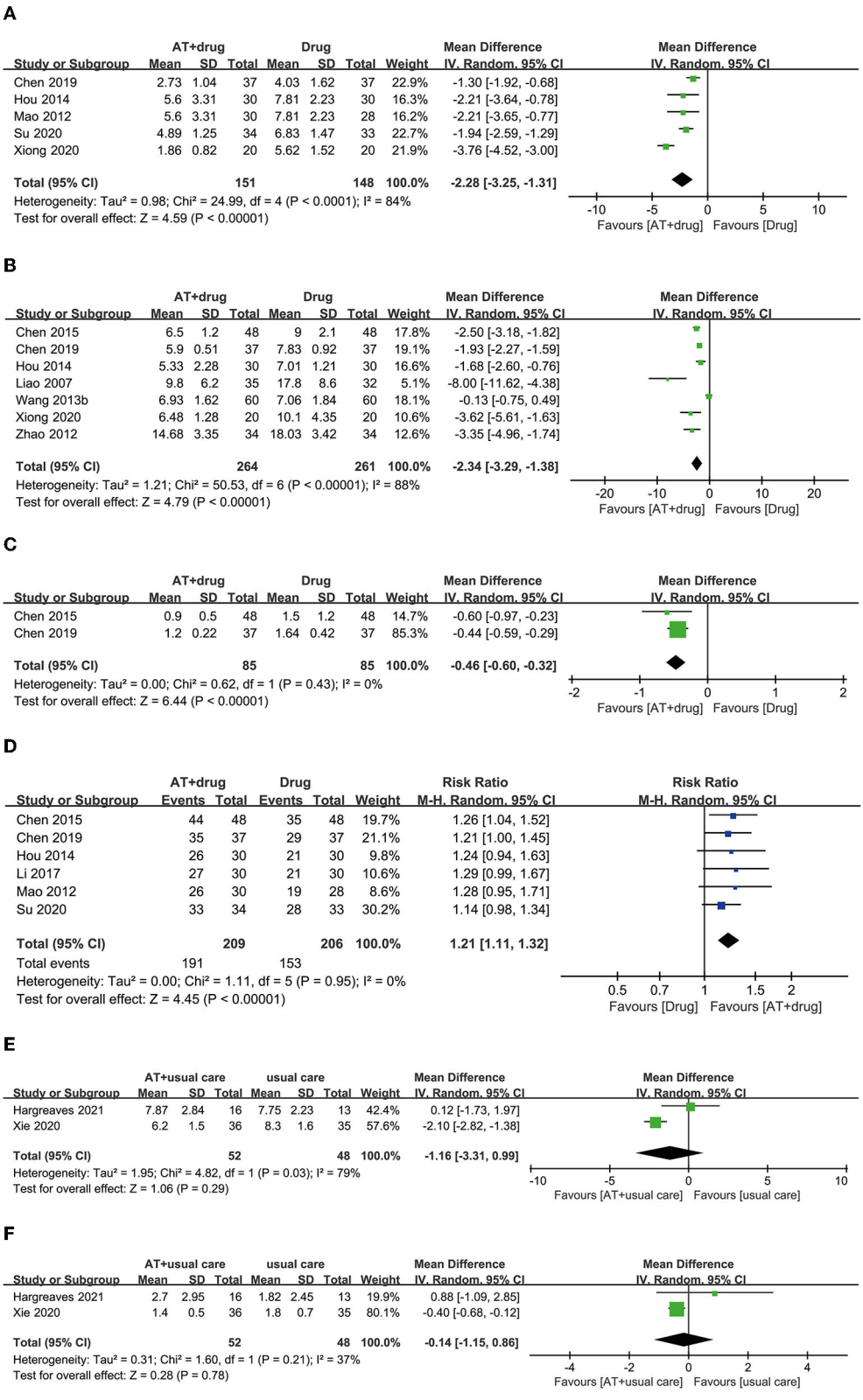


FIGURE 5
Forest plot of **(A)** OABSS, **(B)** frequency, **(C)** incontinence, and **(D)** response rate according to the comparison of AT plus drug therapy vs. drug therapy. **(E)** Frequency, **(F)** incontinence according to the comparison of AT plus usual care vs. usual care.

had an equivalent effect on drug therapy alone (41). Meta-analysis revealed that AT plus drug therapy had favorable effects on reducing urinary frequency compared with drug therapy alone (MD: −2.34, 95% CI: −3.29 to −1.38, $p < 0.00001$, $I^2 = 88\%$, Figure 5B).

Incontinence

Two RCTs reported the number of patients experiencing urinary incontinence, and both RCTs showed more favorable effects of AT plus drug therapy for reducing urinary incontinence than drug therapy alone (38, 40). A meta-analysis also revealed favorable effects of the combination of AT and drug therapy over drug therapy alone (MD: −0.46, 95% CI: −0.60 to −0.32, $p < 0.00001$, $I^2 = 0\%$, Figure 5C).

Response rate

Six RCTs reported the response rate, and four RCTs showed equivalent effects for the combination of AT plus drug therapy and drug therapy alone (25, 34–36). However, two RCTs showed that AT combined with drug therapy had more favorable effects on the response rate than drug therapy alone (38, 40). Meta-analysis revealed that the combination of AT and drug therapy had a more favorable effect on the response rate than drug therapy alone (RR: 1.21, 95% CI: 1.11 to 1.33, $p < 0.00001$, $I^2 = 0\%$, Figure 5D).

AT plus usual care vs. usual care

Frequency

Three studies selected AT plus usual care as an intervention and usual care as a control (43–45). Two RCTs reported urinary frequency. One of these RCTs showed equivalent effects (43). In contrast, the other showed a more favorable effect of AT plus usual care compared with usual care alone (44). Meta-analysis revealed equivalent effects of AT plus usual care and usual care alone for reducing urinary frequency (MD: −1.16, 95% CI: −3.31 to 0.99, $p = 0.29$, $I^2 = 79\%$, Figure 5E).

Incontinence

Two RCTs reported urinary incontinence. One RCT showed an equivalent effect (43), whereas the other showed a more favorable effect of AT plus usual care than usual care alone (44). The meta-analysis revealed equivalent effects of AT plus usual care and usual care alone for reducing urinary incontinence (MD: −0.14, 95% CI: −1.15 to 0.86, $p = 0.78$, $I^2 = 37\%$, Figure 5F).

Response rate

Only one RCT reported the response rate, and a more favorable effect of AT plus usual care was noted compared with usual care alone (44).

Total AEs

A total of 15 studies did not report AEs (19, 23–25, 28, 30, 31, 33, 36–38, 41, 42, 44, 45). In seven studies, AEs of AT did not occur (18, 20, 27, 34, 35, 39, 40). Eight studies reported minor AEs, such as needling pain, bruising, and bleeding. However, no severe AEs were reported (16, 17, 21, 22, 26, 29, 32, 43).

Albatross plot and publication bias

For the continuous outcomes, including pain, function, and QoL, most points were scattered and accumulated on the right side of the plot with many points clustered around the null line, failing to show specific effects of AT on these outcomes (Figures 6A, B). For the total effective rate, the points were scattered across the contour lines (Figure 6C). All the points were clustered on the positive association side of the plot, indicating that ginseng is favorable for the management of OAB by AT.

Summary of findings

The certainty of evidence (CoE) was assessed using the GRADEpro program, and a summary of the findings, including studies with low or very low CoE, is shown in Table 2.

Discussion

In this review, the advantages and possibilities of the use of AT for the treatment of OAB were identified. In the AT vs. sham AT comparison, significant effects in reducing OABSS and improving the response rate were noted for AT with very low certainty of evidence (CoE). Moreover, AT had a more favorable effect on reducing urinary frequency than sham AT with a low CoE. No significant differences in reducing urinary incontinence with a very low CoE were noted. However, AT exhibited effects equivalent to anticholinergic conventional drug therapy for reducing OABSS, urinary frequency, and urinary incontinence with a very low CoE. AT also had an equivalent effect as drug therapy for enhancing the response rate with a low CoE. Furthermore, the incidence of adverse effects was significantly lower with ATs compared with drug therapy with a low CoE. The combination of AT with drug therapy had a more favorable effect on reducing OABSS than drug therapy alone with a very low CoE. For reducing urinary frequency and incontinence, the combination of AT with drug therapy had a more favorable effect than drug therapy alone with a low CoE. Moreover, the combination of AT with drug therapy had a more favorable effect on enhancing the response rate than drug therapy alone with a low CoE. In the comparison of AT plus usual care with usual care, the AT plus usual care exhibited equivalent effects on reducing

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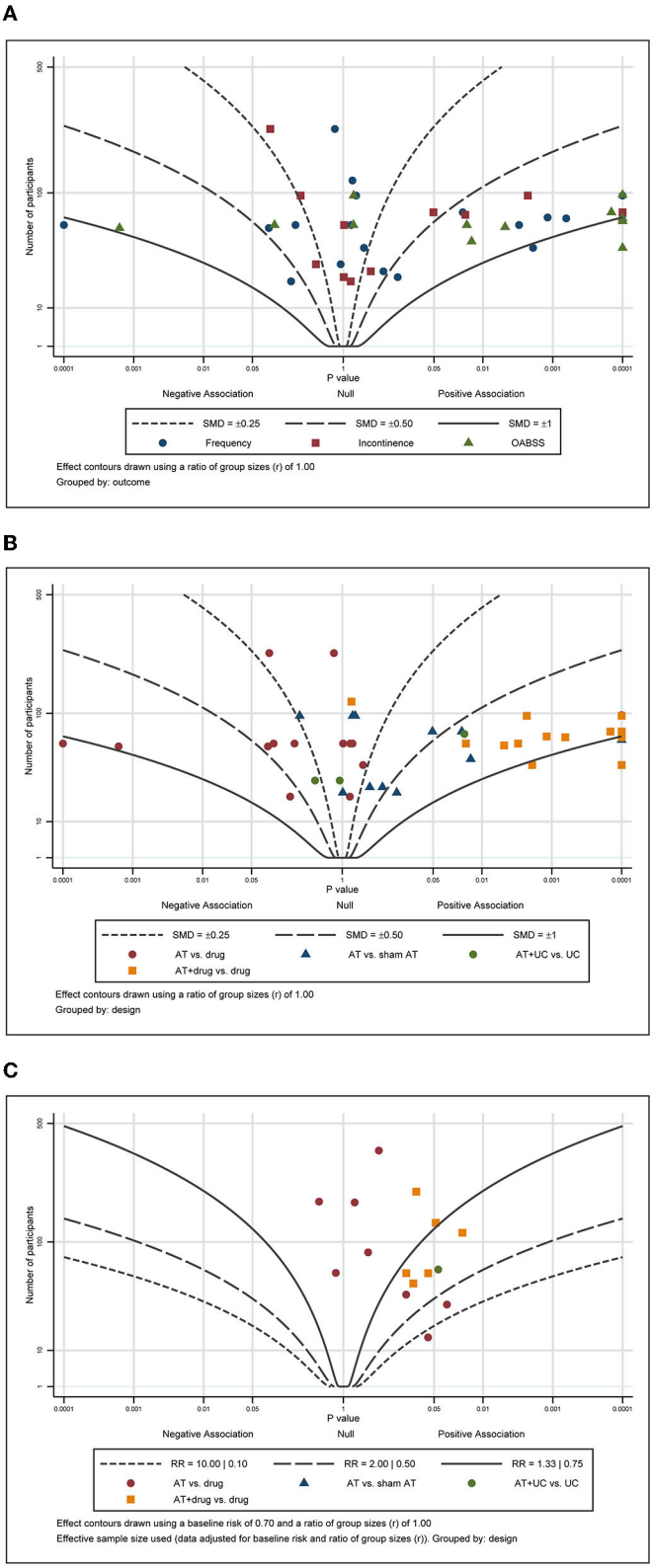

FIGURE 6
Albatross plot of **(A)** frequency, **(B)** incontinence, and **(C)** response rate according to the comparison of MA plus standard care vs. standard care.

TABLE 2 Summary of findings.

Outcome	No of Participants (studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with sham AT	Risk with AT (MA + EA)
AT compared to sham AT for overactive bladder					
OABSS	205 (3 RCTs)	⊕◯◯◯ Very low[a,b,c,d]		The mean OABSS was −1.13	MD 1.13 lower (2.01 lower to 0.26 lower)
Frequency	217 (4 RCTs)	⊕⊕◯◯ Low[a,d]		The mean frequency was −0.35	SMD 0.35 lower (0.62 lower to 0.08 lower)
Incontinence	217 (4 RCTs)	⊕◯◯◯ Very low[a,b,d]		The mean incontinence was −0.16	SMD 0.16 lower (0.62 lower to 0.3 higher)
Response rate	64 (1 RCT)	⊕⊕◯◯ Very low[a,d]	RR 3.76 (1.78–7.94)	194 per 1,000	534 more per 1,000 (151 more to 1,000 more)
AT compared to drug therapy for overactive bladder					
OABSS	274 (4 RCTs)	⊕◯◯◯ Very low[b,d,e]	–	The mean OABSS was −0.39	MD 0.39 lower (1.92 lower to 1.13 higher)
Frequency	537 (7 RCTs)	⊕◯◯◯ Very low[a,b,c]	–	The mean frequency was 0.74	MD 0.74 higher (0 higher to 1.48 higher)
Incontinence	320 (3 RCTs)	⊕◯◯◯ Very low[a,b,d]	–	The mean incontinence was 0.15	MD 0.15 higher (0.03 lower to 0.32 higher)
Response rate	499 (8 RCTs)	⊕◯◯◯ Low[b,e]	RR 1.09 (0.99–1.21)	746 per 1,000	67 more per 1,000 (7 fewer to 157 more)
Adverse effects	491 (6 RCTs)	⊕◯◯◯ Low[a,b,c]	RR 0.39 (0.16–0.93)	220 per 1,000	134 fewer per 1,000 (185 fewer to 15 fewer)
AT + drug compared to drug for overactive bladder					
OABSS	239 (4 RCTs)	⊕◯◯◯ Very low[a,b,d]	–	The mean OABSS was −2.28	MD 2.28 lower (3.25 lower to 1.31 lower)
Frequency	465 (6 RCTs)	⊕⊕◯◯ Low[a,d]	–	The mean frequency was −2.34	MD 2.34 lower (3.29 lower to 1.38 lower)
Incontinence	170 (2 RCTs)	⊕⊕◯◯ Low[a,d]	–	The mean incontinence was −0.46	MD 0.46 lower (0.6 lower to 0.32 lower)
Response rate	355 (5 RCTs)	⊕⊕◯◯ Low[a,d]	RR 1.21 (1.11 to 1.32)	743 per 1,000	156 more per 1,000 (82 more to 238 more)
AT + usual care compared to usual care for overactive bladder					
Frequency	100 (2 RCTs)	⊕◯◯◯ Very low[a,b,d]	–	The mean frequency was −1.16	MD 1.16 lower (3.31 lower to 0.99 higher)
Incontinence	100 (2 RCTs)	⊕◯◯◯ Very low[a,b,d]	–	The mean incontinence was −0.14	MD 0.14 lower (1.15 lower to 0.86 higher)
Response rate	71 (1 RCT)	⊕⊕◯◯ Low[a,d]	RR 1.30 (1.01 to 1.67)	686 per 1,000	891 more per 1,000 (693 more to 1,000 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; MD, mean difference; SMD, standardized mean difference.
[a]Downgraded by one level for study limitation: no limitation or serious of limitation.
[b]Downgraded by one level: high heterogeneity.
[c]Downgraded by one level for imprecision: confidence interval crossed assumed threshold of minimal clinically important difference or effect size.
[d]Downgraded by one level for imprecision: small sample size.
[e]Downgraded by two levels for study limitation: serious of limitation or very serious limitation. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

urinary frequency and incontinence with a very low CoE. However, regarding the response rate, the combination of AT and usual care had a more favorable effect with a very low CoE.

Our review aimed to evaluate and complete the evidence from recent RCTs of AT for the treatment of patients with OAB. Compared with two previous systematic reviews (46, 47), we identified 18 new RCTs (17, 18, 24, 27–31, 33–39, 43–45) and successfully assessed the evidence for therapy. The results of our review are different from those of the two previously published reviews. One previous review (47) showed that AT may be beneficial for reducing micturition, incontinence, and nocturia episodes, whereas the other review (46) failed to report favorable effects of AT for reducing symptoms of OAB compared with several types of controls. When we examined the results of AT for OAB symptoms, our results showed beneficial effects of AT compared with sham AT. However, one review did not show significant effects of AT compared with sham AT (47). Only two RCTs were included in the meta-analysis of electroacupuncture (EA) vs. sham EA, and EA had no favorable effect on reducing urinary frequency, urgency, or incontinence compared with sham EA. EA showed a favorable effect on decreasing nocturia. Another study (46) performed a meta-analysis of AT vs. sham AT on reducing OABSS based on two RCTs and did not show a significant effect. Instituting an appropriate sham AT condition is always a difficult factor in designing a study to determine the effects of AT. OAB affects the psychology of an individual, and sham AT for OAB was previously reported to produce a placebo effect in ∼33–56% of participants (48). Emmons and Otto postulated a 40% placebo effect and a 59% treatment effect and explained that larger RCTs are needed to statistically show the effects of AT (16). Thus, it seems that the effect of sham AT, which has not been identified in previous reviews, appeared in this review, which includes more studies. However, since the size of the effect is not large, more studies are needed to collect the data. More consideration is needed to establish an appropriate sham AT to demonstrate the effect of AT appropriately.

Based on our assessment, the risk of bias is high in each of the included studies, potentially leading to false positives. Regarding performance bias, 23 studies had a high risk of bias based on the difference between intervention and control as well as AT treatment or drug administration. Although AT has to penetrate the skin and requires time for retention, medication is taken orally as prescribed. Therefore, blinding is difficult because patients can easily distinguish whether they are receiving AT or taking medications. Of the RCTs included in this study, there were no studies using AT and sham AT or drug and placebo drugs interchangeably. Moreover, AT could not be blinded to the performer (18, 23–45). Additional independent studies in different countries are required to determine the generalizability of these results given that 26 studies were conducted in China (17, 19–28, 30–42, 44, 45).

This review has some limitations. First, many included RCTs had an unclear risk of bias given that these studies did not report particular details. Second, despite the large number of RCTs, the outcomes were very diverse, so a large-scale meta-analysis could not be performed. Therefore, the level of evidence is mostly low or very low. Third, the frequency of AT intervention ranged from 2 per day to <1 per week. Fourth, the suitable design of a sham AT condition remains a difficult problem.

Future studies on OAB treatment with AT should report their study design in more detail to obtain a high level of evidence. Moreover, if OABSS, response rate, adverse effects, and quality of life scores are commonly reported in these studies, we can obtain results with a larger population, definitively demonstrate the advantages of AT, and achieve a higher level of consensus. Studies should also be performed that could inform AT guidelines regarding acupoints, retention times, frequency, and treatment period for the application of AT for OAB in the clinical field.

In conclusion, AT had more favorable effects than sham AT in reducing OAB symptoms. AT showed equivalent effects as anticholinergic drugs with fewer AEs. The combination of AT and drug therapy had more favorable effects on OAB than drug therapy alone. However, the level of evidence is low due to the high risk of bias and the small sample size. Future well-designed research is needed to obtain a higher level of evidence to apply AT for the treatment of OAB.

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

J-JL and J-IK: conceptualization. J-JL and J-WH: data curation and resources. J-JL, J-WH, MSL, and J-IK: formal analysis and writing—original draft. J-JL, J-WH, JHJ, and T-YC: investigation. J-JL, J-WH, and MSL: methodology. MSL and J-IK: project administration and supervision. J-WH and J-IK: software. JHJ and T-YC: writing—review and editing. All authors have read and approved the final manuscript.

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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.2022.985288/full#supplementary-material

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A study on the effects of the Qihuang Needle therapy on patients with Parkinson's disease

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Objective: This study aimed to evaluate the effectiveness of the Qihuang Needle (QHN) in treating Parkinson's disease (PD).

Design, setting, and participants: The trial was an 8-week randomized clinical trial (4 weeks of treatment followed by 4 weeks of follow-up) conducted from January 2021 to July 2022 in outpatient settings at three clinical sites in Guangzhou, China. Thirty-four participants with PD were diagnosed based on the diagnostic criteria formulated by the brain bank of the British Parkinson's Disease Society in 1992.

Interventions: Patients in the treatment and control groups received six sessions within 4 weeks of the QHN therapy or the sham acupuncture therapy (two times per week for the first two consecutive weeks and one time per week for the following two consecutive weeks).

Main outcomes and measures: The primary outcome measure was the change in the Parkinson's Disease Rating Scale-Part III Motor Examination (UPDRS III) between baseline and 8 weeks after treatments. Secondary outcome measures were the Non-Motor Symptoms Scale for Parkinson's Disease (NMSS) and Parkinson's Disease Daily Quality of Life-39 (PDQ-39). Real-time shear wave elastography (SWE) was assessed for each patient at baseline and during the 4-week period as the third outcome measure.

Results: A more significant reduction of UPDRS III score, PDQ-39, NMSS, and SWE was observed in the QHN group than in the sham acupuncture group.

Conclusions: The QHN therapy consistently demonstrated superiority and produced clinically meaningful benefits in reducing motor and non-motor symptoms, as well as significantly improving muscle stiffness, in patients with PD.

KEYWORDS

acupuncture, Qihuang Needle therapy, Parkinsion's disease, randomized clinical trial, sham acupuncture

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by tremors and bradykinesia and is a common neurologic ailment. The appearance of motor symptoms accompanies the diagnosis of PD. Specific non-motor symptoms, such as olfactory dysfunction, cognitive impairment, mental symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue, characterize the prodromal stage of PD. Axial movement symptoms, such as frequent falls and postural instability with a frozen gait, often occur in the advanced stages of the disease.

As the second most common neurodegenerative disease, the incidence of PD before the age of 50 is low. However, it increases rapidly with age, peaking in most studies around the age of 80 (1). More than 6 million individuals across the world have PD (2). Drugs that increase the concentration of dopamine in the brain or stimulate dopamine receptors are still the main drugs for treating the motor symptoms of PD. These drugs include levodopa, dopamine agonists, type B monoamine oxidase inhibitors, and amantadine. Unfortunately, these drug treatments for PD usually increase the risk of adverse events (3, 4), including nausea, daytime sleepiness and edema, and impulse control disorders. Due to the limitations of these conventional treatments, efforts have been made to identify practical, low-risk interventions.

In China and Western countries, acupuncture has been widely used to treat PD. Acupuncture and moxibustion can reduce the adverse reactions caused by anti-PD drugs and improve the quality of life of patients (5, 6). Acupuncture has been shown in previous studies to be an effective adjunctive therapy for the treatment of PD, particularly in improving motor and non-motor symptoms. Some studies even suggest that acupuncture may be more effective than western medicine alone in treating PD (7–9).

Qihuang Needle (QHN) therapy is a treatment method developed by Professor Zhenhu Chen from the First Affiliated Hospital of Guangzhou University of Chinese Medicine that combines manipulation with acupuncture. It is based on the principles of tendon differentiation and uses modern anatomical theory to simplify the selection of points, resulting in a treatment that is simple, safe, and effective with fewer points required.

The primary purpose of this randomized, controlled, evaluator-blind trial study was to evaluate the effectiveness of QHN therapy as an adjunctive treatment for PD.

Methods

Study population and protocol

Participants in this study were recruited through advertisements on bulletin boards in the acupuncture and neurology departments at three hospitals: the First Affiliated Hospital of Guangzhou University of Chinese Medicine, the Guangdong 999 Brain Hospital, and the Third Affiliated Hospital of Sun Yat-sen University. An independent assessor working in these departments screened and registered participants who met the inclusion criteria. PD was diagnosed using the diagnostic criteria established by the brain bank of the British Parkinson's Disease Society in 1992 (10). The participants were recruited from January 2021 to July 2022. The Clinical Trial Center study protocol at the First Affiliated Hospital of the Guangzhou University of Chinese Medicine approved the protocol (11). The published protocol is available at the following link: https://www.frontiersin.org/articles/10.3389/fneur.2022.902170/full.

The inclusion criteria were as follows: men or women aged 40–80 years with a diagnosis of PD; patients with experience with PD for at least 1 year; patients whose Hoehn-Yahr (HY) grades range from 1 to 4; patients who were on anti-PD medication and had been on a stable dose for more than 2 months or who had not been on medication for more than 2 months; stable vital signs and clear consciousness; and the provision of written, informed consent by the patients.

Patients with any of the following conditions were excluded: the presence of severe hepatorenal disease, tumors, bleeding disorders, endocrine disease, or infection; schizophrenia or other mental disorders that affected compliance; being deaf or having communication difficulties caused by dementia; having a history of alcohol or drug abuse; or involvement in other clinical trials.

Randomization and blinding

A total of 34 eligible patients were recruited and randomly assigned at a ratio of 1:1 to receive QHN or sham acupuncture (SA) treatment. The Clinical Medical College of Acupuncture, Moxibustion and Rehabilitation, Guangzhou University of Chinese Medicine, Guangdong Province, China performed the central randomization. The random assignment operation was programmed and executed using the SAS9.2 software. An independent researcher received the random numbers and group assignment after inputting the patients' information through the application. Participants in the treatment group (QHN group) and the control group (SA group) were blinded. Acupuncturists could not be blinded to the treatment assignments, given the nature of the interventions. Outcome assessors, data collectors, and statisticians were blinded to the treatment allocation.

Intervention

Patients in the treatment and control groups received six sessions within 4 weeks of QHN or SA therapy (two times per week for the first two consecutive weeks and one time per week for the following 2 weeks) for 4 weeks. Five to six acupoints were used per treatment, located in the four limbs, the neck, and the back. We chose the prescriptions as a result of our experience from our previous study (11). All acupuncturists were trained and licensed with at least 5 years of clinical experience.

Patients in the treatment group were treated with QHN therapy. A tailored, sterile, stainless-steel needle (length: 50 mm; diameter: 0.5 mm; QH; Chongqing) was inserted into the described acupoints at a depth of 25–40 mm. After the patients felt the Deqi sensation, the needles were removed and reapplied at a 30° angle. All needles were withdrawn with clean cotton balls pressed to the skin to prevent bleeding. In addition, more details of the procedure have been published (11).

The number of needles and duration of treatment in the control group were identical to those in the treatment group except that an attempt was not made to induce the Deqi sensation. The control group had undergone insertion of QHN at sham acupoints that did not correspond to acupuncture points. Sham acupoints were defined as 20 mm lateral to the real acupoints. Therefore, a needle was inserted into the sham acupoints at a depth of 3 mm without any subsequent manipulation. At these points, the patient did not feel any Deqi sensation.

To ensure the safety and compliance of participants and meet ethical requirements, we followed the recommendations for managing patients with PD as outlined in the Chinese guidelines (10).

During the treatment period, two groups of patients were orally administered anti-PD drugs. The subjects taking the drugs were responsible for preparing and maintaining their original treatment regimens. In instances where a change in medication was necessary, we carefully recorded details such as the name of the medication, time of administration, and dose.

In addition, frozen gait (FOG) is one of the most disabling gait disorders, affecting 80% of patients with PD. Clinical guidelines recommend that these patients have gait rehabilitation as soon as possible (12). Some studies (13–15) also demonstrated that gait rehabilitation has immediate real-life benefits on FOG symptoms among patients with mild-to-moderate PD. Therefore, subjects were instructed to perform home-based rehabilitation training according to Parkinson's easy quintile, one time in the morning and one time at night. The five pieces of the brief parkinsonian movement were designed and guided by Professor Zhenhu Chen and included *in situ* steppings, left-right translation, finger percussion, head massage, and abdominal massage.

Measurements

Data collection

All outcome measurements were taken at baseline (before treatment), 4 weeks after, and 8 weeks after treatment. At each follow-up, two blinded evaluators at each clinical center reminded patients by phone or text message to return the headache diary to the trial offices *via* email or to outpatient offices at follow-up visits.

Outcome measures

The primary outcome was the change in the PD Rating Scale-Part III Motor Examination (UPDRS III) between baseline and 8 weeks after randomization. Secondary outcome measures included the Non-Motor Symptoms Scale for PD (NMSS) and the PD Daily Quality of Life-39 (PDQ-39). In addition, real-time shear wave elastography (SWE) was assessed at baseline and every 4 weeks.

Sample size calculation

This trial used a clinical-superiority design to verify that QHN therapy's effect was superior to SA. The primary outcome measure was the UPDRS III score difference before and after the treatment. According to previous research (16), we assumed the standard deviation (SD) to be 8.0 and the mean of the treatment effect of the two groups to be 4.36 and 0.25, respectively, during which the statistical power was 80%, and the significance level was 0.05. Using PASS software meant each group had to contain more than 17 patients.

Statistical analysis

We used mean and SD for normally distributed variables or median (interquartile range) for the variables not normally distributed to summarize the participants' demographics, health conditions, and clinical outcomes at two different time points. Two statisticians, blinded to the group setting, analyzed the data independently *via* SPSS software (version 23) and R (version 4.1.0). Furthermore, the data were analyzed using the intent-to-treat principle. The normality of the variables was assessed using the standard probability plot. The continuously distributed variables were customarily assessed by the student's *t*-test. Otherwise, the Mann–Whitney or Wilcoxon test was applied. Fisher's exact test was adopted for categorical data, and statistical significance was set at a *p*-value of <0.05.

Results

Demographic and clinical characteristics

Thirty-four participants, 40–80 years old, were randomized. A total of 55.8% were women. Fifteen patients in the QNH group and 19 in the SA group were separated from 34 patients with PD. Intent-to-treat (ITT) analysis was conducted on the two groups. The baseline characteristics did not differ significantly between the groups. All participants completed the assessments without the occurrence of significant adverse events. The flowchart of this study is shown in Figure 1.

Primary outcome

Before treatment, the UPDRS III myotonia scores for both groups did not follow a normal distribution. We used the Mann–Whitney *U* test, a non-parametric test for independent samples, to compare the scores between the two groups and found that there was no statistically significant difference, with a *p*-value of $0.477 > 0.05$. This indicates that the baseline scores for the treatment group and the control group were similar, allowing for meaningful comparison. The Wilcoxon signed rank sum test, a non-parametric test for paired samples, was used to compare the scores before and after treatment within each group. The treatment group showed a statistically significant difference, with a *p*-value of $0.00 < 0.05$, as did the control group, with a p-value of 0.00–0.05. These results suggest that both groups had significant changes in UPDRS III myotonia scores following treatment. After treatment, the Mann–Whitney *U* test was used to compare groups. From Figure 2B, the *P*-value was determined to be <0.01. The difference in the UPDRS III myotonia score between the two groups after treatment was statistically significant. The UPDRS III decreased in the QHN group by 15. A more significant reduction was observed in the QHN group than in the SA group.

Secondary outcomes

Furthermore, the effects of acupuncture on the secondary outcomes seemed to be consistent during the follow-up (Figures 2A, B). In patients with PD of the QHN group, the score of the NMSS decreased by 11, and the score of the PDQ-39 decreased by 19 than before treatment. At the same time, we observed that NMSS and PDQ-39 were significantly reduced in the QHN group compared with the SA group, and the two groups had significant differences.

Moreover, the total score of SWE was significantly lower in the QHN group than in the SA group in each interview during weeks

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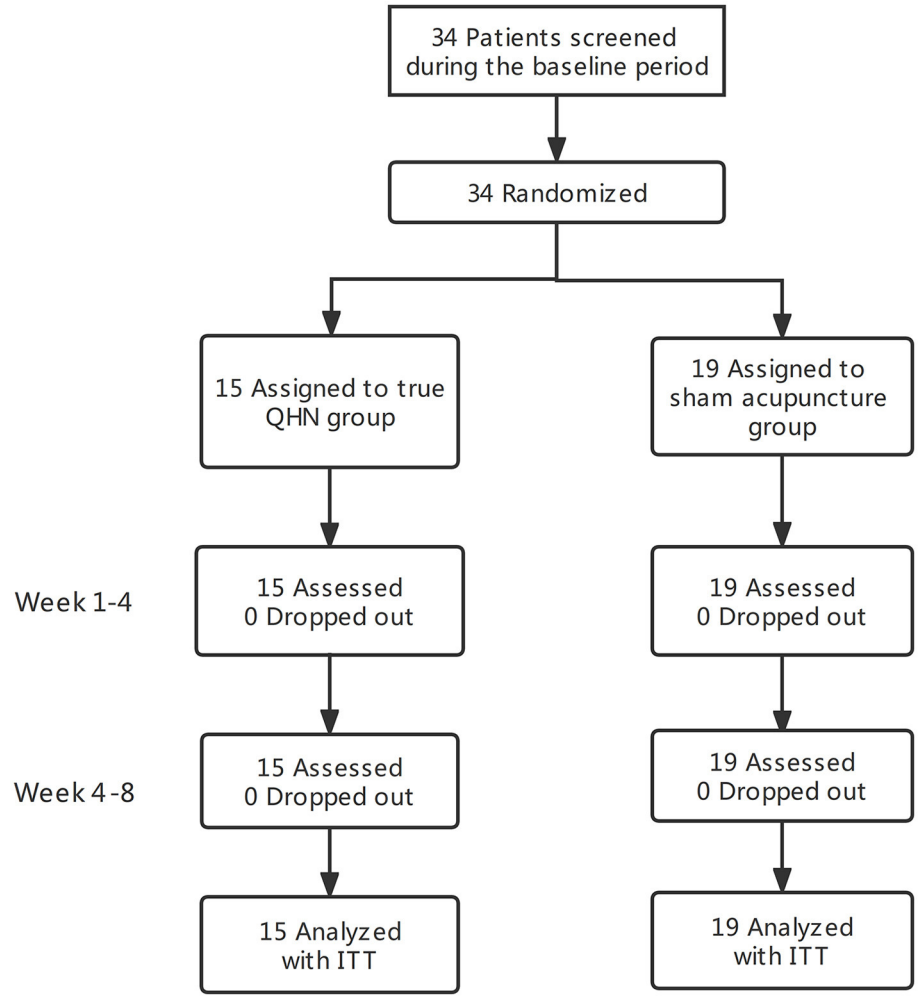

FIGURE 1
A flowchart of the screening, enrollment, randomization, and follow-up of this study.

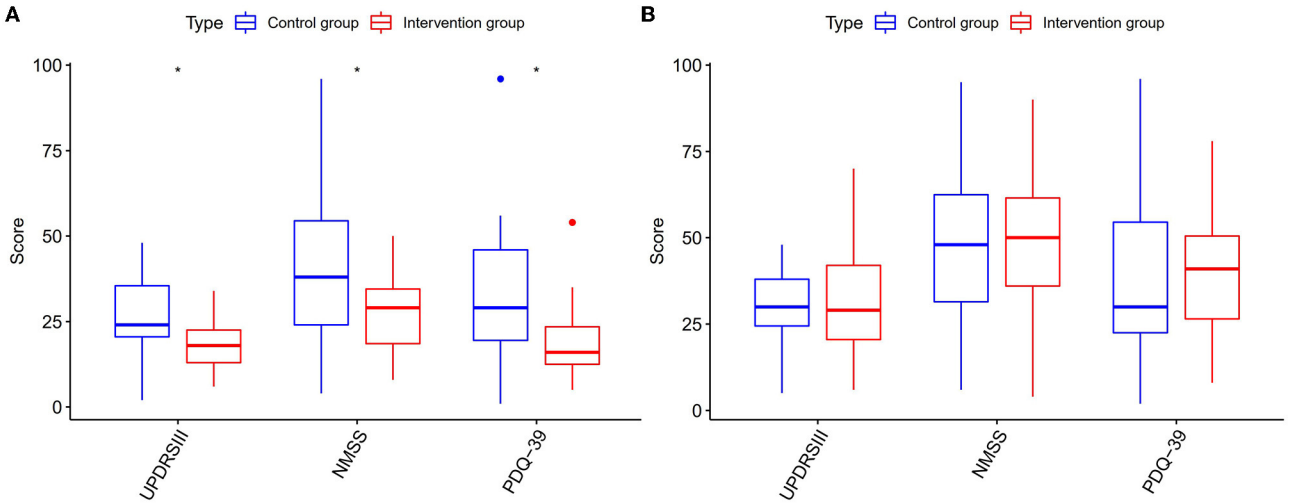

FIGURE 2
Multi-evaluation score (UPDRS III, NMSS, and PDQ-39) of PD status. Intervention group: QHN group. Control group: SA group. **(A)** The evaluation scores before treatment between two groups. **(B)** The evaluation scores after treatment between two groups.

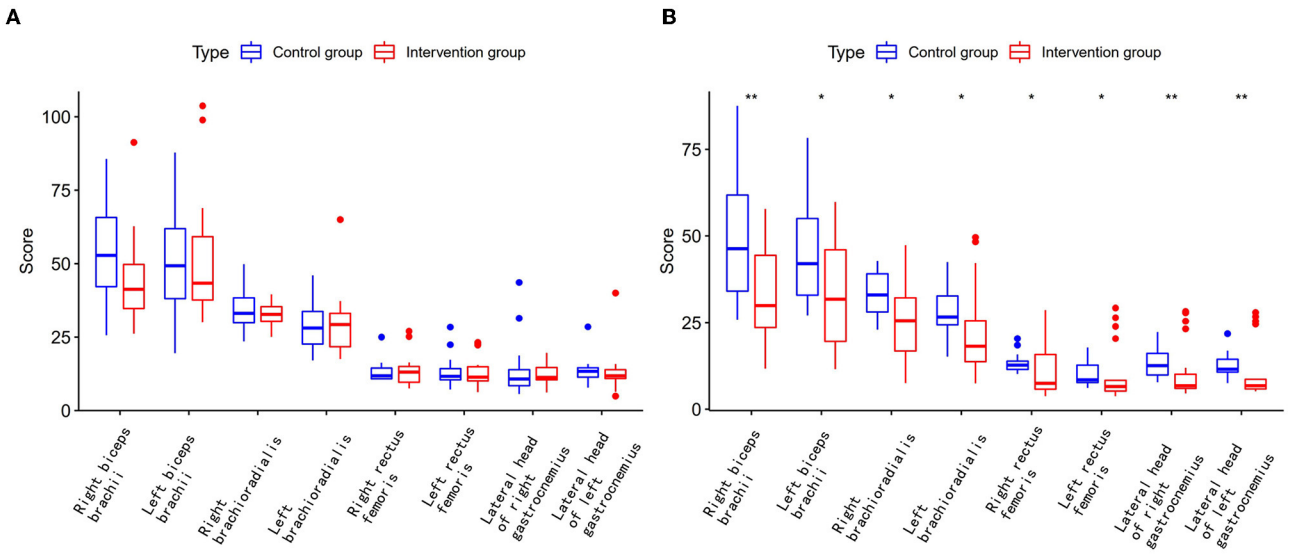

FIGURE 3
Real-time shear wave elastography score of PD patients. Intervention group: QHN group. Control group: SA group. **(A)** The SWE score before treatment between two groups. **(B)** The SWE score after treatment between two groups.

3–6 (Figures 3A, B). We found that the SWE score for the right biceps brachii, the left biceps brachii, the right brachioradialis, the left brachioradialis, the right rectus femoris, the left rectus femoris, the lateral head of the right gastrocnemius, and the lateral head of the left gastrocnemius were significantly decreased before QHN treatment. It was comparable with the SA group, which illustrated that QHN had a superior efficacy on the tension situation of patients' body muscles and joints to achieve greater freedom of movement. We observed significant differences in the SWE score between the two groups at weeks 2, 3, and 4 of the follow-up period. The QHN group showed a reduction in patient discomfort during treatment compared to the SA control group.

Discussion

In our study, we investigated whether a 4-week QHN treatment improved activities of daily living and motor symptoms in patients with PD. We obtained vital evidence to help interpret previous clinical trials that studied the effects of QHN treatment on patients with PD. In psychophysical responses, the UPDRS III, NMSS, PDQ-39, and SWE were statistically lower after acupuncture treatment for 4 weeks, and the UPDRS III, NMSS, and PDQ-39 remained stable for at least the next 8 weeks (8-week follow-up). Decreases in these scores mean improvements in the symptoms related to these scores in patients with PD. In addition, after 4 weeks of treatment, the control group also showed significant changes compared to the baseline, and there were significant differences between the control and treatment groups. There were no serious adverse events due to the treatment. These results indicate the safety and usefulness of the combined treatment of QHN for patients with PD as an adjunctive treatment.

There have been observations and research reports on the population of patients with PD (8, 17, 18), which confirmed the effectiveness of acupuncture and moxibustion in treating PD. These studies reported improvements in PD symptoms, especially in those with milder disease. Hong et al. (19) compared two groups, one treated with VR rehabilitation training and one treated with Jiao's scalp acupuncture. For 8 weeks, selected participants received acupuncture one time a day, five times a week. Outcomes reveal that acupuncture could improve gait parameters, walking ability, and motor function in patients with PD.

Second, SWE is a new ultrasound technique capable of measuring the shear wave velocity of tissues and calculating Young's modulus values reflecting this index to evaluate tissue elasticity. Real-time shear wave elastography uses the shear wave of an ultrasound probe to create pressure on tissues and avoid the influence of artifacts, in addition to the advantages of non-invasive, convenient, and reproducible detection (20). It has recently been shown that the upper limbs of patients with PD are mainly the flexor and adductor muscles with increased muscle tone, such as the biceps brachii. Yin et al. (21) found that the values of Young's modulus of the gastrocnemius medialis (GM) in the lower leg of patients with PD on the symptomatic side were higher than those of healthy individuals ($P < 0.05$) and also higher than those on the less symptomatic side ($P < 0.05$). Clinically, PD muscle tone rises gradually, so generalized muscle stiffness often appears in the end stage of the disease. There are also findings suggesting that shear wave elastography in patients with PD also presents this feature, as Ding et al. (22) found that the shear wave velocity of the biceps brachii on the ankylosed side, the non-ankylosed side, and the brachioradialis on the tonic side in patients with PD was correlated with disease duration ($P < 0.05$).

The QHN body is hollow, and the needle's hardness is high, which strengthens the stimulation of acupuncture and thus improves clinical efficacy. Based on the theory of meridians and tendons, the acupoints for treating PD by QNH therapy mainly select the tendons near the joints. Relevant studies (23) found that acupuncture of tendon nodes can quickly relieve the spasticity of local soft tissues, accelerate blood circulation, increase local tissue nutrition, and finally improve the related symptoms of patients with high muscle tension

rapidly, such as muscle stiffness and pain. In selecting needling methods, QNH therapy inherits the five needling methods of classical needling. It is recorded in *Su Wen Ji Zhu that the Qi of the five viscera is external to the skin, veins, muscles, and bones, and the five viscera are in the middle*, so the external combination should be applied to the five viscera. It can be seen that the five-needling method has a targeted therapeutic effect. The location of PD involves the liver, the spleen, the kidney, the muscles, the tendons, and the bones. Therefore, the clinical operation is mainly based on Guan-needling, Hegu-needling, and Shu-needling.

Currently, many clinical studies and animal experiments show that acupuncture has an excellent effect on PD without apparent toxic or side effects. Relevant literature (24) pointed out that the mechanism of acupuncture treatment for PD includes promoting the expression of neurotrophic factors in the brain, reducing abnormal metabolites in the brain, reducing the aggregation of a-synuclein, inhibiting neuronal apoptosis, inhibiting oxidative stress, inhibiting endoplasmic reticulum stress, and regulating intestinal flora. The pathogenesis of PD is complex, but the current acupuncture research only starts from a specific mechanism and fails to comprehensively explain the relationship between various mechanisms and what mechanism plays a leading role (25). QHN therapy is a new acupuncture method. There are few studies on the mechanism of QHN therapy in treating PD, and its therapeutic mechanism is unclear. However, the clinical effect of this therapy is accurate, and the prospects are good. It is worth further exploring its mechanism.

Limitations

Our study also has three limitations: a small sample size of only 34 subjects due to the effects of COVID-19, the study's duration, and human constraints. The subjects were mainly from Guangzhou City, which may limit the generalizability of the results and impact the study findings as well as the short follow-up period of this study, preventing us from observing the long-term effectiveness of QHN therapy for treating PD.

Conclusion

For at least 8 weeks, QHN therapy demonstrated persistent superiority and clinically relevant benefits in Parkinson's disease, including a reduction in motor and non-motor symptoms and a significant improvement in muscle stiffness.

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 human participants were reviewed and approved by the Clinical Trial Center study protocol at The First Affiliated Hospital of Guangzhou University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XL designed and analyzed the research study. XL and JZ wrote and revised the article. RH, JL, CH, SY, and JJ collected and analyzed the data. All authors have read and approved the article.

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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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Mechanism of Qihuang needle therapy in the management of tic disorders: a clinical trial protocol

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Background: Qihuang needle therapy is a newly developed acupuncture therapy to treat tic disorders in clinical practice. However, the mechanism to reduce tic severity remains unknown. Changes in intestinal flora and circulation metabolites are perhaps the potential pathogenesis of tic disorders. As a result, we present a protocol for a controlled clinical trial using multi-omics analysis to probe the mechanism of the Qihuang needle in managing tic disorders.

Methods: This is a matched-pairs design, controlled, clinical trial for patients with tic disorders. Participants will be allocated to either an experimental group or a healthy control group. The main acupoints are Baihui (GV20), Yintang (EX-HN3), and Jueyinshu (BL14). The experimental group will receive Qihuang needle therapy for a month, while the control group will receive no interventions.

Expected outcomes: The change in the severity of the tic disorder is set as the main outcome. Secondary outcomes include gastrointestinal severity index and recurrence rate, which will be calculated after a 12-week follow-up. Gut microbiota, measured by 16S rRNA gene sequencing; serum metabolomics, assessed *via* LC/MS; and serum zonulin, assessed by enzyme-linked immunosorbent assay (ELISA), will be used as biological specimen analysis outcomes. The present study will investigate the possible interactions between intestinal flora and serum metabolites and the improvement of clinical profiles, which may elucidate the mechanism of Qihuang needle therapy for tic disorders.

Trial registration: This trial is registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/). Registration number: ChiCTR2200057723, Date: 2022-04-14.

KEYWORDS

multi-omics analysis, clinical trial protocol, acupuncture, Qihuang needle therapy, tic disorders

1. Introduction

Tic disorders are neurodevelopmental disorders characterized by recurrent motor and/or vocal tics (1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (2), defines the following five tic disorders: provisional tic disorder; persistent (chronic) motor or vocal tic disorder; Tourette's disorder (also known as Tourette's syndrome [TS]); other specified tic disorder; and unspecified tic disorder. Tic disorders are common in China, with a prevalence of transient tic disorder (TTD), chronic tic disorder (CTD), and Tourette syndrome (TS) of 1.7, 1.2, and 0.3%, respectively (3).

Tics usually begin between the ages of 3 and 8 years and become worse between the ages of 8 and 12 years for most patients. The first tic symptoms are usually simple motor tics, restricted to one muscle or a single muscle group. Tics then progress to involve more muscle groups or present with mimicking. Simple vocal tics, demonstrating meaningless sounds, usually occur after motor tics. For children or adolescents, the features of tics wax and wane in severity and frequency, and new tic symptoms replace, combine with, or even exacerbate the old ones (4, 5). Academic stress and family pressure may increase the incidence of tic disorders among school-age children. Excessive attention from parents, ridicule from peers, or incomprehension from teachers contribute to the aggravation of tics. Despite reports that tics tend to mitigate spontaneously throughout adolescence and reach complete remission in early adulthood, tics do not always remit within a year in most children with recent-onset tic disorders, and recurrence may occur even after long-term remission among patients with CTD (6). Attention-deficit hyperactivity disorder, obsessive-compulsive disorder, and autism spectrum disorder are the most common psychiatric comorbidities that impair social, behavioral, or emotional functioning (7).

Psychoeducation is recommended as the initial intervention, and behavior therapy is recommended as a first-line intervention for children and adults with CTD or TS (8). Nevertheless, education and behavior therapy are aimed at older patients or children with insufficient evidence to prove effectiveness and safety (9). Pharmacotherapy is recommended as the second option but may cause considerable adverse effects (10). Furthermore, for refractory tic disorders, surgical interventions using deep brain stimulation have been suggested as an alternative option (11), but the efficacy and safety thereof are non-conclusive. Although various neural regulation therapies, such as repetitive transcranial magnetic stimulation (rTMS), cranial electrotherapy stimulation, and electroencephalographic biofeedback, have been used in clinical practice, the effects of such treatments are still a matter of debate (5). Thus, a therapeutic strategy for tic disorders is required.

A growing body of evidence has proven that acupuncture is an effective treatment for tic disorders (12, 13). Acupuncture, especially electroacupuncture or scalp acupuncture alone, demonstrates a positive effect in terms of total clinical effectiveness rate, the incidence of adverse events, and recurrence. Currently, common methods of acupuncture treatment for tic disorders include traditional Chinese medicine acupuncture, electroacupuncture, scalp acupuncture, and auricular acupuncture (14). However, these methods have some disadvantages, such as long-time needle retention, challenges in electric current control, or the necessity for the child to take the initiative. In addition, most patients are school-aged children with academic pressure, requiring short-course therapies with flexible treatment times.

Qihuang (QH) needle, invented by Dr. Zhenhu Chen, is a new acupuncture instrument developed from the Jiuzhen (Nine Needles) created in ancient times (15). Qihuang needle therapy (QHN therapy) absorbs the essence of the meridian sinew theory and the "five thorns" that originated from the Inner Canon of Huangdi (16). QHN therapy has advantages compared with traditional acupuncture (17). First, it is less painful, with almost no pain when the needle punctures the skin. Second, the manipulation of the QH needle is swift, without needle retention. Third, point selection is simple and usually involves no more than five acupoints in one treatment session. Finally, the treatment period is shorter than traditional Chinese acupuncture, especially for intractable pain.

Recently, several cases that investigate the clinical efficacy of QHN therapy for various kinds of diseases such as low back pain (18, 19), acute gouty arthritis (20), and Parkinson's disease (21) have been reported. QHN therapy has been used in the field of pediatric neuropsychiatric disorders such as tic disorders (22) and spastic hemiplegic cerebral palsy (23). QHN therapy seems to be a potential treatment method for tic disorders, and further studies exploring its efficacy and mechanisms are needed.

Tic generation is caused by dysfunction of the cortico-basal ganglia neuronal networks (24). Changes in the gut microbiota could serve as a significant or moderating factor in the etiology of basal ganglia-associated diseases, such as tic disorders. A descriptive model of the microbiota-gut-brain axis in tic disorders has been reported (25, 26): genetic and environmental factors alter the gut microbial composition and its activity; disturbances in intestinal flora induce escalation of gastrointestinal permeability; and intestinal-derived molecules may pass into the peripheral circulation and permeate into the brain through the damaged blood-brain barrier, which may cause altered basal ganglia function. The gut microbial alteration may lead to other risk factors, including altered short-chain fatty acid levels, increased vagal stimulation, and the release of other bacterial metabolites. Zonulin is a human protein that could reversibly regulate intestinal permeability (27). Increased zonulin indicates impaired gut barrier integrity, and serum zonulin has been applied as a peripheral biomarker to assess human intestinal barrier permeability in neurological or mental diseases to explore the roles of dysbiosis and gut barrier integrity (28, 29). Under the hypothesis that intestinal-derived molecules penetrate the gut barrier into the peripheral circulation, corresponding molecular changes could be assessed *via* serum metabolomics. In addition, the interaction between the gut microbiome and serum metabolites can be explored to identify some previously unknown links between intestinal microbiota alterations, circulating metabolites, and physical disorders (30, 31).

Most studies regarding the mechanism of acupuncture therapy for tic disorders are conducted *via* animal model experiments, which focus on acupuncture regulating neurotransmitters (32, 33). Studies investigating the mechanism in the clinical context are insufficient. Recently, omics analyses have been used as prospective methods to probe acupuncture mechanisms in the clinical context. Using gut microbiome sequencing, acupuncture was found to modulate the structures and diversity of the gut microbiome, inhibit inflammation of the central nervous system (34, 35), gradually improve gut barrier function, and regulate neurotransmitters (36, 37) in various neuropsychiatric diseases. As for metabolomics assays, the potential mechanisms of acupuncture to treat neuropsychiatric disorders may be associated with modulating systematic inflammation and improving lipid metabolism (38–40). QHN therapy shows effectiveness in the treatment of tic disorders in clinical practice and is worth investigating to determine the specific mechanism. Nevertheless, omics studies of tic disorders are in their infancy (25, 41), with few studies on acupuncture. We aimed to determine how QHN therapy works in the treatment of tic disorders by investigating how it influences the gut microbiota and serum metabolites in children with tic disorders and to analyze possible correlations between clinical profiles and the changes in the gut flora and serum metabolites.

2. Methods and analysis

2.1. Study design and participants

This is a matched-pairs design, controlled, clinical trial with two groups (experimental group and healthy control group). Patients with tic disorders and age–gender-matched healthy children will be recruited through advertisements posted on web pages and display boards or through the outpatient system recommended by doctors at Panyu Hospital of Chinese Medicine (Guangzhou, China) and Foshan Fosun Chancheng Hospital (Foshan, China). Both hospitals are tertiary hospitals. All participants will be screened according to the inclusion and exclusion criteria. The guardians of eligible participants will sign a written informed consent (see Supplementary material 1) after a detailed explanation of the study by the investigators and will be provided with a baseline assessment. Participants are free to withdraw from the study at any time. This protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (42) and the Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation, and Elaboration (SPIRIT-TCM Extension 2018) (43). The study was registered in the Chinese Clinical Trial Registry (ChiCTR2200057723).

2.2. Eligibility criteria

Participants must fulfill the diagnostic criteria for provisional tic disorder and persistent motor or vocal tic disorder according to the DSM-5 (2). Patients will be screened according to the inclusion and exclusion criteria listed in Table 1.

2.3. Sample size

Considering that the focus of omics studies is the mechanism of the intervention effect, the sample size estimation of our exploratory research is distinctive compared with classical randomized control trials. Given previous literature regarding the omics analysis of acupuncture (44–46), at least 15 participants in each group are required. Thus, we set at least 15 participants in each group in the present design. Allowing for a 20% dropout rate, we plan to recruit 40 participants (20 participants per group).

2.3.1. Recruitment strategies

Participants were enrolled between April 2022 and March 2023. The current study utilized two primary resources to identify and recruit potential subjects: advertisements, including printed media such as roll-up banners and social media such as WeChat, and patients recommended by doctors. No registration fee was charged, and acupuncture treatments and scale assessments were provided free of charge. The flow of the trial is presented in Figure 1. The schedule of enrollment, interventions, and assessment, as well as visits for participants during the trial, is shown in Figure 2.

2.4. Intervention

To ensure the optimal effects of acupuncture stimulation, all treatments were performed by one certified acupuncturist with more than 3 years of experience in practice. Before the trial, special training regarding the process and standard operation of the treatment will be provided.

2.4.1. Qihuang needle therapy

The QH needle is divided into four parts as follows: the tip, the shaft, the handle, and the protective cap (Figure 3). Its tip is flat-bottomed, circular, and three-edged, ensuring safety and reducing stabbing pain at the moment of penetration (47). The needle body is a hollow tube with higher strength and toughness compared with common filiform needles. Its transparent and anti-slip handle facilitates the observation of hemorrhages, and the protective cap is made of disposable material that is non-toxic.

Based on the meridian sinew theory and clinical experience, Baihui (GV20), Yintang (EX-HN3), and Jueyinshu (BL14) will be selected as the main acupoints. Xiyangguan (GB33), Fuliu (KI7), Danzhong (CV17), and Qihaishu (BL24) are additional acupoints. KI7 will be chosen for patients with leg twitches, and CV17 will be used where vocal tic disorders occur. BL24 is for waist movement disorder. BL14, GB33, KI7, and BL24 will be stimulated bilaterally. The acupuncture points are described in Table 2 and presented in Figure 4.

We aim to apply QH needles (patent no. ZL2015 20271867.0; 0.3 × 0.13 × 30 mm; QH; Chongqing Figure 3) in the acupuncture treatment. Manipulation (48) will be done as follows. After skin disinfection, the QH needles will be inserted vertically into the myofascial. Then, the needle will be directed toward the diseased site, and its handle will be gently moved from side to side at an angle of 15–30. When the "de qi" sensation (feelings of numbness, tingling, swelling, soreness, or muscle weakness) becomes obvious (∼10 s after stimulation), the needle will be withdrawn. The pinholes will be pressed with a sterile, dry cotton ball without needle retention. As for the Baihui acupoint, the needle will be inserted perpendicularly into the galea aponeurotica, then withdrawn slightly, and the abovementioned manipulation will be performed. As for the Yintang acupoint, the needle will be inserted obliquely into the subcutaneous, and the abovementioned manipulation will be performed.

Participants in the experimental group will receive eight sessions of acupuncture treatment (two times a week for 4 weeks), and participants in the healthy control group will not receive the intervention.

2.5. Outcome evaluations

The clinical evaluations include the assessment of the severity of tics and gastrointestinal symptoms. The recurrence rate will be measured after a 12-week follow-up. The primary outcome measure will be the Yale Global Tic Severity Scale (YGTSS), and secondary outcomes will consist of the gastrointestinal severity index (GSI) and the recurrence rate. Biological specimen analysis outcomes will include changes in the composition of intestinal microbiota, serum metabolites, and serum zonulin. YGTSS and GSI will be assessed at baseline and after 4 weeks when the interventions have been

TABLE 1 Eligibility criteria.

	TD patients	Healthy controls
Inclusion Criteria	1. Aged between 4 and 18 years	1. Matched age, sex, family history of a psychiatric condition, parental marital status, mode of delivery and birth weight to the TD group*
	2. Meeting the diagnostic criteria of transient tic disorder and Persistent Motor or Vocal Tic Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (1, 2)	2. No current or history of head trauma, convulsions, epilepsy, growth and development disorders, mental illness, digestive system disease, abdominal operation or asphyxia at birth
	3. The course of a provisional tic disorder is more than 3 months	3. No current or history of medication of mental disorders especially drug influencing neurotransmitters
	4. The score of YGTSS >12	4. The mother is healthy during pregnancy (no history of infection, digestive system disease, trauma or taking any medication)
	5. Have not received acupuncture or moxibustion within 3 months, and drug withdrawal period ≥12 weeks	
	6. Guardians are willing to sign the informed consents	
Exclusion Criteria	1. Secondary tic disorders	
	2. Patients with severe diseases of important organ systems: liver and kidney damage, cardiovascular insufficiency, metabolic diseases, malignant tumors, etc., which may adversely affect our clinical observation	
	3. Obsessive-compulsive disorder, depression, Attention deficit hyperactivity disorder, anxiety, autism spectrum disorder, eating disorder, or a history of substance abuse	
	4. Epilepsy, Huntington's disease, rheumatic chorea, hepatolenticular degeneration, substantia nigra degeneration, psychogenic tics and other extrapyramidal disorders	
	5. The use of antibiotics, probiotics, high-dose vitamin or immunomodulatory medications within 4 weeks before the fecal sample collection	
	6. Conditions like any infective diseases or other severe disorders that may influence the gut microbiota	
	7. Ulcers or surgical scars on the acupoint area	
	8. Children who are participating or participated in other clinical trials within 1 month	
Withdrawal criteria and management	1. Misdiagnosis, violation of the inclusion criteria	
	2. Self-use of prohibited treatment	
	3. Poor cooperation with the established treatment or data collection procedures	
	4. Serious adverse events or life-threatening diseases or an acute progression of the disease occurs during the trial	
	5. Obvious discomforts arise because of the therapy	
	6. Participants request withdrawal voluntarily	

American Psychiatric Association (1).
*Healthy control matching procedure: To select a healthy control group comparable in size to the experimental group. The criteria used for this procedure (with match tolerance) are as follows: (1) age (±1 year), (2) sex (exact match), (3) family history of the psychiatric condition (exact match), (4) parental marital status (exact match), (5) mode of delivery (exact match), and (6) birth weight (±100 g). We chose to match these variables as they may be the risk factors influencing the development of tic disorders.

completed. Data relating to the recurrence rate will be collected after a 12-week follow-up. Feces and serum samples will be collected at baseline and 4 weeks after the interventions. If sample collection is concurrent with a treatment, sample collection will be performed after all interventions have been completed. The feces sample will be collected as soon as possible after completing all interventions.

2.5.1. Primary outcomes

2.5.1.1. Change in YGTSS score

The YGTSS is the most widely used rating scale for tic assessment, both in clinical practice and research. It has the best evidence in the assessment of tic severity and indicates acceptable psychometric quality (49, 50). An experienced pediatric clinician carries out the YGTSS by asking the parents or guardians of the participants to answer the questions and by observing participant performance during visits to the clinic. The total score (maximum rating of 100) is the sum of the scores of motor and vocal tics and functional impairment. A YGTSS score < 25 indicates mild severity; 25–50, moderate; >50, severe.

2.5.2. Secondary outcomes

2.5.2.1. Change in GSI

The GSI, applied in the present study to rate the gastrointestinal signs and symptoms, was originally used in a 2006 study by Schneider et al. (51). This 9-item GSI rating scale was used to assess gastrointestinal symptoms in children with tic disorders, and its correlation with the gut microbiome was investigated (25). The rating scale consists

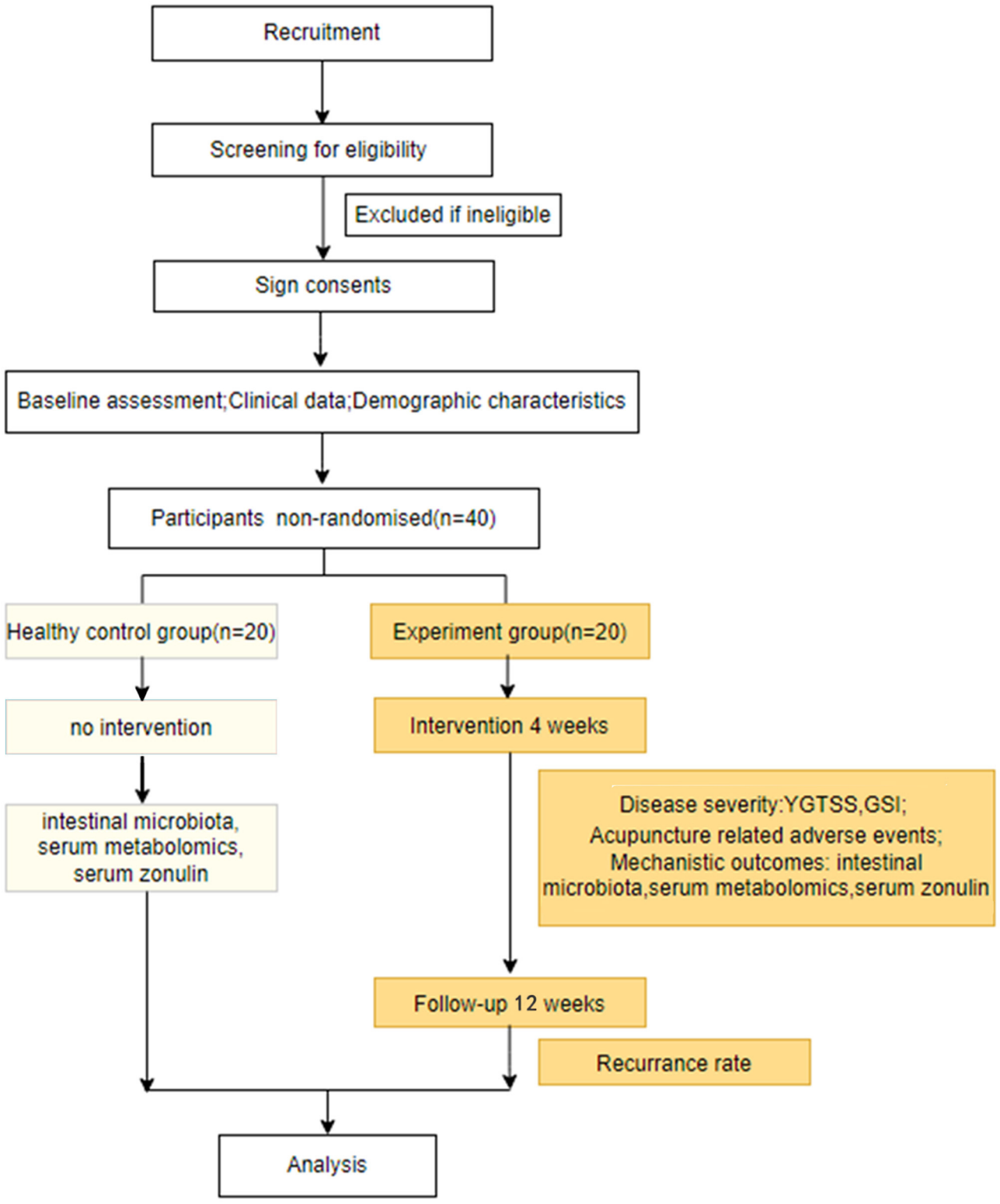

FIGURE 1
Flow diagram.

of nine gastrointestinal signs and symptoms (constipation, diarrhea, average stool consistency, stool smell, flatulence, abdominal pain, unexplained daytime irritability, nighttime awakening, and abdominal tenderness), and the total possible severity score is 17, with a higher score corresponding to greater severity.

TIMEPOINT		STUDY PERIOD				
		Enrolment	Allocation	1st intervention	After 8th intervention	12 weeks after 8th intervention
Eligibility Screen		X				
Informed Consent		X				
Recruitment form		X				
Allocation			X			
Primary outcome	YGTSS		X		X	
Secondary outcomes	GSI		X		X	
	Recurrence rate					X
Biological specimen analysis outcomes	Gut Microbiota		X		X	
	Serum Metabolomics		X		X	
	Serum Zonulin		X		X	
Adverse events of acupuncture				⟷		

FIGURE 2
Schedule of trial enrollment, interventions, and assessments.

2.5.2.2. Recurrence rate

The rate of recurrence will be calculated as the number of recurrences divided by the number of participant return visits.

2.5.3. Biological specimen analysis outcomes

2.5.3.1. Gut microbiota composition

Each participant will be asked to collect fresh feces in the morning, load them into a sterile container, and quickly place them into an ice box. The samples will be transferred to the laboratory with an ice pack for storage at −80°C. A DNA extraction kit will be used to extract the genomic DNA from the stool samples. The DNA will be purified, and its concentration will be detected using agarose gel electrophoresis. The DNA will be diluted with sterile water to 1 ng/nl for 16S rRNA amplification and sequencing. The 16S V3–V4 region (343F and 798R) or V4–V5 region will be amplified. DNA will be sequenced on the Illumina Novaseq 6000 platform, and paired-end reads (2 × 480 bp) will be generated. Sequencing and bioinformatics analysis will be conducted using OE Biotech (Shanghai, China) on the QIIME2 platform. Sequencing data analysis will be performed on amplicon sequence variants (ASVs).

2.5.3.2. Serum metabolomics

The blood sample will be collected using a butterfly needle and syringe. In total, 3 ml of blood will be drawn into a serum tube and centrifuged, and 1 ml of aliquots will be transferred into three tubes and stored in a freezer at −80°C for the analysis of metabolomics. Metabolic profiling in both electrospray ionization (ESI) positive and ESI negative ion modes will be analyzed using the AB ExionLC System (ABSCIEX, Framingham, MA) coupled with a Q-Exactive quadrupole-Orbitrap mass spectrometer with a heat ESI source (Thermo Fisher Scientific, Waltham, MA). An ACQUITY UPLC HSS T3 column (100 × 2.1 mm, 1.8 μm) will be used in the positive and negative modes. The binary gradient elution system consists of (A) water (containing 0.1% formic acid, v/v) and (B) acetonitrile (containing 0.1% formic acid, v/v). The flow rate is 0.35 ml/min, and the column temperature is 45°C. A non-targeted metabolite analysis will be performed by Luming Biological Technology Co. Ltd. (Shanghai, China).

2.5.3.3. Serum zonulin

Extraction and sample preparation will be performed according to the protocol described above. The concentrations of zonulin in all samples will be measured with a commercial kit (Elabscience, Houston, TX; Diaclone, Besancon, France;

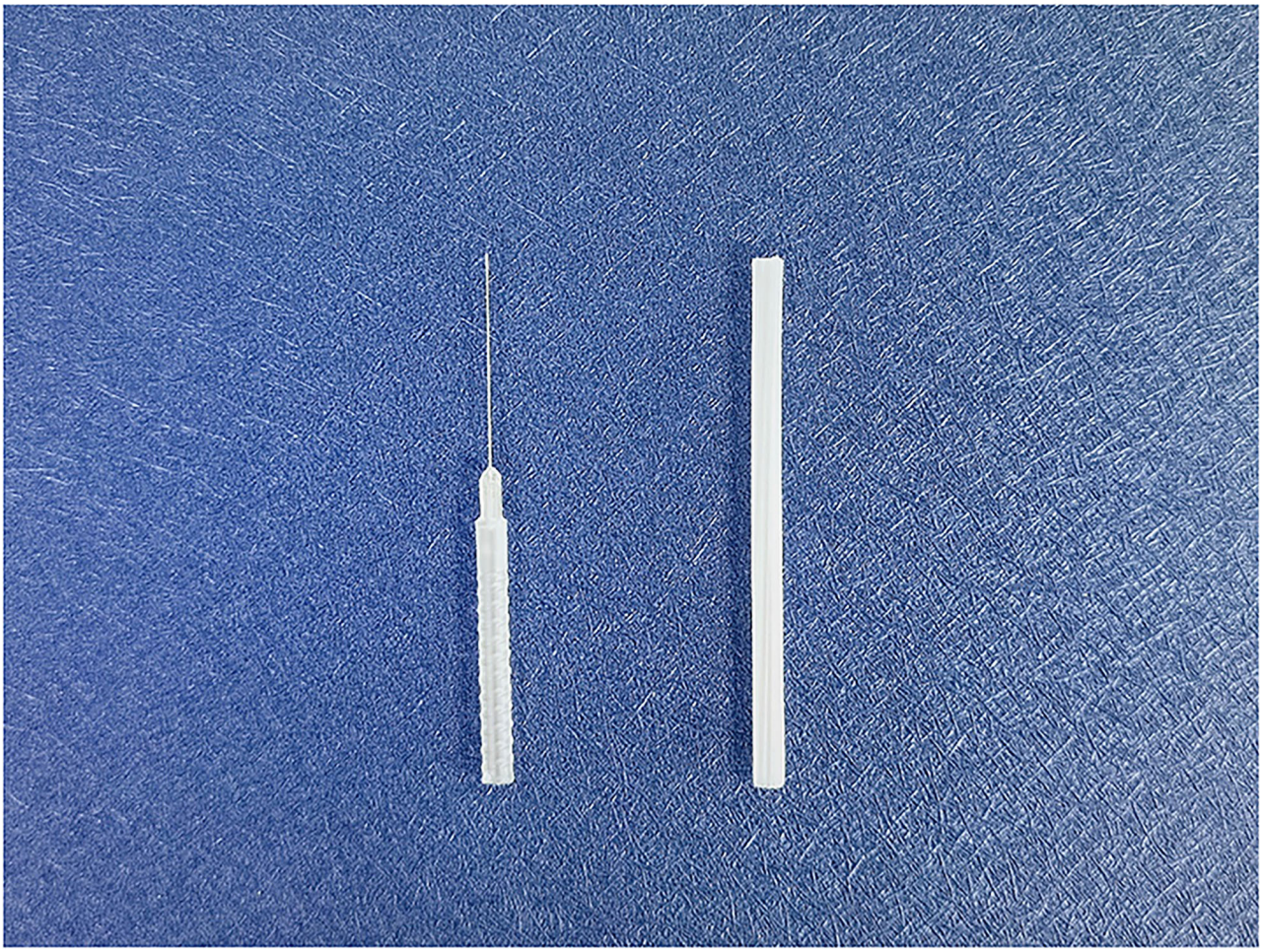

FIGURE 3
Qihuang needle **(left)** and the protective cap **(right)**.

Boster Biological Technology, Pleasanton, CA; R&D Systems, Minneapolis, MN) using the enzyme-linked immunosorbent assay (ELISA) method.

2.5.3.4. Adverse events

Acupuncture-related adverse events, including dizziness after acupuncture, local hematoma, infection, abscesses, and other unforeseen adverse events, will be recorded during all trial periods.

3. Data management and monitoring

Clinical data will be recorded in case report forms (CRFs) and imported into an electronic database. The CRFs and electronic databases will be locked after the study is completed. The personal data of all participants are kept anonymous and confidential. The original CRFs and other documents will be preserved securely at the South China Research Center for Acupuncture and Moxibustion at the Guangzhou University of Chinese Medicine. The relevant research team will supervise data quality, safety, and progress of the research.

3.1. Statistical analysis

3.1.1. Clinical data and serum zonulin

For the clinical data, statistical analyses will be performed using SPSS Statistics 24.0 (IBM SPSS Statistics, Armonk, NY). Children in the experimental group will be matched to their peers in the healthy control group on age, sex, family history of a psychiatric condition, parental marital status, mode of delivery, and birth weight. Categorical variables will be described in the form of frequencies or percentages. Continuous variables will be presented as mean ± standard deviation or median and range. The chi-square test or Fisher's exact test will be used to compare the change in the categorical variables. Changes in YGTSS, GSI, and concentration of serum zonulin in the experimental group before and after treatment will be analyzed using paired sample t-test if the data conform to a normal distribution. The Wilcoxon paired-samples signed-rank test will be performed if the data do not conform to normal distribution or if there are differences in variance uniformity. Differences in concentration of serum zonulin between two matched groups at baseline will be analyzed with the above statistical methods. The results are based on two-sided tests, and a P-value of <0.05 will be considered statistically significant.

TABLE 2 Framework of the acupuncture point prescription.

Acupuncture points	Description
GV20: Baihui (p213)	On the head, 5B-cun superior to the anterior hairline, on the anterior median line
EX-HN3: Yintang	On the head, between the right medial end of the eyebrow and the left one
BL14: Jueyinshu (p116)	In the upper back region, at the same level as the inferior border of the spinous process of the fourth thoracic vertebra (T4), 1.5 B-cun lateral to the posterior median line
GB33: Xiyangguan (p188)	On the lateral aspect of the knee, in the depression between the biceps femoris tendon and the iliotibial band, posterior and proximal to the lateral epicondyle of the femur
KI 7: Fuliu (p139)	On the posteromedial aspect of the leg, anterior to the calcaneal tendon, 2 B-cun superior to the prominence of the medial malleolus
CV17: Danzhong (p228)	On the anterior medial line of the chest, at the midpoint between the two nipples, at the level of the fourth intercostal space
BL24: Qihaishu (p111)	In the lumbar region, at the same level as the inferior border of the spinous process of the third lumbar vertebra (L3), 1.5 B-cun lateral to the posterior median line.

The prescribed acupoints come from the WHO Standard Acupuncture Point Locations in the Western Pacific Region.

3.2. Gut microbiota

A *t*-test and Wilcoxon analysis will be used to identify the different microorganisms. A principal component analysis (PCA), a principal coordinate analysis, a non-metric multidimensional scaling, and a unweighted pair-group method with arithmetic means will be used to analyze beta diversity. An alpha diversity analysis will be performed using violin plots consisting of the chao1 index, the Shannon index, and the Simpson index. The COG family information and functional prediction of intestinal microbiota will be performed on Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt2).

3.3. Serum metabolomics

3.3.1. Metabolomic data preprocessing

Raw data are acquired using UNIFI 1.8.1, and the resulting mass spectra will be exported into Progenesis QI version 2.3 (Non-linear Dynamics, Newcastle, UK) for further analysis, including baseline filtering, peak identification, integral, retention time correction, peak alignment, and normalization, with the main parameters as follows: 5 ppm precursor tolerance, 10 ppm product tolerance, and 5% production threshold. Qualitative analysis will be performed *via* the Human Metabolome Database (HMDB), Lipidmaps (version 2.3), Metlin, the Electron Microscopy Data Bank, Protein Model Data Base, and self-built databases.

The extracted data will be removed if there are any peaks with a missing value of more than 50% or if the compounds with the resulting scores are below 36 (out of 60) points. A data matrix will be formed and imported into R. PCA will be carried out to observe the overall distribution among the samples and the stability of the whole analysis process.

3.3.2. Differential expression analysis of metabolomics data

Orthogonal partial least squares discriminant analysis (OPLS-DA) and partial least squares discriminant analysis (PLS-DA) will be applied to seek differential metabolites between the healthy control and experimental group. Variable importance in projection (VIP) in the OPLS-DA model will be applied to investigate differentially expressed metabolites with biological significance. We will further perform a two-sided Student's *t*-test to verify whether the metabolite differences between the two groups are significant. If a metabolite has VIP values >1.0 and a *P*-value of <0.05, it will be selected as a differential metabolite. Functional pathway and network analysis *via* KEGG (https://www.kegg.jp/) database will be used to explore potential therapeutic targets of QHN therapy in children with tic disorders.

3.4. Correlation analysis of the microbiome and metabolome

Spearman's rank correlation coefficient will be calculated for all ASV-metabolite pairs and clinical parameters using the data across the same samples. A network analysis is to be performed on the interaction matrix using the fast greedy community algorithm in the igraph R package. This algorithm identifies subgraphs using direct optimization of a modularity score. Each discovered community is annotated according to the KEGG pathways of the metabolites within the community.

3.5. Trial status

Participants are currently being recruited for the present study.

4. Machine learning model on acupuncture response prediction

We will develop a machine-learning model to predict the acupuncture (QH needle) response. Transfer learning will be adopted. 16S rRNA, serum metabolomics, and clinical profile data will be downloaded from published data or public databases as source domains to generate a deep neural network (DNN) model. Data from the present study are set as the target domain to fine-tune the DNN model. An additional file shows the method in more detail (see Supplementary material 2).

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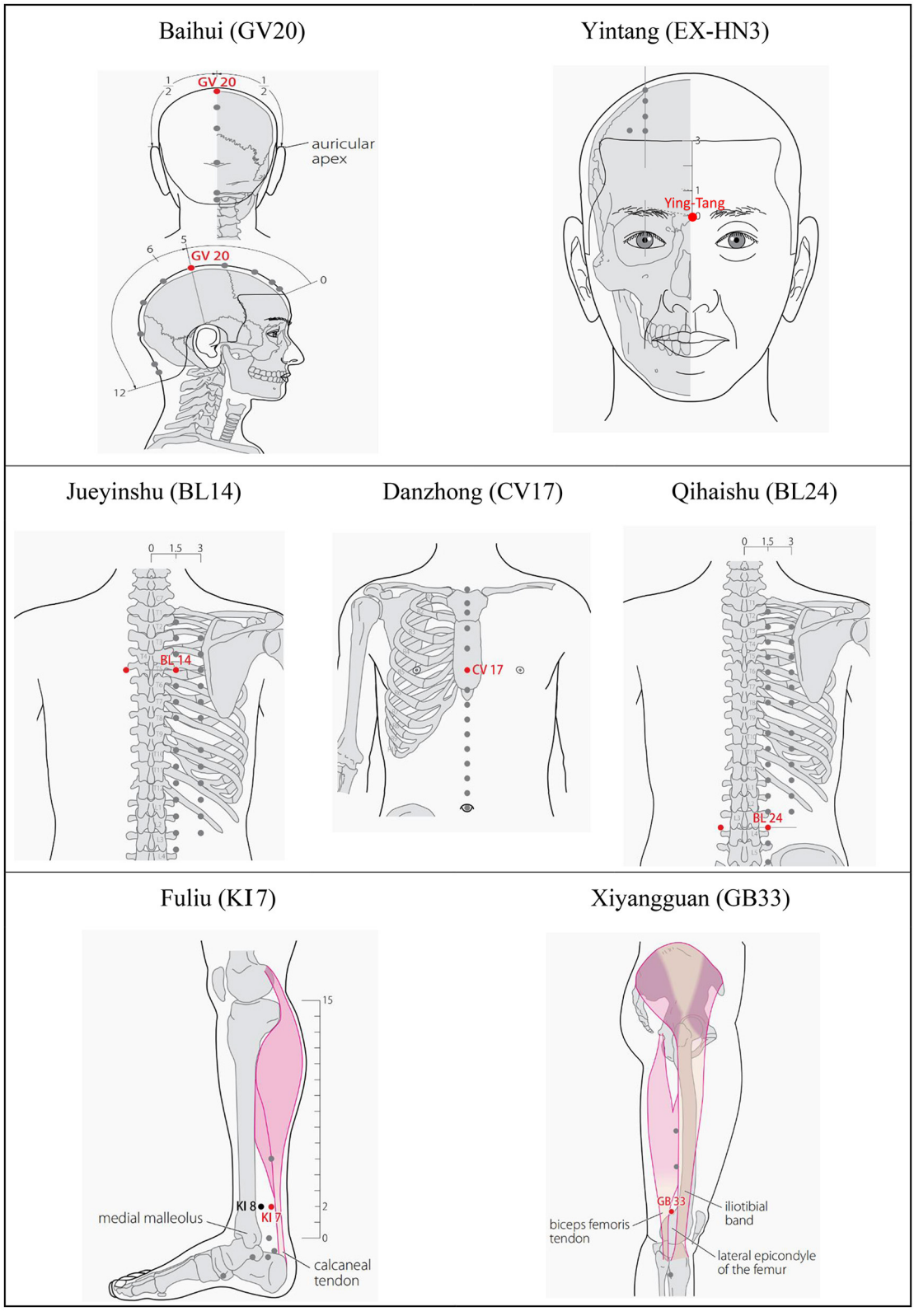

FIGURE 4
Location of acupoints.

5. Discussion

This is a matched-pairs design, controlled, clinical trial to investigate how QHN therapy relieves tic disorders *via* the modulation of gut microbiota and serum metabolites. To the best of our knowledge, the management of tic disorders is largely through psycho-behavioral therapy, which is not easy to access in many developing countries. Medicine is usually not the optimal selection because most patients are children. A search for a feasible and economic therapy for tic disorders should be promoted.

Acupuncture, as traditional Chinese medicine, has been widely accepted for its ready availability and lower cost. Its clinical efficacy in the treatment of pediatric neurological diseases, including cerebral palsy, autism spectrum disorders, and intellectual delay, has been proven. In addition, a growing body of research has proven that acupuncture shows good results in relieving tic symptoms, reducing recurrence rates, and causing fewer adverse events.

The main acupoints selected in the present protocol are under the sinew meridian theory based on traditional acupuncture. Tic disorders are categorized as meridian sinew disorders, and their pathogenesis is that qi and blood fail to nourish meridian sinew, resulting in trembling of the tendons and muscles, tics, and contractures. GV20 and EX-HN3 are the acupoints of the governor vessel that is located on the head or face. The governor vessel communicates with and governs all the yang meridians and runs into the brain. The three-foot yang and three-hand yang sinew channels start from four extremities and end at the face or the angle of the forehead. Acupuncturing at GV20 and EX-HN3 adjusts the yangqi of the entire human body and warms and nourishes the sinews. Furthermore, GV20 and EX-HN3 are widely used in neurological diseases, and it is reported that these two acupoints have positive effects in regulating neurotransmitter levels (52). BL14 is adjacent to the course of the meridian sinews of foot taiyang. Acupuncturing at BL 14 restores the balance of yangqi in meridian-sinews and is a transport point for the pericardium. It has been reported that BL14 is used in the treatment of tic disorders (53).

Qihuang needle therapy has advantages compared with traditional acupuncture among the pediatric population. First, it is less painful, with almost no pain when it penetrates the skin, which alleviates the fear of acupuncture in children. The manipulation of the QH needle is also swift, without needle retention, and point selection is usually simplified to no more than five acupoints in one treatment session. The design of the QH needle contributes to greater stimulation intensities at acupoints and meridians, which reduces treatment frequency. Because most patients are school-aged children, they do not have enough time to receive long-term acupuncture treatment as they are under academic pressure, and children do not usually tolerate long-term needle retention. These advantages help increase treatment adherence, yielding good efficacy.

16S rRNA has been used to identify the structure and diversity of gut microbes. Metabolomics has been applied to identify the metabolite profile of biofluid and the changes in small-molecule metabolites and related metabolite pathways in the disease state. The integration of both omics analyses is a prospective way to reveal the mechanism of acupuncture in the clinical context. Using 16S rRNA, some investigators have found that massage combined with acupuncture alleviated the severity of tics and improved gut permeability as well as intestinal flora (54). Aspartate/asparagine metabolism pathways and some metabolites were reportedly related to TS *via* metabolomics (41). It is feasible to explore the possible interactions between the metabolic phenotype and the alterations in the gut microbiota in tic disorders through the integrated application of 16S rRNA and serum metabolomics. Furthermore, potential therapeutic targets will be elucidated *via* multi-omics analysis.

16S rRNA sequencing from feces samples, UPLC-MS metabolomics from serum, and the assessment of serum zonulin will be performed in the present study to probe the potential mechanism and therapeutic targets of QHN therapy for tic disorders. The integration of 16S rRNA, metabolomics, and tic syndrome is likely to reveal the possible correlations between tic-associated metabolomes and tic-linked gut microbiomes, which may further explore the potential molecular mechanism underlying tic disorders. Furthermore, to investigate how QH needle treatment alters gut barrier function, serum zonulin will be used as an intestinal permeability assay in the present study.

In addition, to improve the clinical practice of acupuncture, we will further construct a prediction model based on multi-omics data and clinical profiles. Considering the small sample size, we will attempt to use the transfer learning method to develop a prediction model for personalized acupuncture treatment. Transfer learning is used to transfer knowledge from a generalized model to a more domain-specific model. It would enable the utilization of biological data published in the literature and reduce the demand for data collection when investigating new processes. Rogers et al. (55) showed that transfer learning is a highly data-efficient technique to predict the modeling of bioprocesses, a typically low-dimensional, small-data problem, but its usage in the biomedical field is scarce. In the present study, we will extract generalizable knowledge from well-understood published biological data, capturing essential process mechanisms to set a source model. We will then apply this understanding to characterize and screen novel samples and refine the model with our data. Our study is a new attempt to develop a prediction model for personalized acupuncture treatment.

Because most participants enrolled are school-aged children, they may have class during normal working hours, which may affect timely treatment. Therefore, we will make an appointment with parents after enrollment and keep in touch with them every week during the treatment sessions. In addition, we will do a 6-month follow-up to reduce the number of patients lost to follow-up. We will also maintain contact with the parents *via* WeChat or telephone and follow up through these channels.

This study has some limitations. There have been no acknowledged biomarkers for the assessment of tic severity. The rating of YGTSS is based on clinical experience in working with patients with tic disorder and their families, which is probably subjective. The sample size is small, and the follow-up duration is not very long.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethical Committee of Panyu Hospital of Chinese Medicine (Guangdong, China. Ethic Approval Number: 2022028) Foshan Fosun Chancheng Hospital (Guangdong, China. Ethic Approval Number: CYIRB-LCYJ-2022006-PJ-20221227). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YT, BJ, CT, and XL conceived and designed the study. YT and ZX drafted the manuscript and all authors revised the manuscript critically. YT, BF, and JW developed the statistical analysis of the trial and contributed to the content of the article. CT obtained funding. CT and XL are the study guarantors. All authors have read and approved the final manuscript.

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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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SUPPLEMENTARY MATERIAL 1
Participant information letter.

SUPPLEMENTARY MATERIAL 2
Machine learning method.

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Acupuncture for tension-type headache: a systematic review and meta-analysis of randomized controlled trials

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Background: Tension-type headache (TTH) is the most common neurologic disease worldwide. Acupuncture is commonly applied to treat TTH, but evidence of acupuncture for TTH is contradictory based on previous meta-analyses. Therefore, we conducted this systematic review and meta-analysis to update the evidence of acupuncture for TTH and aimed to provide a valuable reference for clinical application.

Methods: We searched 9 electronic databases from their inceptions to July 1, 2022 for randomized controlled trials (RCTs) of acupuncture for TTH. We also manually searched reference lists and relevant websites, and the experts in this field were consulted for possible eligible studies. Two independent reviewers conducted literature screening, data extraction, and risk of bias assessment. The revised Cochrane risk-of-bias tool (ROB 2) was used to assess the risk of bias of included studies. Subgroup analyses were carried out based on frequency of acupuncture, total sessions, treatment duration, needle retention, types of acupuncture and categories of medication. Data synthesis was performed using Review Manager 5.3 and Stata 16. The Grading of Recommendations Assessment, Development and Evaluation Approach (GRADE) was used to evaluate the certainty of evidence of each outcome. Meanwhile, the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) was used to assess the reporting quality of interventions in clinical trials of acupuncture.

Results: 30 RCTs involving 2,742 participants were included. According to ROB 2, 4 studies were considered as low risk, and the rest studies were some concerns. After treatment, compared with sham acupuncture, acupuncture had greater effect in improvement of responder rate [3 RCTs, RR = 1.30, 95%CI (1.13, 1.50), I^2 = 2%, moderate certainty] and headache frequency [5 RCTs, SMD = −0.85, 95%CI (−1.58, −0.12), I^2 = 94%, very low certainty]. In contrast to medication, acupuncture was more effective to reduce pain intensity [9 RCTs, SMD = −0.62, 95%CI (−0.86, −0.38), I^2 = 63%, low certainty]. Adverse events were evaluated in 16 trials, and no serious event associated with acupuncture occurred.

Conclusions: Acupuncture may be an effective and safe treatment for TTH patients. Due to low or very low certainty of evidence and high heterogeneity, more rigorous RCTs are needed to verify the effect and safety of acupuncture in the management of TTH.

KEYWORDS

acupuncture, safety, tension-type headache, systematic review, meta-analysis, clinical effects

1. Introduction

Tension-type headache (TTH) is manifested by bilateral compression or crunching pain in head, which is usually accompanied by photophobia or phonophobia (1), and is more prevalent in women than in men. The International Headache Society (IHS) claimed that TTH was the most common neurological disease in the world, with a reported incidence of 30–78% in the general population (2). According to data from the Global Burden of Disease (GBD), 2.33 billion individuals worldwide had TTH in 2017 (3). Of note, over the past 10 years, the global prevalence of TTH increased at a rate of 15.3% (4). Additionally, anxiety, depression and sleep issues were prevalent in patients with TTH (5–7). About 60% of TTH patients reported diminished social and occupational function (8). According to a cross sectional epidemiological survey from Danish, the absence days from work due to headache were estimated to be 820 days per 1,000 TTH patients a year (9), which bring a significant financial burden to patients and society (10).

According to the latest diagnostic criteria (2), TTH could be divided into three subtypes based on headache frequency: episodic (<1 headache day/month), frequent (1–14 headache days/month), and chronic (≥15 headache days/month). Episodic TTH can be controlled with acute medication and lifestyle modification, while frequent or chronic TTH may require special interventions, such as pharmacotherapy, acupuncture, exercise, stress reduction, etc. Antidepressants or non-steroidal anti-inflammatory medicines (NSAIDs) are main medications to treat TTH (11, 12). Currently, amitriptyline is the most widely used prophylactic medication for TTH (13). It is reported that the common adverse effects of amitriptyline are urine retention, constipation, agitation, cognitive dysfunction, etc. (14, 15). Thus, undesirable adverse events and low adherence rate of medication may be associated with poor clinical outcome (16). Furthermore, the studies revealed that TTH patients who experienced frequent headache, were more prone to take medication in excess, and increased the risk of developing medication overuse headache (17, 18). As a consequence, non-pharmacological therapy is important for TTH sufferers (17).

As an alternative medicine treatment, acupuncture is commonly used for headache sufferers with better clinical efficacy and less side effects (19, 20). Endres et al. found that acupuncture was superior to sham acupuncture in increasing responder rate for TTH patients (21). Melchart and his colleagues concluded that manual acupuncture was better than no treatment in reducing headache frequency of TTH (22). Zheng et al. reported that 8-week acupuncture treatment was effective to alleviate pain intensity in patients with chronic TTH (23). However, previous systematic reviews and meta-analyses of acupuncture for TTH hold inconsistent results (20, 24–26). In addition, several randomized controlled trials (RCTs) have been carried out in recent years (23, 27–36). Therefore, we conducted this systematic review and meta-analysis to update the evidence of the effect and safety of acupuncture for TTH.

2. Methods

This systematic review and meta-analysis was conducted in accordance with A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) (37) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (38). The protocol of this systematic review and meta-analysis was registered in the INPLASY (https://inplasy.com/inplasy-2022-3-0047/).

2.1. Inclusion criteria

We employed the following inclusion criteria when selecting studies: (1) Participants: adults who were diagnosed with TTH (diagnostic criteria released by the International Headache Society) (2, 39–41); (2) Intervention: acupuncture (manual acupuncture/electro-acupuncture) (42); (3) Control: sham acupuncture, medication, exercise, and other controls (such as waiting list, usual care, etc.); (4) Outcomes: primary outcome was responder rate, and secondary outcomes included headache frequency, pain intensity, headache duration, consumption of medication, other relevant outcomes and acupuncture related adverse events; (5) Study design: RCTs, or cross-over RCTs which investigated the effect and safety of acupuncture for TTH.

2.2. Exclusion criteria

We adopted the following exclusion criteria: (1) Full text or data could not be obtained through useful approaches; (2) Acupuncture combined with traditional Chinese medicine therapy (other types of acupuncture, moxibustion, herbal medicine, etc.); (3) No details of diagnostic criteria, acupuncture treatment or control intervention were provided; (4) Overlapping publications.

2.3. Literature search

We searched 5 English databases (PubMed, Web of Science, Embase, the Cochrane Library and Epistemonikos) and 4 Chinese databases (China National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Periodical Database and China Biology Medicine) from their inceptions to July 1, 2022. To retrieve additional trials, we manually searched reference lists of included articles and relevant reviews. The gray literature including dissertations and conference proceedings was also examined. In addition, we searched clinical registries (e.g., Chinese Clinical Trial Registry, Clinical Tials.gov), and the experts in this field were consulted for possible eligible studies. The search strategies of the above databases are shown in Appendix 1.

2.4. Outcome measurement

2.4.1. Primary outcome

Responder rate (43): at least 50% reduction of headache days.

2.4.2. Secondary outcomes

Headache frequency: number of headache days per defined period.

Pain intensity: (1) Visual Analog Scale (VAS); (2) Von Korff (questions 1–3) pain intensity score; (3) German version of the pain disability index; (4) Numerical Rating Scale (NRS); (5) Verbal Rating Scale (VRS).

Headache duration: hours with headache per defined period.

Consumption of medication: sum of analgesics taken per month.

Other related outcomes: depression and anxiety level assessed with valid and reliable scales.

Acupuncture-related adverse events: subcutaneous hematoma, pain, acupuncture syncope reaction, etc.

2.5. Literature screening

ENDNOTE X9 was used to manage the retrieved records. After removing duplicates, two reviewers (WLK & XJX) independently scrutinized the titles and abstracts for potential eligible literature. Then, two reviewers (RF & JS) independently screened the full text according to inclusion and exclusion criteria. After cross-checking, disagreements were settled through consultation with an experienced reviewer (JL).

2.6. Data extraction

Two reviewers (RF & JS) extracted data using a pre-designed extraction form. The following data were extracted: (1) Study information (e.g., first author, year, country, etc.); (2) Participant characteristics (e.g., gender, age, etc.); (3) Details of intervention and control group (e.g., duration, types of acupuncture, etc.); (4) Results of each outcome; (5) Information related to the risk of bias. In case of missing data, we contacted the corresponding authors for necessary data. As for overlapping publications, the most recent report or complete report was included for data analysis. With regard to cross-over RCTs, the data before the intersection was extracted. For data expressed as mean and standard error, mean and 95% confidence intervals (CI), or median and interquartile range, we converted these data into mean and standard deviation. If the data was displayed in the graph, the GetData Graph Digitizer 2.26 was used to extract the data. After extraction, two reviewers (RF & JS) cross-checked the extracted data. Any inconsistency during the process of data extraction was resolved through discussions with an experienced reviewer (DLZ).

2.7. Risk of bias assessment

Two researchers (YXL & DLZ) independently used the version 2 of the Cochrane tool for assessing risk of bias in randomized trials (ROB 2) (44) to appraise the risk of bias of the included RCTs. The ROB 2 considers bias from 5 different domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The risk of bias in each domain and overall are categorized into "low risk of bias", "some concerns", or "high risk of bias". In the case of disagreements, a third reviewer (JL) was involved.

2.8. Evaluation of the reporting quality of interventions in clinical trials of acupuncture

The Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (45) is designed to assess the reporting quality of interventions in clinical trials of acupuncture. The revised STRICTA checklist comprises six items, including the acupuncture rationale, the details of needling, the treatment regimen, other components of treatment, the practitioner's background, and the control or comparator interventions. Two reviewers (DLZ & YXL) independently evaluated the included RCTs with the revised STRICTA checklist, and any disagreement was arbitrated by consultation with a third reviewer (JL).

2.9. Certainty of evidence assessment

The certainty of the evidence was evaluated by two independent reviewers (WLK & RF) using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system (46). Additionally, the "Summary of findings" table was constructed to present the certainty of each outcome with GRADE pro V 3.6 software.

2.10. Data analysis

Since responder rate was dichotomous data, risk ratio (RR) was used for data synthesis. Due to the different scoring standards of outcomes, such as headache frequency, pain intensity, headache duration, anxiety, depression and medication consumption, standardized mean difference (SMD) was calculated. The uncertainty was expressed with 95% confidence intervals (CI), and $P < 0.05$ was considered significant. Chi-square test and I^2 statistic were used to test the statistical heterogeneity of included studies. We utilized a random-effect model (REM) to aggregate studies when $I^2 > 50\%$ and $P > 0.05$, and a fixed-effect model (FEM) to merge studies in case of $I^2 \leq 50\%$ and $P \leq 0.05$. We conducted subgroup analyses based on: (1) frequency of acupuncture, (2) total sessions, (3) treatment duration, (4) needle retention, (5) types of acupuncture, and (6) categories of medication. We carried out sensitivity analysis to verify the robustness of the results by excluding the literature one by one. Publication bias of the primary outcome was assessed by funnel plot, *Begg's* and *Egger's* test when ≥10 studies of the same comparison were synthesized. Statistical analyses were performed with Review Manager 5.3 and Stata 16.

3. Results

We retrieved 20,700 articles from 9 databases and relevant websites. After excluding 7,563 duplicates and 13,076 irrelevant records by screening the titles and abstracts,

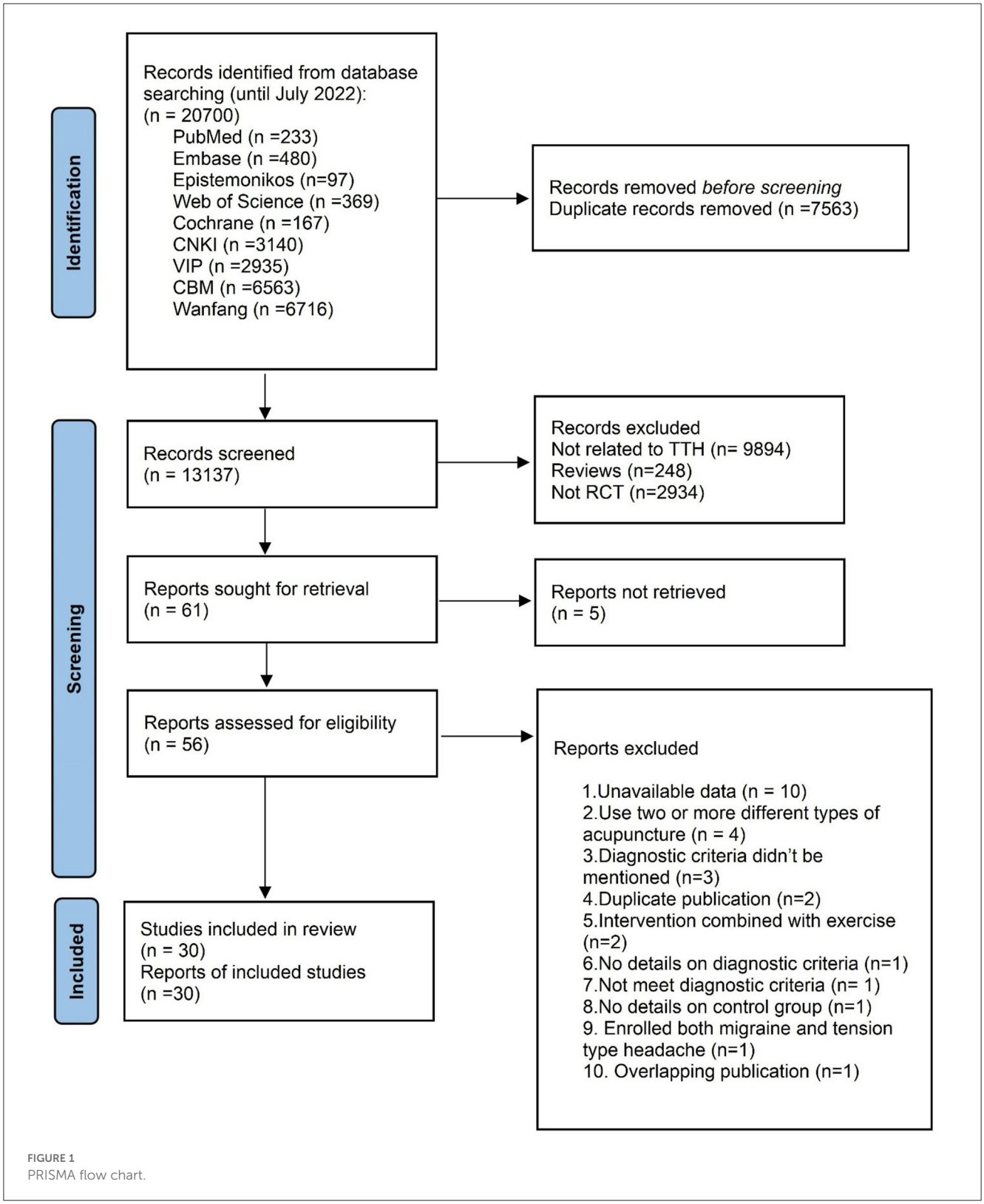

FIGURE 1
PRISMA flow chart.

and 5 RCTs were not retrieved, 56 articles remained for further assessment. Through reading full texts, 26 studies were excluded, and the reasons for exclusion are listed in Appendix 2. We included an article (47) as a supplement to Zhang (34), a total of 30 RCTs (21–23, 27–36, 48–64) involving 2,742 participants were included (1,349 in the intervention group and 1,393 in the control group) (Figure 1).

TABLE 1 The details of the included studies.

References	Country	Diagnostic criterion	Sample size	Gender (male/female)	Mean age (year)	Intervention	Frequency and sessions of acupuncture	Needle retention	Treatment duration	Comparison	Outcome	Follow-up
Chassot et al. (57)	Brazil	ICHD-3	EA:18 SA:16	EA: 0/18 SA: 0/16	EA: 39.11 ± 10.5 SA: 41.44 ± 10.5	EA	Twice a week, 10 sessions	30 min	5 weeks	SA	3, 8	NR
Duan (62)	China	ICHD-2	MA:48 M:48	MA: 14/34 M: 17/31	MA: 42.7 ± 11.5 M: 43.5 ± 11.2	MA	Once a day, 21 sessions	40 min	3 weeks	Eperisone Hydrochloride 50mg, tid	3	NR
Deng (63)	China	ICHD-2	EA:25 M:25	EA: 8/17 M: 6/19	EA:32.18 ± 11.56 M: 31.62 ± 10.07	EA	Once a day, 10 sessions	30 min	10 days	Acetaminophen 0.5g, qid + Amitriptyline 25mg, qn	2,3	NR
Endres et al. (21)	Germany	ICHD-2	MA:208 M:195	MA: 46/163 M: 42/158	MA: 39.2 ± 11.4 M: 38.9 ± 12.2	MA	Twice a week, 10 sessions	30 min	6 weeks	SA	1,2,3,8	6 weeks, 18 weeks
Guo (31)	China	ICHD-2	MA:50 M:50	MA: 16/34 M: 19/31	MA: 33.2 ± 10.2 M: 34.0 ± 10.6	MA	Once every other day, 14 sessions	30 min	4 weeks	Eperisone Hydrochloride 50 mg, tid; + Flunarizine hydrochloride 5mg, qd	3	NR
Guo (28)	China	ICHD-2	MA:32 M:32	MA: 25/70 M: 26/68	MA: 42.5 ± 7.13 M: 41.77 ± 8.42	MA	Once every other day, 14 sessions	30 min	4 weeks	Deanxit bid	6, 7	4 weeks
Huang (51)	China	ICHD-3	MA:34 M:21	MA: 16/17 M: 8/9	MA:49.39 ±7.49 M:51.94 ± 7.79	MA	Once every other day, 14 sessions	30 min	4 weeks	Acetaminophen 0.3 g, qd or bid	8	NR
Jeon and Lee (29)	Korea	ICHD-3	EA:15 SA:15	EA: 6/9 SA: 8/7	EA:40.00 ±13.11 SA:34.33 ± 11.48	EA	3 times a week, 3 sessions	20 min	1 week	SA	2,3	1 week
Karst et al. (58)	Germany	IHS1988	MA:34 SA:35	MA: 17/17 SA: 14/21	MA: 47.9 ±13.8 SA: 48.2 ±14.6	MA	Twice a week, 10 sessions	30 min	5 weeks	SA	2,3,5	6 weeks, 20 weeks
Kwak et al. (59)	Korea	ICHD-2	MA:17 SA:15	MA: 3/14 SA: 3/12	MA:45.05 ± 12.57 SA: 49.4 ±11.14	MA	Twice a week, 8 sessions	25 min	4 weeks	SA	3,8	4 weeks, 8 weeks, 12 weeks
Koran et al. (64)	Turkey	ICHD-3	MA:40 SA:41 M:48	MA: 18/22 SA: 18/23 M: 22/26	NR	MA	2–3 times a week, 8 sessions	20 min	4 weeks	1.SA 2. Antidepressant + analgesic	3	1 week, 12 weeks

(Continued)

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TABLE 1 (Continued)

References	Country	Diagnostic criterion	Sample size	Gender (male/female)	Mean age (year)	Intervention	Frequency and sessions of acupuncture	Needle retention	Treatment duration	Comparison	Outcome	Follow-up
Liu (36)	China	ICHD-3	MA:32 M:30	MA: 13/19 M: 12/18	MA:50.53 ± 13.70 M: 48.33 ± 13.17	MA	5 times a week, 20 sessions	30 min	4 weeks	Escitalopram oxalate 10 mg, qd	7,8	4 weeks
Melchart et al. (22)	Germany	ICH-10	MA:132 SA:63 WT:75	MA: 72/95 SA: 73/46 WT:77/58	MA:42.3 ±13.5 SA:43.4 ± 12.9 WT:42.8 ± 13.2	MA	1–2 times a week, 12 sessions	30 min	8 weeks	1.SA 2.WT	1,2,3 4,7,8	4 weeks, 16 weeks
Nie (30)	China	ICHD-3	MA:41 M:41	MA: 12/29 M: 18/23	MA:50.02 ± 10.66 M: 46.54 ±11.46	MA	3 times a week, 12 sessions	20 min	4 weeks	Eperisone Hydrochloride 50 mg, tid	2,3,8	4 weeks, 8 weeks
Söderberg et al. (60)	Sweden	IHS1988	MA:30 E:30 RT:30	MA: 7/23 E: 7/23 RT: 3/27	MA: 35 ± 10.25 E: 35 ± 9.5 RT: 43.5 ± 9.25	MA	Once a week, 10–12 sessions	30 min	10–12 weeks	1.E 2.RT	3	12 weeks, 24 weeks
Schiller et al. (33)	Germany	ICHD-3	MA:24 UC:24 E:24 MA+E:24	MA: 6/18 UC:7/17 E: 5/18 MA+E: 2/22	MA: 39.8 ±12.2 UC: 38.7 ±14.6 E: 37 ±15.3 MA+E: 39 ± 11.6	MA	1–3 times a week, 12 sessions	30 min	6 weeks	1.UC 2.E 3. MA+E	1,3,8	6 weeks, 18 weeks
Tavola et al. (48)	Sweden	IHS 1988	MA:15 SA:15	MA: 2/13 SA: 2/13	MA: 32.5 ± 10 SA: 33.3 ± 13.3	MA	Once a week, 8 sessions	20 min	8 weeks	SA	5	4 weeks, 16 weeks, 40 weeks
White et al. (49)	England	IHS 1988	MA:25 SA:25	MA: 7/18 SA: 5/20	MA: 49.8 ± 2.9 SA: 48.2 ± 2.9	MA	Once a week, 6 sessions	Without needle retention	6 weeks	SA	1,2,3,4	4 weeks, 8 weeks
Wu (52)	China	ICHD-2	MA:30 M:30	MA: 18/12 M: 15/15	MA: 44.3 ± 12.49 M: 42.87 ± 9.38	MA	5 times a week, 10 sessions	30 min	2 weeks	Eperisone Hydrochloride 50 mg, tid	6,7,8	NR

(Continued)

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TABLE 1 (Continued)

References	Country	Diagnostic criterion	Sample size	Gender (male/female)	Mean age (year)	Intervention	Frequency and sessions of acupuncture	Needle retention	Treatment duration	Comparison	Outcome	Follow-up
Wang (27)	China	ICHD-2	MA:29 M:27	MA: 8/21 M: 7/20	MA: 38 ± 10 M: 39 ± 11	MA	3 times a week, 18 sessions	30–45 min	48 days	Eperisone Hydrochloride 50 mg, tid	3,4	NR
White et al. (61)	England	IHS 1988	MA:4 SA:5	MA: 1/3 SA: 1/4	MA: 57.2 ±13.6 SA: 57.4 ±19.9	MA	Once a week, 6 sessions	Without needle retention	6 weeks	SA	8	NR
Wang (35)	China	ICHD-3	MA:150 M:100	MA: 63/87 M: 42/58	MA: 44 ± 13 M: 43 ±13	MA	3 times a week, 9 sessions	4–6 hours	3 weeks	Eperisone Hydrochloride 50mg, tid	3	NR
Xiang (53)	China	ICHD-2	MA:30 M:30	MA: 13/17 M: 10/20	MA: 40.7 ± 10.6 M: 40.43 ± 12.92	MA	6 times a week, 24 sessions	30 min	4 weeks	Amitriptyline hydrochloride 25mg, tid	3	NR
Xue et al. (50)	Australia	IHS 1988	EA:20 SA:20	EA: 7/13 SA: 7/13	EA: 42.6 ±1.8 SA: 41.5 ±1.9	EA	Twice a week, 8 sessions	30 min	4 weeks	SA	2,3,8	NR
Yang (32)	China	ICHD-2	MA:41 M:41	MA: 46/163 M: 42/158	MA: 40.96 ± 8.23 M: 41.29 ± 8.32	MA	Once a day, 14 sessions	30 min	2 weeks	Ibuprofen 0.3 g, bid	3	NR
Zheng et al. (23)	China	ICHD-3	MA:110 SA:108	MA: 28/82 SA: 33/75	MA: 43 ± 12.5 SA: 43.2 ± 12.8	MA	2–3 times a week, 20 sessions	30 min	8 weeks	SA	1,2,3,8	4, 8, 12, 16, 20, 24 weeks
Zhou (55)	China	ICHD-2	MA:30 M:30	MA: 12/18 M: 14/16	MA: 44.77 ±12.42 M: 45.93 ±12.30	MA	5 times a week, 20 sessions	30 min	4 weeks	Amitriptyline hydrochloride 25 mg, qd	6,7	NR
Zhang (54)	China	ICHD-2	MA:26 SA+M:20	NR	NR	MA	3 times a week, 12 sessions	30 min	4 weeks	SA+ Estazolam 0.5 mg, qn	1,2,4,8	12 weeks
Zhang (34, 47)	China	ICHD-3	MA:29 M:30	MA: 13/16 M: 13/17	MA: 31.79 ± 8.56 M: 32.03 ± 6.49	MA	Once a day, 28 sessions	30 min	4 weeks	Amitriptyline	3,6,7	NR
Zhu (51)	China	ICHD-2	MA:30 M:30	MA: 9/21 M: 7/23	MA: 39.17 ± 10.15 M: 40.07 ± 9.82	MA	6 times a week, 24 sessions	30 min	4 weeks	Amitriptyline 25 mg, bid; + Oryzanol 30 mg, tid	8	4 weeks

1. Responder rate (at least 50% reduction of headache days); 2. Headache frequency; 3. Pain intensity; 4. Headache duration; 5. Consumption of medication; 6. Anxiety; 7. Depression; 8. Adverse event. MA, manual acupuncture; EA, electro-acupuncture; SA, sham acupuncture; RT, relaxation training; WT, waiting list; UC, usual care; M, medication; E, exercise; NR, no report; IHS, International Headache Society; ICHD, International Classification of Headache Disorders; min, minutes.

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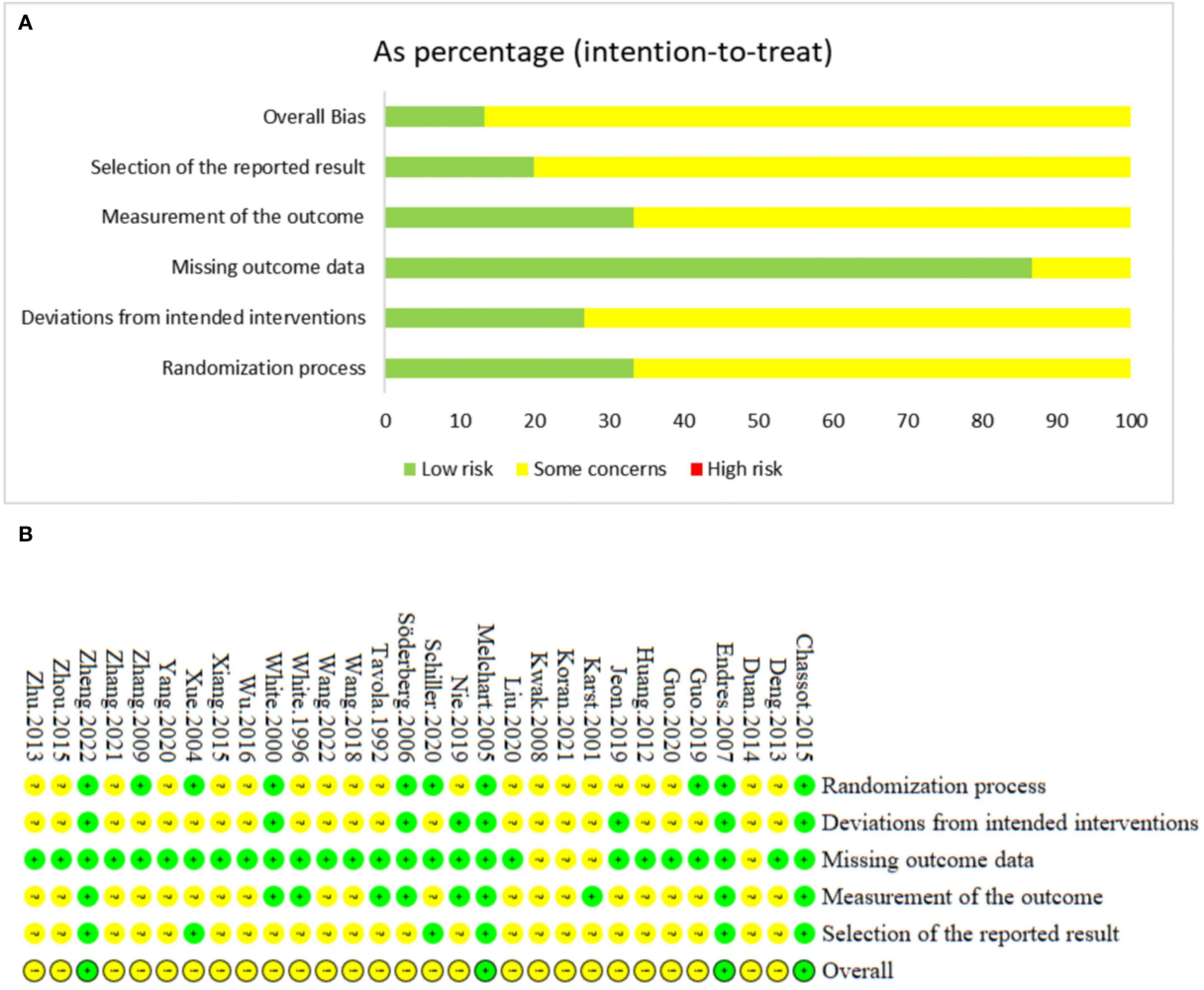

FIGURE 2
(A) The graph of risk of bias. **(B)** The summary of risk of bias.

3.1. Study characteristics

The details of the included studies are shown in Table 1. Sample size ranged from 9 (61) to 409 (21). The average age of patients varied from 31 to 58 years old. The trials were conducted in 7 countries [China (23, 27, 28, 30–32, 34–36, 51–56, 62, 63) (n = 17), Germany (21, 22, 33, 58) (n = 4), Korea (29, 59) (n = 2), Sweden (48, 60) (n = 2), England (49, 61) (n = 2), Brazil (57) (n = 1), Australia (50) (n = 1), and Turkey (64) (n = 1)]. Among the included studies, two were cross-over RCTs (50, 57).

For acupuncture treatment, 4 RCTs applied electro-acupuncture (29, 50, 57, 63), and the rest 26 studies used manual acupuncture. With regard to the needle retention time, 2 studies applied no needle retention (49, 61), 1 RCT retained for 4–6 hours (35), the remaining RCTs retained needles from 20 to 45 minutes. The frequency of acupuncture treatment was usually 2 or 3 times per week. The treatment duration of acupuncture ranged from 1 week (29) to 12 weeks (60). A total of 16 RCTs (21–23, 28–30, 33, 36, 48, 49, 54, 56, 58–60, 64) observed the effect of follow-up, the follow-up period was from 1 week (29) to 40 weeks (48). Among included studies, 1 study was four-arm trial (33), 3 RCTs were three-arm (22, 60, 64), the rest studies were two-arm. With regard to comparison, 16 studies applied medication [*antidepressant* (28, 34, 36, 53, 55, 56), *muscle relaxant* (27, 30, 31, 35, 52, 62), *analgesics* (32, 51), *antidepressant plus analgesics* (63, 64)], 12 studies used sham acupuncture (21–23, 29, 48–50, 57–59, 61, 64), 2 applied exercise (33, 60), 1 utilized relaxation training (60), 1 applied usual care (33), 1 was waiting list (22), 1 was acupuncture plus exercise (33), and 1 adopted sham acupuncture plus medication (54). The most commonly used acupoints were Baihui (GV20), Taiyang (EX-HN5), Fengchi (GB20), Hegu (LI4), Yintang (GV29), Taichong (LR3), Neiguan (PC6), Zusanli (ST36), and "Ashi" points (Appendix 3).

3.2. The reporting quality of interventions in clinical trials of acupuncture

The STRICTA checklist is shown in Appendix 4. All studies reported the acupoint selection, needle retention time, total

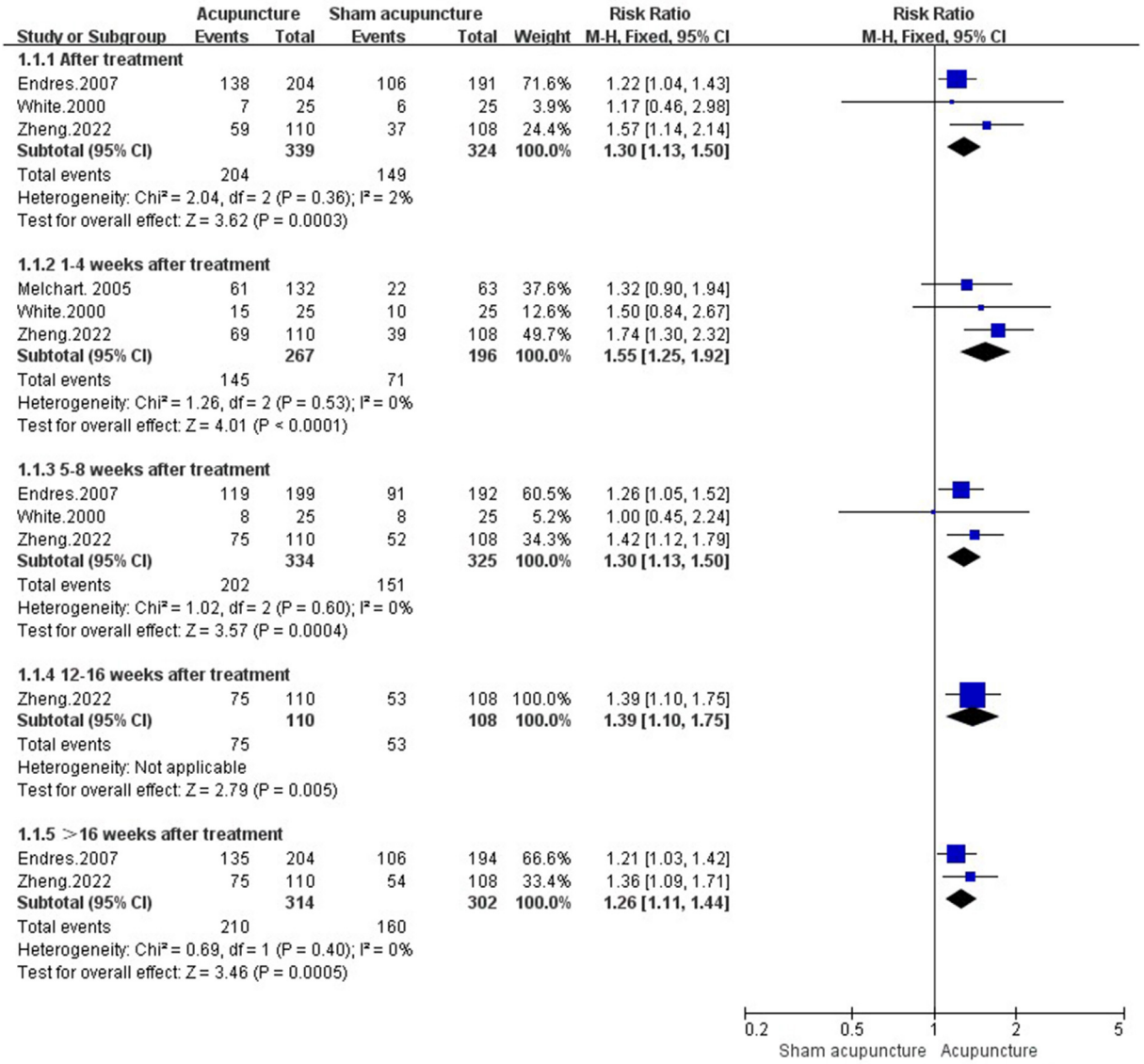

FIGURE 3
Responder rate in comparison of acupuncture vs. sham acupuncture.

sessions of treatment, frequency and duration. Five studies (49, 57, 58, 60, 61) did not describe the style of acupuncture. 17 trials (21–23, 28, 31, 33, 35, 36, 48–53, 60, 63, 64) specified the reasoning of treatment. Patients in 10 RCTs (23, 27, 29, 32, 34, 36, 52, 53, 57, 62) were treated with fixed acupoint protocols, 14 studies (21, 22, 28, 31, 33, 49, 54–56, 58, 60, 61, 63, 64) used a fixed set of acupoints combined with acupoints based on syndrome differentiation, and 5 RCTs (30, 35, 48, 50, 59) applied individualized acupoint protocols. A total of 15 studies (21–23, 27, 29, 31, 33, 36, 48, 52, 57, 58, 60, 61, 64) mentioned the number of needle insertions. More than half of the studies (21, 23, 27, 30–36, 48, 51–53, 55, 60, 63, 64) described the depth of insertion. De qi sensation or other response sought were required in 21 RCTs (21–23, 27, 30, 33, 36, 48–56, 60–64). Except for 5 trials (21–23, 33, 64), the rest studies did not specify the setting and context of treatment. Among included studies, 9 RCTs (21–23, 33, 49, 57, 60, 61, 64) provided information about the acupuncturist's background. Six studies (21–23, 33, 55, 64) reported details of other interventions administered to the acupuncture group. All studies described the control group in detail, and 13 RCTs (21–23, 33, 48–50, 57–61, 64) elucidated the rationale of control group.

3.3. Risk of bias of included studies

The results of risk of bias are shown in Figure 2. In the randomization process, a total of 10 studies (21–23, 28, 33, 49, 50, 54, 57, 60) were judged as low risk, while the rest 20 studies were assessed as some concerns because of neglecting the allocation concealment. As for deviation from intended interventions, 8 trials (21–23, 30, 33, 49, 57, 60) reported that no deviations from the intended intervention were related to experimental context

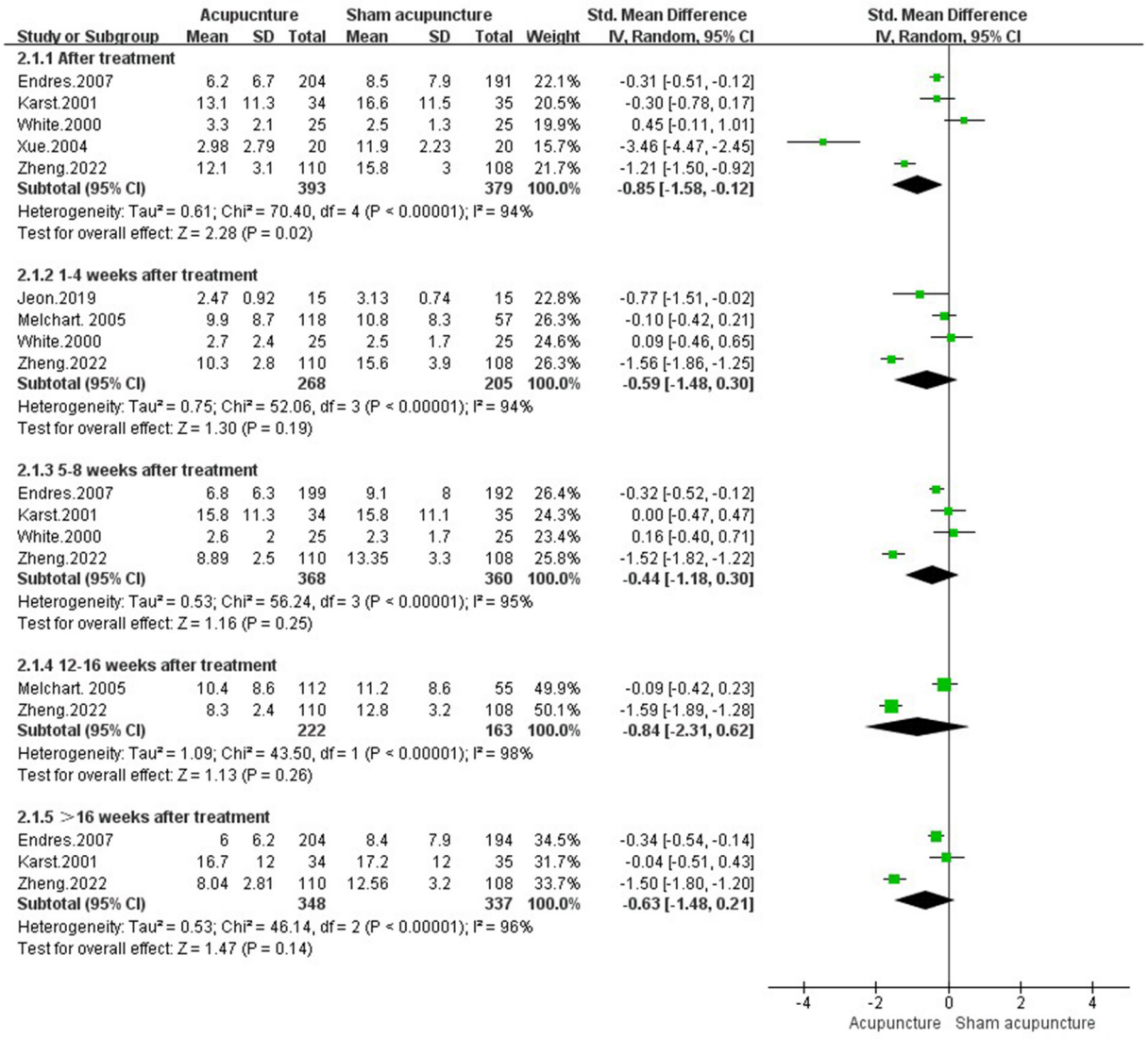

FIGURE 4
Headache frequency in comparison of acupuncture vs. sham acupuncture.

and intention-to-treat (ITT) analysis was applied, thus they were considered as low risk. The remaining 22 RCTs were judged as some concerns due to no double-blinding and lacking of ITT analysis. For the missing outcome, 4 RCTs (58, 59, 62, 64) did not provided details of dropped-outs, which were assessed as some concerns. The rest 26 RCTs were judged as low risk. Considering the measurement of outcomes, 10 studies were rated as low risk (21–23, 30, 48, 49, 57, 58, 60, 61). The rest 20 RCTs were judged as some concerns for lacking of blinding method of outcome assessors. With regard to the selection of the reported result, 6 trials (21–23, 33, 50, 57) provided protocol information and reported all the expected outcomes, thus were considered as low risk. The rest 24 RCTs were some concerns. In summary, the overall bias of 4 RCTs were judged as low risk, and the rest 26 trials were some concerns (Appendix 5).

3.4. Effects of acupuncture for TTH

3.4.1. Acupuncture vs. sham acupuncture

3.4.1.1. Responder rate

Four studies (I: 471 participants, C: 387 participants) (21–23, 49) reported the responder rate. After treatment, the responder rate in acupuncture group was higher than sham acupuncture group [RR = 1.30, 95%CI (1.13, 1.50), $P = 0.0003$, $I^2 = 2\%$]. During the follow-up, acupuncture had long-term therapeutic effect in improving responder rate [1–4 weeks after treatment: RR = 1.55, 95%CI (1.25, 1.92), $P < 0.0001$, $I^2 = 0\%$; 5–8 weeks after treatment: RR = 1.30, 95%CI (1.13, 1.50), $P = 0.0004$, $I^2 = 0\%$; 12–16 weeks after treatment: RR = 1.39, 95%CI (1.10, 1.75), $P = 0.005$; >16 weeks after treatment: RR = 1.26, 95%CI (1.11, 1.44), $P = 0.0005$, $I^2 = 0\%$] (Figure 3).

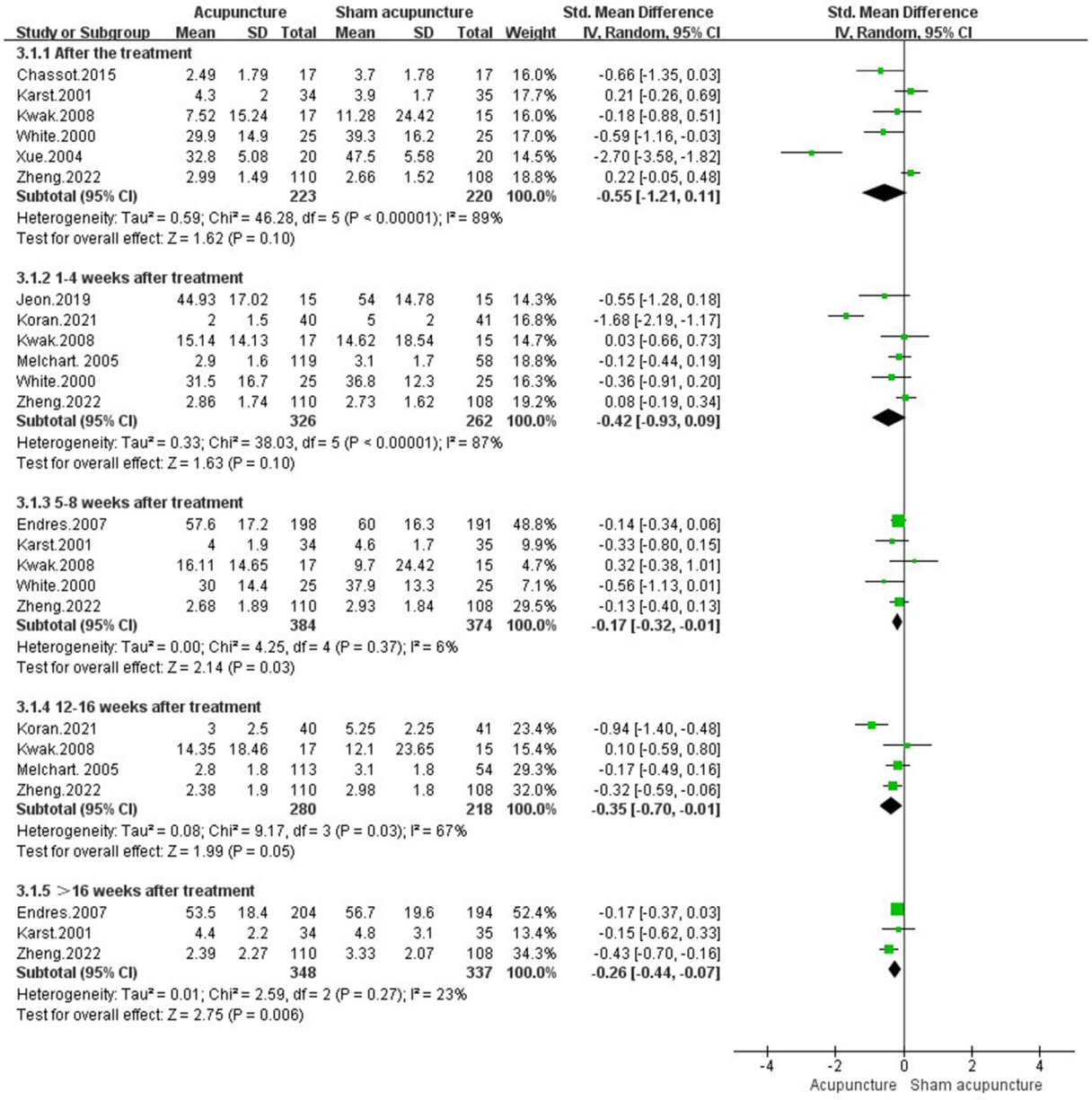

FIGURE 5
Pain intensity in comparison of acupuncture vs. sham acupuncture.

3.4.1.2. Headache frequency

Seven studies (21–23, 29, 49, 50, 58) evaluated headache frequency in comparison of acupuncture vs. sham acupuncture. Results demonstrated that acupuncture had less frequent headache attacks [SMD = −0.85, 95%CI (−1.58, −0.12), $P = 0.02$, $I^2 = 94\%$]. While there was no long-term therapeutic effect in acupuncture group [1–4 weeks after treatment: SMD = −0.59, 95%CI (−1.48, 0.30), $P = 0.19$, $I^2 = 94\%$; 5–8 weeks after treatment: SMD = −0.44, 95%CI (−1.18, 0.30), $P = 0.25$, $I^2 = 95\%$; 12–16 weeks after treatment: SMD = −0.84, 95%CI (−2.31, 0.62), $P = 0.26$, $I^2 = 98\%$; >16 weeks after treatment: SMD = −0.63, 95%CI (−1.48, 0.21), $P = 0.14$, $I^2 = 96\%$] (Figure 4).

3.4.1.3. Pain intensity

Ten studies with 1,129 participants (I: 601, C: 528) observed pain intensity (21–23, 29, 49, 50, 57–59, 64). After treatment, there was no difference between acupuncture and sham acupuncture [SMD = −0.55, 95%CI (−1.21, 0.11), $P = 0.10$, $I^2 = 89\%$]. However, 5 weeks after treatment, acupuncture showed significant effect in reducing pain intensity [5–8 weeks after treatment: SMD = −0.17, 95%CI (−0.32, −0.01), $P = 0.03$, $I^2 = 6\%$; 12–16 weeks after treatment: SMD = −0.35, 95%CI (−0.70, −0.01), $P = 0.05$, $I^2 = 67\%$;>16 weeks after treatment: SMD = −0.26, 95%CI (−0.44, −0.07), $P = 0.006$, $I^2 = 23\%$] (Figure 5).

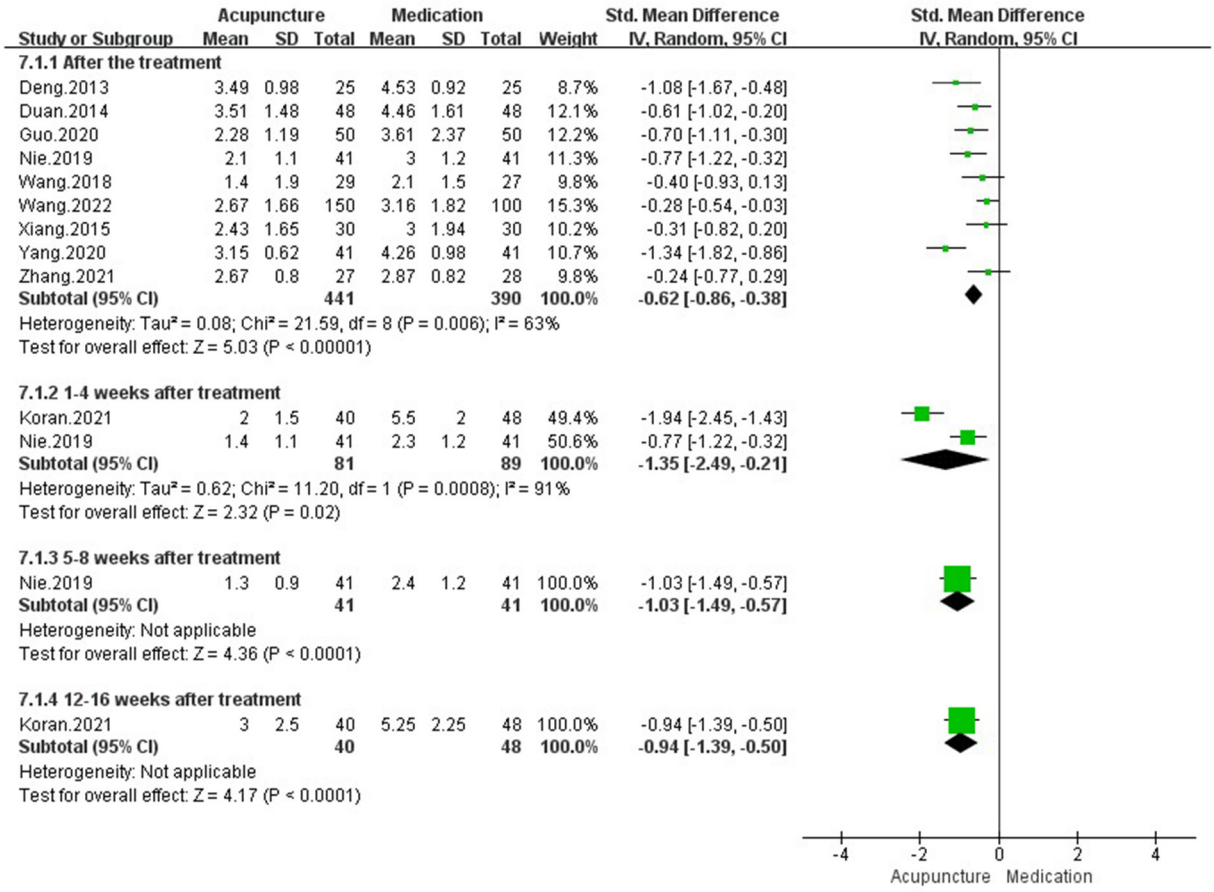

FIGURE 6
Pain intensity in comparison of acupuncture vs. medication.

3.4.1.4. Headache duration

Results of 2 RCTs (I: 143 participants, C: 82 participants) (22, 49) showed that there was no difference between acupuncture and sham acupuncture in reducing headache duration whether after treatment [SMD = 0.34, 95%CI (−0.21, 0.90), $P = 0.23$] or during follow up [1–4 weeks after treatment: SMD = −0.14, 95%CI (−0.41, 0.14), $P = 0.32$, $I^2 = 0\%$; 5–8 weeks after treatment: SMD = 0.28, 95%CI (−0.28, 0.84), $P = 0.33$; 12–16 weeks after treatment: SMD = −0.15, 95%CI (−0.47, 0.18), $P = 0.37$] (Appendix Figure 1).

3.4.1.5. Consumption of medication

Two studies reported consumption of analgesics after treatment (48, 58). However, no significant difference was detected between acupuncture and sham acupuncture after treatment [SMD = −1.23, 95%CI (−3.24, 0.78), $P = 0.23$, $I^2 = 93\%$]. However, the effect of acupuncture during follow-up was inconsistent [1–4 weeks after treatment: SMD = −1.90, 95%CI (−2.78, −1.02), $P < 0.0001$, $I^2 = 93\%$; 5–8 weeks after treatment: SMD = −0.39, 95%CI (−0.86, 0.09), $P = 0.11$; 12–16 weeks after treatment: SMD = −1.86, 95%CI (−2.73, −0.98), $P < 0.0001$; >16 weeks after treatment: SMD = −1.35, 95%CI (−2.15, −0.54), $P = 0.001$] (Appendix Figure 2).

3.4.1.6. Depression

Two trials involving 233 adults (I:145, C:88) focused on depressive state of TTH patients (22, 58), and no difference was identified between acupuncture and sham acupuncture after treatment [SMD = −0.04, 95%CI (−0.51, 0.43), $P = 0.87$] or during follow up period [1–4 weeks after treatment: SMD = −0.16, 95%CI (−0.49, 0.17), $P = 0.34$; 5–8 weeks after treatment: SMD = −0.31, 95%CI (−0.78, 0.17), $P = 0.20$; 12–16 weeks after treatment: SMD = −0.07, 95%CI (−0.40, 0.27), $P = 0.69$] (Appendix Figure 3).

3.4.2. Acupuncture vs. medication

3.4.2.1. Pain intensity

After pooling data from 10 studies (27, 30–32, 34, 35, 53, 62–64) with 919 adults (I: 481, C: 438), we found acupuncture could relieve more pain intensity than medication after treatment [SMD = −0.62, 95%CI (−0.86, −0.38), $P < 0.00001$, $I^2 = 63\%$] and during follow up period [1–4 weeks after treatment: SMD = −1.35, 95%CI (−2.49, −0.21), $P = 0.02$, $I^2 = 91\%$; 5–8 weeks after treatment: SMD = −1.03, 95%CI (−1.49, −0.57), $P < 0.0001$; 12–16 weeks after treatment: SMD = −0.94, 95%CI (−1.39, −0.50), $P < 0.0001$] (Figure 6).

TABLE 2 The results of subgroup analyses.

			No. of studies	No. of patients	RR/SMD (95% CI)	*P*	I^2
Acupuncture vs. sham acupuncture							
Responder rate	Frequency of acupuncture	Once a week	1	50	1.17 (0.46, 2.98)	0.748	0%
		2–3 times a week	2	613	1.31 (1.13, 1.51)	<0.001	50.4%
	Total sessions	<10 sessions	1	50	1.17 (0.46, 2.98)	0.748	0%
		≥10 sessions	2	613	1.31 (1.13, 1.51)	<0.001	50.4%
	Needle retention	0 minutes	1	50	1.17 (0.46, 2.98)	0.748	0%
		25–30 minutes	2	613	1.31 (1.13, 1.51)	<0.001	50.4%
Headache frequency	Frequency of acupuncture	Once a week	1	50	0.46 (−0.10, 1.02)	0.110	0%
		2–3 times a week	4	722	−1.19 (−2.00, −0.38)	0.004	94.9%
	Total sessions	<10 sessions	2	90	−1.51 (−5.42, 2.40)	0.448	97.8%
		≥10 sessions	3	682	−0.62 (−1.25, 0.01)	0.055	92.5%
	Treatment duration	4–5 weeks	3	109	−1.89 (−5.05, 1.27)	0.242	96.9%
		6–8 weeks	2	663	−0.39 (−1.17, 0.40)	0.334	94.7%
	Needle retention	0 minutes	1	50	0.46 (−0.10, 1.02)	0.110	0%
		30 minutes	4	722	−1.19 (−2.00, −0.38)	0.004	94.9%
	Types of acupuncture	EA	1	40	−3.53 (−4.54, −2.52)	<0.001	0%
		MA	4	732	−0.37 (−0.98, 0.23)	0.228	92.2%
Pain intensity	Frequency of acupuncture	Once a week	1	50	−0.60 (−1.17, −0.04)	0.037	0%
		2–3 times a week	5	393	−0.57 (−1.37, 0.24)	0.166	91.1%
	Total sessions	< 10 sessions	3	122	−1.15 (−2.51, 0.21)	0.096	91%
		≥ 10 sessions	3	321	0.01 (−0.44, 0.46)	0.964	65.4%
	Treatment duration	4–5 weeks	4	175	−0.81 (−1.95, 0.32)	0.161	91.5%
		6–8 weeks	2	268	−0.15 (−0.96, 0.65)	0.709	84.9%
	Needle retention	0 minute	1	50	−0.60 (−1.17, −0.04)	0.037	0%
		25–30 minutes	5	393	−0.57 (−1.37, 0.24)	0.166	91.1%
	Types of acupuncture	EA	2	74	−1.70 (−3.73, 0.34)	0.102	92.5%
		MA	4	369	−0.03 (−0.40, 0.34)	0.873	60.1%
Acupuncture vs. medication							
Pain intensity	Categories of medication	Antidepressant	2	115	−0.28 (−0.65, 0.08)	0.131	0%
		Muscle relaxant	5	584	−0.52 (−0.73, −0.31)	<0.001	30.1%
		Analgesics	1	82	−1.35 (−1.83, −0.87)	<0.001	0%
		Antidepressant + Analgesics	1	50	−1.09 (−1.69, −0.50)	<0.001	0%
Depression	Categories of medication	Antidepressant	4	239	−0.18 (−0.65, 0.29)	0.451	70%
		Muscle relaxant	1	60	−1.19 (−1.75, −0.64)	<0.001	0%
Anxiety	Categories of medication	Antidepressant	3	177	0.14 (−0.22, 0.50)	0.442	32.4%
		Muscle relaxant	1	60	−0.94 (−1.47, −0.40)	0.001	0%

No, number; EA, electro-acupuncture; MA, manual acupuncture; CI, confidence interval.

3.4.2.2. Headache frequency

The synthesized results from 2 studies (I: 66 participants, C: 66 participants) (30, 63) showed that acupuncture was not superior to medication in reducing headache attacks after treatment [SMD = −0.60, 95%CI (−1.41, 0.20), $P = 0.14$, $I^2 = 79\%$] or during follow up [1–4 weeks after treatment: SMD = −0.20, 95%CI (−0.64, 0.23), $P = 0.36$; 5–8 weeks after treatment: SMD = −0.30, 95%CI (−0.73, 0.14), $P = 0.18$] (Appendix Figure 4).

3.4.2.3. Headache duration

Wang et al. (27) reported that acupuncture could decrease more headache duration than medication after treatment ($P<0.05$).

3.4.2.4. Depression

Five studies (I: 150 participants, C: 149 participants) evaluated the depressive symptoms of patients with TTH (28, 36, 47, 52, 55), and no difference was found between acupuncture and medication in relieving depression after treatment [SMD = −0.37, 95%CI (−0.90, 0.15), $P = 0.161$, $I^2 = 80\%$] or during follow up [1–4 weeks after treatment: SMD = −0.05, 95%CI (−0.65, 0.56), $P = 0.88$, $I^2 = 65\%$] (Appendix Figure 5).

3.4.2.5. Anxiety

Four studies (I: 118 participants, C: 119 participants) observed anxiety in TTH patients (28, 47, 52, 55), and acupuncture was not better than medication in relieving anxiety after treatment [SMD = −0.12, 95%CI (−0.69, 0.45), $P = 0.68$, $I^2 = 79\%$] or during follow up [1–4 weeks after treatment: SMD = 0.09, 95%CI (−0.41, 0.60), $P = 0.71$] (Appendix Figure 6).

3.4.3. Acupuncture vs. exercise

3.4.3.1. Responder rate

Schiller et al. (33) found that acupuncture was not superior to exercise in improving responder rate ($P > 0.05$) during follow up period.

3.4.3.2. Headache frequency

Schiller et al. (33) discovered that no differences were detected between acupuncture and exercise in reducing headache frequency during follow up period.

3.4.3.3. Pain intensity

Two studies (33, 60) reported the pain intensity after treatment, the result showed that acupuncture did not differ from exercise in ameliorating pain intensity after treatment [SMD = 0.36, 95%CI (−0.15, 0.87), $P = 0.16$] or during follow up [5–8 weeks after treatment: SMD = −0.11, 95%CI (−0.68, 0.46), $P = 0.70$; 12–16 weeks after treatment: SMD = 0.14, 95%CI (−0.37, 0.65), $P = 0.59$; >16 weeks after treatment: SMD = 0.25, 95%CI (−0.13, 0.63), $P = 0.20$, $I^2 = 0\%$] (Appendix Figure 7).

3.4.4. Acupuncture vs. waiting list

One study (22) demonstrated that acupuncture had better improvement of responder rate, headache frequency, pain intensity, and depression score than waiting list group. Nevertheless, there was no difference between acupuncture and waiting list in improving Medical Outcomes Study Short-Form 36 mental health.

3.4.5. Acupuncture vs. usual care

Schiller et al. (33) investigated the effect of acupuncture in contrast with usual care for TTH. The patients in usual care group were allowed to take preventive medication. At 6 weeks after treatment, acupuncture had better effect over usual care in reducing pain, but no difference in responder rate and headache frequency between acupuncture and usual care. At 18 weeks after treatment, acupuncture increased more responder rate than usual care, but no difference was found in headache frequency.

3.4.6. Acupuncture vs. relaxation training

Söderberg et al. (60) found relaxation training was superior to acupuncture in reduction of headache frequency after treatment, but no significant differences during follow up. And there was no differences between acupuncture and relaxation training in relieving pain intensity.

3.4.7. Acupuncture vs. sham acupuncture plus medication

Zhang (54) reported that, acupuncture group had higher responder rate than sham acupuncture plus medication (Estazolam 0.5 mg per day) group ($P < 0.05$), and the number of headache days and headache hours in the acupuncture group was shorter than those in sham acupuncture plus medication group ($P < 0.05$).

3.4.8. Acupuncture vs. acupuncture plus exercise

Schiller et al. (33) demonstrated that no differences were found between acupuncture and acupuncture plus exercise in improving responder rate and pain intensity.

3.5. Adverse events

In total of 16 studies evaluated the adverse events (21–23, 29, 30, 33, 36, 49–52, 54, 56, 57, 59, 61), among which 7 RCTs reported no adverse events (29, 50, 52, 54, 57, 59, 61), and the rest 9 RCTs documented relevant adverse events. The common acupuncture related adverse events were hematoma, post-needling pain, exacerbation of headache, and acupuncture syncope reaction. Endres et al. (21) found one severe headache was possibly triggered by sham acupuncture.

3.6. Subgroup analysis

The results of subgroup analysis in the comparison of acupuncture vs. sham acupuncture or medication are shown in Table 2 (Appendix 7).

In comparison of acupuncture vs. sham acupuncture, we conducted subgroup analyses based on frequency of acupuncture,

total sessions, treatment duration, needle retention and types of acupuncture.

Acupuncture with a frequency at 2–3 times a week was superior to sham acupuncture in improving responder rate and headache frequency. And once a week acupuncture treatment had better efficacy than sham acupuncture in relieving pain intensity. As for total sessions, acupuncture with total sessions ≥10 was more effective than sham acupuncture to improve responder rate. With regard to needle retention, acupuncture with 25–30 minutes needle retention could improve more responder rate and headache frequency than sham acupuncture. Whereas acupuncture with retaining needle eased more pain intensity than sham acupuncture. For types of acupuncture, EA was more effective than sham acupuncture in the reduction of headache frequency.

Subgroup analyses in comparison of acupuncture vs. medication were performed according to categories of medication. The results demonstrated that acupuncture had better effect than muscle relaxants in improvement of pain intensity, depression and anxiety. While there was no difference between acupuncture and antidepressants in relieving the above symptoms.

3.7. Sensitivity analysis

Sensitivity analysis was performed by omitting study one by one. Except for responder rate [*acupuncture vs. sham acupuncture* (after treatment)], the pooled results of the rest outcomes were robust (Appendix 8).

3.8. Publication bias

Due to insufficient studies of primary outcome ($n \leq 10$), we failed to explore the publication bias.

3.9. Assessment of evidence

The outcomes of pain intensity [>16 weeks after treatment (acupuncture vs. sham acupuncture)] were rated as "High" certainty. The outcomes of responder rate [after treatment, 1–4 weeks after treatment, 5–8 weeks after treatment, >16 weeks after treatment (acupuncture vs. sham acupuncture)] and pain intensity [5–8 weeks after treatment (acupuncture vs. sham acupuncture)] were rated as "Moderate" certainty, while the remaining outcomes were considered as "Low" or "Very low" certainty. The certainty of evidence was primarily downgraded by the inconsistency and imprecision of results in the included studies. The summary of findings is presented in Appendix 10.

4. Discussion

4.1. The effect of acupuncture for TTH

In the present study, the results showed that acupuncture had better efficacy than sham acupuncture in improvement of responder rate and headache frequency, the findings were consistent with previous systematic reviews from Linde (20, 25). In addition, acupuncture was more effective than medication to alleviate pain intensity. Patients receiving acupuncture fared significantly better than waiting list in outcomes of responder rate, headache frequency, pain intensity, and depression score. Acupuncture did not differ from exercise in ameliorating pain intensity after treatment. There was no difference between acupuncture and relaxation training in relieving pain intensity. Moreover, acupuncture had long-term therapeutic effect to improve responder rate and pain intensity, and the improvement persisted for at least 16 weeks. According to subgroup analysis, acupuncture was not effective than antidepressants in relieving pain intensity, depression and anxiety. Due to the undesirable side effects of antidepressants (65–67), acupuncture may be a reasonable option for patients with TTH.

Different parameters (frequency, total sessions, treatment duration, retention time, and types of acupuncture etc.) are important to the effect of acupuncture treatment for TTH. As for total sessions, the effect sizes of acupuncture (≥10 sessions) were better than sham acupuncture. In terms of the types of acupuncture, EA could reduce more headache frequency than MA. Acupuncture with a frequency at 2–3 times a week was superior to sham acupuncture in improving responder rate and headache frequency. And acupuncture treatment once a week had better efficacy than sham acupuncture in relieving pain intensity. With regard to needle retention, acupuncture with 25–30 minutes needle retention could improve more responder rate and headache frequency than sham acupuncture. Whereas acupuncture without needle retention eased the pain intensity better than sham acupuncture. However, these findings should be treated with caution, and more rigorous RCTs are needed to explore optimal acupuncture protocol.

4.2. Implications for future studies

The overall risk of bias of 4 RCTs was considered as low risk of bias, the remaining 26 studies were rated as some concerns. The main problems existed in neglection of the allocation concealment, no ITT analysis, lack of the appropriate blinding methods, no details of drop-outs, no pre-specified protocol and registration information. Therefore, investigators should pay attention to these issues during the whole process of clinical trial (68). The Consolidated Standards of Reporting Trials (CONSORT) (69) was recommended to improve the reporting quality of RCTs.

Based on the assessment of STRICTA, most included studies did not report the following items: (1b) the reasoning of acupuncture treatment. (2a) the number of needle insertions, (2c) depth of insertion, (2d) response sought, (4a) details of other interventions administered to the acupuncture group, (5) information about the acupuncturist's background, (6b) rationale for the control or comparator. To improve the reporting quality of interventions in clinical trials of acupuncture, STRICTA (45) should be used.

Among included studies, the meta-analysis involved 3 comparisons including acupuncture vs. sham acupuncture, acupuncture vs. medication, acupuncture vs. exercise. And descriptive analysis included 5 comparisons such as acupuncture

vs. waiting list, acupuncture vs. usual care, acupuncture vs. relaxation training, acupuncture vs. sham acupuncture plus medication, acupuncture vs. acupuncture plus exercise. Nevertheless, due to limited RCTs, high heterogeneity and low or very low certainty of evidence, the above results should be interpreted with caution. More RCTs comparing acupuncture with other active control groups (medication, exercise, etc.) are needed.

4.3. Strengths and limitations

This is the lasted systematic review and meta-analysis of acupuncture for TTH. We comprehensively assessed the risk of bias of included studies using ROB 2, utilized STRICTA to appraise the reporting quality of interventions in clinical trials of acupuncture, and employed GRADE to evaluate the certainty of evidence. Meanwhile, this systematic review and meta-analysis was conducted in accordance with AMSTAR 2 and reported complying the PRISMA.

However, some limitations should be considered. First, since the certainty of majority outcomes was assessed as low or very low, and the risk of bias in most included studies was some concerns, the findings should be treated with discretion. Second, owing to limited studies, the optimal protocol of acupuncture for patients with TTH was not identified. More RCTs are required to investigate the optimal protocol of acupuncture for TTH in the future. Third, the majority of the included patients were from China, which might limit the applicability of the findings to other races.

5. Conclusion

Acupuncture may be an effective and safe treatment for patients with TTH. Notwithstanding, due to the low and very low certainty of most evidence and high heterogeneity, more rigorous RCTs are needed to verify the effect and safety of acupuncture in the management of TTH.

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

W-lK, RF, and X-jX designed the protocol and drafted the manuscript. YF, JL, and R-jJ revised the manuscript. D-lZ, JS, and Y-xL screened the articles, extracted data, and conducted data synthesis. All authors reviewed and approved this 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.

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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.2022.943495/full#supplementary-material

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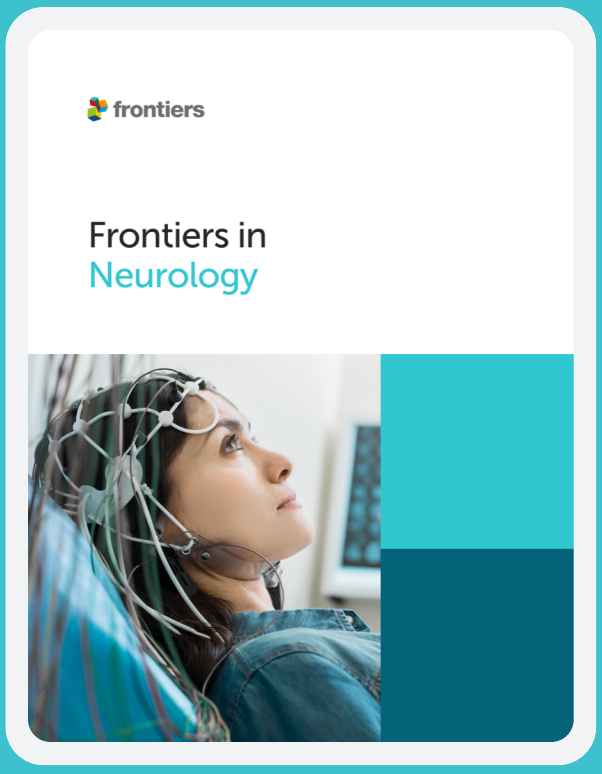

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