Acupuncture for mild cognitive impairment: A systematic review with meta-analysis and trial sequential analysis

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Background: There is insufficient evidence to support the use of acupuncture for mild cognitive impairment (MCI), and there is no consensus on its efficacy. This review aimed to determine the acupuncture effect in patients with MCI.

Methods: Relevant and potentially eligible randomized controlled trials (RCTs) of acupuncture for MCI were obtained from four Chinese databases, four English databases, and additional resources up to 1 August 2022. The primary outcome was the improvement in overall cognitive function (OCF). Secondary outcomes were improved memory function (MF) and activities of daily living (ADLs). The revised Cochrane collaboration risk of bias (ROB) assessment tool (ROB 2.0) was applied to evaluate their methodological quality. The Review Manager software v 5.4 was used for analyses. Trial sequential analysis (TSA) 0.9.5.10 β software was used to estimate the required sample size and test the reliability of the pooled outcome. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Results: This meta-analysis included 11 RCTs with a total of 602 patients. The methodological quality of all trials was moderate. Low-quality evidence showed that acupuncture significantly improved OCF (Mini-Mental State Examination (MMSE): mean difference (MD) = 1.22, 95% confidence interval (CI): 0.78−1.66; the Montreal Cognitive Assessment Scale (MoCA): MD = 1.22, 95% CI: 0.47−1.97). In subgroup analyses, it was revealed that acupuncture significantly increased OCF in patients with MCI when compared to conventional medicine (CM) and sham acupuncture (SA). TSA's findings indicated that the evidence of improving OCF with acupuncture for patients with MCI was conclusive. Meanwhile, there is no statistical difference in the improvement of MF and ADL between acupuncture and CM. TSA showed that the evidence of improving MF and ADL for patients who had MCI and received acupuncture was inconclusive. The shreds of evidence of improving MF and ADL were ranked from low to critically low.

Conclusion: Acupuncture appears to be an effective clinical application method for improving OCF in patients with MCI. However, due to low-quality

evidence, more relevant and high-quality research is needed in this field.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021291284, PROSPERO, No. CRD42021291284.

Introduction

According to the World Health Organization report, more than 55 million people worldwide are living with dementia in 2021. By 2050, the total number of people affected by dementia is expected to reach 139 million (1, 2). Mild cognitive impairment (MCI) represents a possible prodrome of dementia (3, 4). The prevalence rate of in people over the age of 65 ranges from 3 to 42%, of which MCI in ∼20% of them progress to develop dementia (5–7). Currently, the management of MCI has been extensively explored by researchers and clinicians, but treatment options are limited (8–10). Several studies illustrated that pharmaceutical treatments commonly applied to treat dementia might neither improve nor slow cognitive test performance decline in MCI patients (11, 12). Furthermore, these treatment options are expensive and pose health burdens associated with MCI control. Due to these factors, MCI is considered a prominent target symptom for early detection and intervention of dementia.

Acupuncture, part of traditional Chinese medicine, has been widely used as a non-pharmaceutical therapy for various cognitive dysfunctions, including MCI (13), postoperative cognitive impairment (14), vascular cognitive impairment (15), and so on. Numerous systematic reviews/meta-analyses (SRs/MAs) (13, 16–18) showed that acupuncture is an effective treatment for patients with MCI by improving cognitive function. Furthermore, several experimental studies demonstrated that acupuncture can enhance hippocampal synaptic transmission, inhibit neuroinflammation, release central neurotransmitters, and relieve oxidative stress (19–21).

There were numerous previous SRs/MAs (16–18); however, the sample size of the included randomized controlled trials (RCTs) from SRs/MAs was frequently small, and no research was conducted to estimate the sample size of the included studies, which might point out the risks of bias and false-positive results. Moreover, the quality of evidence derived from RCTs is unclear. These limitations obstructed the development of recommendations for clinical practice. Trial sequential analysis (TSA) might calculate the required information size (RIS) and assess futility boundaries to guide future trials (22). Therefore, in this study, MA and TSA of RCTs were conducted to evaluate acupuncture in the treatment of MCI to address the abovementioned issues, provide evidence for clinical applications, and serve as a reference for future clinical research.

Methods

Study design

This review protocol was registered in PROSPERO (No. CRD42021291284). SR/MA and TSA were implemented based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (23) and A Measure Tool to Assess Systematic Reviews-2 (AMSTAR-2) checklists (24).

Inclusion and exclusion criteria

Types of studies

We included all peer-reviewed articles published on parallel RCTs and in English or Chinese. In contrast, quasi or cluster RCTs, non-RCTs, animal studies, letters, reviews, duplicated trails, and articles without data were excluded.

Types of participants

We included subjects with MCI who were diagnosed with specific criteria [such as Petersen's criteria (25), Jak/Bondi diagnosis (26), and National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (27)]. Meanwhile, trials without detailed criteria were excluded.

Types of intervention group

The intervention group received acupuncture [using the insertion of needles into the specific acupoints (skin and underlying tissues)], as a monotherapy using manual/electronic/warm acupuncture, regardless of the acupoint selections.

Types of control group

The control group included conventional medicine (CM), which could enhance the cognitive ability of patients (such as

Donepezil, Nimodipine, and Ginkgo biloba extract), regardless of the contents; and sham acupuncture (SA) (contact with skin without penetrating the exact acupoints; or insert into non-acupoints).

Types of outcome measures

The primary outcome measure was the improvement in cognitive function, as determined by the Montreal Cognitive Assessment Scale (MoCA) and the Mini-Mental State Examination (MMSE). The secondary outcome was the improvement in memory function (MF) and activities of daily living (ADLs). The inclusion criterion was any study that reported the primary or secondary outcome.

Search strategy

Two reviewers independently performed a comprehensive search of the following electronic databases: four English databases [PubMed, Embase, Cochrane Central Register of Controlled Trials database (CENTRAL), and Web of Science (WOS)], four Chinese databases (China National Knowledge Infrastructure (CNKI), SinoMed Database (CBM), VIP Database, and WF Database), other included resources (Gray Literature Database (GLD), Allied and Complementary Medicine Database (AMED), WHO ICTRP, ClinicalTrials.gov, and ChiCTR), and published SRs on acupuncture for AD from inception to 1 August 2022. The following terms were imposed: (1) clinical conditions: MCI, cognitive dysfunction, etc.; (2) acupuncture-related words: acupuncture, acupoint, acupuncture plus moxibustion, electronic acupuncture, auricular acupuncture, etc.; and (3) trial type: a RCT. The terms "and" and "or" were combined between the search terms. Search strategies for these sources are shown in Appendix 1.

Study selection and data extraction

All investigators received professional, evidence-based medicine training to implement this SR. After excluding duplicate articles and uploading potentially eligible studies to NoteExpress V.3.0, two reviewers (MX and ZC) independently screened the titles, abstracts, and keywords of all searched items. They identified the trials that met the abovementioned inclusion criteria. Divergences between the two reviewers were resolved through discussion between the two. A third party also assisted with the final decision.

Two reviewers independently accomplished data extraction using standardized tabulation. Extracted data included first author, publication date, country, standard of diagnosis, sample size, allocation ratio, age, gender, details of acupuncture and

control groups, and outcomes. In case of any disagreement, the corresponding authors helped us in making a decision. Once the required information was inadequate, the corresponding author of the included studies was contacted.

Quality assessment

Two investigators independently evaluated the risk of bias (ROB) using the revised Cochrane collaboration ROB assessment tool (ROB 2.0) (28). We evaluated the five items (randomization process bias, deviations from intended intervention bias, bias of missing outcome data, bias of measurement of an outcome, and the selection bias of the reported results). Each part was assessed and classified as high risk, low risk, or risk of some concern. The third intercessors were supposed to resolve any disagreements.

Statistical analysis

For each study, we used pre- and post-differences or end-point scores as outcome indicators. The retrieved data were analyzed using the Review Manager (RevMan) version 5.4 software (Cochrane, London, UK). The Mantel–Haenszel method used the fixed-effects model for MAs, whereas the Der Simonian–Laired method used the random-effects model. The I^2 statistic was used to identify and measure heterogeneity among RCTs. We considered heterogeneity when the p-value was < 0.1 and I^2 was > 50%. In addition, all data were analyzed using a 95% confidence interval (CI). Mean differences (MDs) were applied for continuous data. To identify trials with possible heterogeneity, we used a subgroup analysis. Furthermore, when the number of included RCTs was > 2, potential reporting bias was explored using funnel plots.

Trial sequential analysis

Conventional pairwise/cumulative MAs do not estimate the RIS using an empirical method. RIS was explored using TSA 0.9.5.10 β software (available at http://www.ctu.dk; Copenhagen Trial Unit, Denmark) to determine the sample size required for MA and explore whether the evidence included in our MA is credible and conclusive (29). A priori diversity-adjusted information size ($\alpha = 5\%$, $\beta = 20\%$, relative risk reduction (RRR), and control event rates (CER) were calculated for each study) and an eventual breakthrough of the cumulative Z-curve of futility boundaries based on the O'Brien-Fleming alpha-spending function were used to estimate RIS with a critical value for a significant statistical effect of acupuncture.

Quality of evidence

Subsequently, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (30) to evaluate the quality of evidence and categorize it into four, namely, high, moderate, low, and critically low.

Assessment of reviewer agreement

The intraclass correlation coefficient (ICC) was applied to measure the consistency between the two investigators using a κ value (κ score, 0.89) (31).

Results

Study description

Literature search

Through comprehensive research, we identified 2,877 studies. After eliminating duplicate trials, we had 1,881 studies. After the initial screening, 31 articles remained. Finally, after reading the full-text articles, 19 papers were excluded (10 studies with non-acupuncture, nine with ineligible outcomes, and one with duplicate content), leaving 11 RCTs (32–42). The flowchart of PRISMA is depicted in Figure 1, and the reasons for the exclusion of full-text studies are detailed in Appendix 2.

Study characteristics

Table 1 presents the basic characteristics of 11 studies included in MA. A total of 11 trials with 602 subjects were implemented in China. Only one study (39) had a sample size of more than 100, whereas the other studies had low sample sizes. In the studies, 1:1 was regarded as a generally applied allocation ratio. The Diagnostic and Statistical Manual of Mental Disorders (DSM) or Petersen's criteria were frequently used for diagnosis. In addition, the mean patient age is 60–80 years, and the male-to-female ratio is largely consistent. Meanwhile, CM was the most commonly used comparator intervention. The course of the disease was reported in nine articles. The most documented outcome was an improvement in the MMSE score. A follow-up period was not covered in any of the articles.

Acupuncture details

According to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (43), acupuncture details are summarized in Table 2. In the acupuncture rationale, all the included 11 RCTs were mentioned. In the section on acupuncture details, the number of needle insertions per participant in each session of included studies ranged from 3 to 18; Baihui (GV 20) and Sishencong (EX-HN1) were the

frequently applied acupuncture points; acupuncture insertion depth was 7.5–40 mm; Deqi was mentioned in 10 studies; the electronic method was applied to five studies, the manual method to four articles, and the warm method to two articles. The most frequently used brand of acupuncture was Hwato, and the diameter and length of a needle were 0.30 and 25/40 mm, respectively. The electroacupuncture apparatus was G6805. For treatment regimens, the number of treatment sessions ranged from 20 to 60; the frequency of treatment sessions was daily, and the session duration of acupuncture ranged from 28 to 180 days. In other components, three researchers documented the details of other interventions; only one article provided a detailed setting and treatment context. Notably, only one study (34) described details about acupuncturists. In the section on comparator interventions, eight trials documented the rationale for a comparator; all trials had a complete description of the control/comparator.

Quality assessment

The risk of bias of RCTs was assessed using RoB 2. Meanwhile, ROB graphs were performed using the Shiny app (https://mcguinlu.shinyapps.io/robvis/). In the section on the randomization process, although all articles documented that they were randomized, only four trials (36–39) were ranked as low risk and the rest of the trials had certain concerns due to the generation of an unclear random sequence. For deviations from the intended interventions, only two studies (32, 34) were ranked as low risk, the remaining studies were ranked as the risk of some concerns due to their short descriptions. For missing outcome data, two trials (32, 40) had a risk of some concerns. All trials were ranked as low risk in the measurement of an outcome. Notably, in the selection of the reported results, all RCTs were assessed for some concerns due to a lack of a protocol/registration about a pre-specified analysis plan. Figure 2 illustrates the ROB results.

Effects of intervention

Primary outcome: Improvement in overall cognitive function
Improvement in MMSE

We explored 10 RCTs for the beneficial effects of acupuncture on overall cognitive function (OCF) in subjects with MCI using MMSE (Figure 3A). Differences between acupuncture and comparator interventions were statistically significant (MD = 1.22; 95% CI: 0.78, 1.66). Due to the existence of heterogeneity ($I^2 = 62\%$, $p = 0.005$), a random-effects model was applied. In a comparison between acupuncture and the comparator intervention, TSA revealed that the cumulative Z-curve had crossed the RIS boundary (RIS =

FIGURE 1
The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart of a selection process.
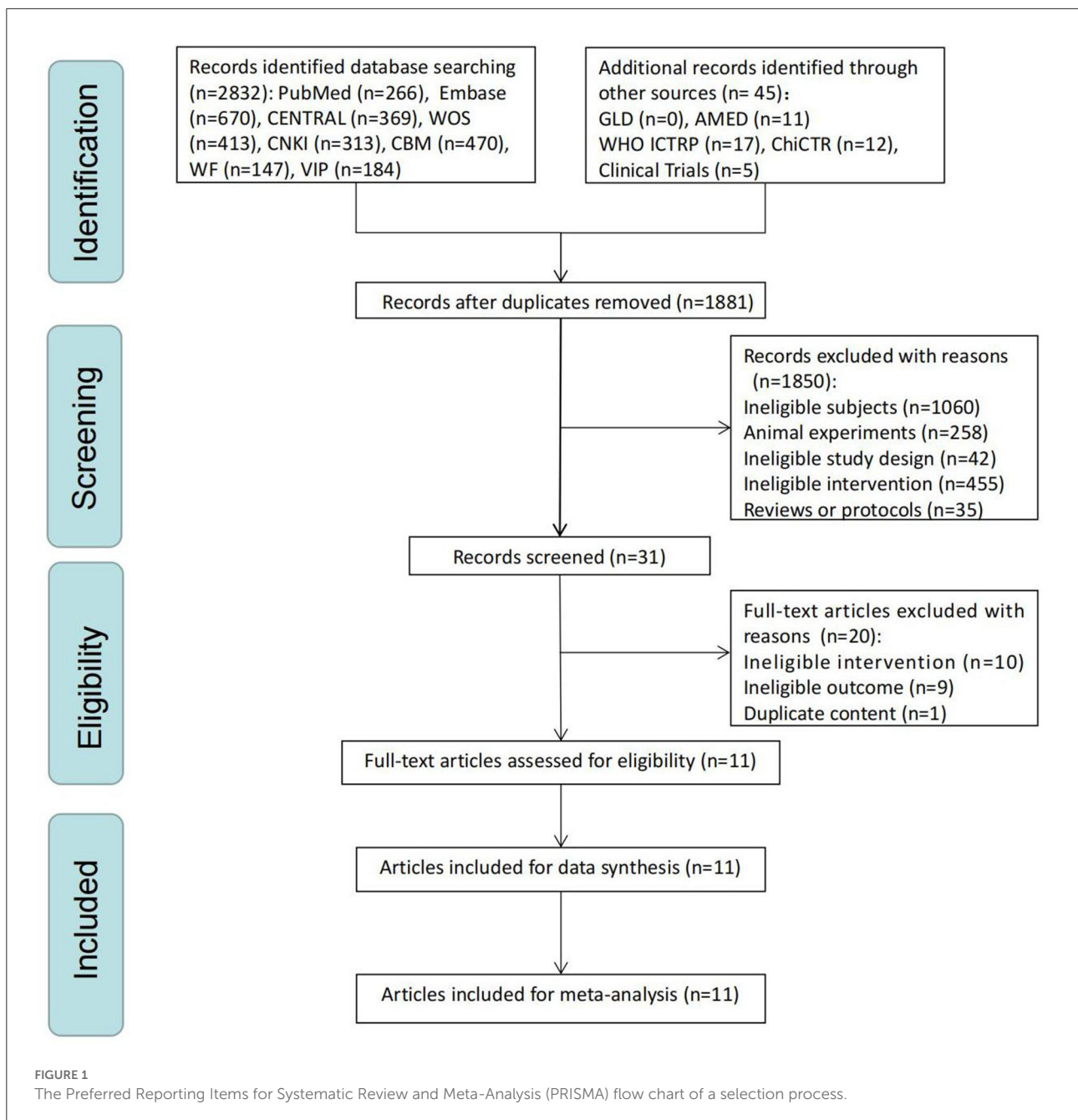
170), indicating that the sample size was sufficient to determine whether acupuncture treatment was superior to comparator interventions in improving MMSE on MCI (Figure 3B). As illustrated in Figure 3C, a funnel plot manifested a low ROB of publication. The GRADE approach evaluated that the quality of evidence in improving MMSE was "low" (Table 3).

Due to significant heterogeneity, a subgroup analysis was applied. Given that control groups (CM and SA) were different, a subgroup analysis was performed. Heterogeneity was significantly reduced ($I^2 = 7\%$, $p = 0.37$), and a fixed-effects model was applied. The results of the MA found statistical differences between acupuncture and CM (MD = 1.09, 95% CI: 0.83, 1.36). The MA results found statistical differences between acupuncture and SA (MD = 2.82, 95% CI: 1.99, 3.65). These findings demonstrated that acupuncture increased MMSE scores more effectively than CM and SA.

Reduction of MoCA

Seven studies explored the beneficial effects of acupuncture on OCF in subjects with MCI using MoCA (Figure 4A). The

TABLE 1 Main characteristics of included randomized controlled trials (RCTs).

Study	Country	Sample size	Allocation ratio	Diagnostic criteria	Age	Gender (M/F)	Course of the disease (month)	(A) Treatment Group	(B) Control Group	Follow-up period	Efficacy criteria	Main Results
Zheng et al. (32)	China	60	1:1	①	A: 63.52 ± 6.20 B: 66.00 ± 6.42	A: 9/16 B: 7/17	A: 38.52 ± 22.2 B: 42.84 ± 15.48	Acupuncture	CM (6 ml/day dose of Ginkgo biloba extract drops)	/	1. MMSE 2. MoCA	1. A>B 2. A>B
Tan et al. (34)	China	32	1:1	②	A: 65.88 ± 4.66 B: 64.56 ± 5.25	A: 10/6 B: 6/10	/	Acupuncture	Sham acupuncture	/	1. MMSE 2. MoCA	1. A>B 2. A>B
Xu and Peng (33)	China	60	1:1	③	A: 62.12 ± 8.01 B: 61.20 ± 7.63	A: 16/14 B: 16/14	A: 8.55 ± 3.10 B: 9.60 ± 2.72	Acupuncture	CM (60 mg/day dose of Nimodipine)	/	1. MMSE 2. MoCA	1. A>B 2. A>B
Liu (35)	China	32	15:17	④	A: 73.00 ±7.67 B: 77.22 ±5.65	A: 9/6 B: 9/8	/	Acupuncture	CM (2.5 mg/day dose of Donepezil)	/	1. MMSE 2. CMS	1. A>B 2. A=B
Du (36)	China	40	1:1	④	A: 69.03 ± 5.47 B: 68.25 ± 5.80	A: 11/9 B: 13/7	A: 10.08 ± 2.79 B: 10.01 ± 2.39	Acupuncture	CM (5 mg/day dose of Donepezil)	/	1. MMSE 2. MoCA	1. A>B 2. A>B
Zhu et al. (37)	China	60	1:1	⑤	A: 62.13 ± 7.99 B: 60.90 ±7.52	A: 17/13 B: 16/14	A: 8.73 ± 3.05 B: 9.50 ± 2.82	Acupuncture	CM (90 mg/day dose of Nimodipine)	/	1. MMSE 2. MoCA	1. A>B 2. A=B
Zhu et al. (38)	China	60	1:1	⑥	A: 45-75 B: 46-74	A: 19/11 B: 21/9	A: 3-17 B: 6-16	Acupuncture	CM (90 mg/day dose of Nimodipine)	/	1. MMSE 2. MoCA 3. ADL	1. A>B 2. A>B 3. A>B
Zhao et al. (39)	China	192	1:1	①	A: 69 ± 7 B: 67 ± 6	A: 46/48 B: 44/49	/	Acupuncture	CM (90 mg/day dose of Nimodipine)	/	MMSE	A>B
Liu (40)	China	36	17:19	④	A: 66.00 ± 6.84 B: 69.32 ± 6.86	A: 7/10 B: 9/10	A: 27.84 ± 7.94 B: 30 ± 11.11	Acupuncture	CM (2.5 mg/day dose of Donepezil)	/	MMSE	A>B
Jin (41)	China	30	7: 8	②	A: 72.54 ± 7.07 B: 73.67 ± 3.27	A: 8/6 B: 9/7	A: 30.24 ± 10.25 B: 31.10 ± 10.39	Acupuncture	CM (90 mg/day dose of Nimodipine)	/	1. MoCA 2. CMS	1. A>B 2. A=B
Wang (42)	China	60	1:1	②	A: 65.80 ± 5.08 B: 65.57 ± 5.22	A: 16/14 B: 17/13	A: 7.80 ± 2.52 B: 7.83 ± 2.46	Acupuncture	CM (90 mg/day dose of Nimodipine)	/	1. MMSE 2. ADL	1. A=B 2. A=B

① International Working Group criteria; ② Petersen RC. Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 1999, 56, 303-308; ③ National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; ④ Diagnostic and Statistical Manual of Mental Disorders (DSM); ⑤ Guidelines for the diagnosis and treatment of dementia and cognitive Impairment in China; ⑥ Expert consensus on the prevention and treatment of Cognitive Impairment in China; CM, conventional medicine; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment Scale; CMS, Clinical Memory Scale; ADL, activity of daily living.

TABLE 2 Details of acupuncture methods according to Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).

Study	Acupuncture rationale			Details of needling							Treatment regimen		Other components		Practitioner	Comparator interventions	
	1a	1b	1c	2a	2b	2c	2d	2e	2f	2g	3a	3b	4a	4b	5	6a	6b
Zheng et al. (32)	TCM	Y	NA	10	GV 24, GB 20 (bilateral), GV 23, GV 29, LI 20 (bilateral), LI 4 (bilateral), ST 36 (bilateral)	15-40 mm	Deqi	Manual	40 min	Diameter and length: 0.30 mm & 40 mmNeedle brand: Zhongyan-Electroacupuncture apparatus: 6805C	60	Frequency: five times per week Duration: 84 days	NA	NR	NR	Y	Y
Tan et al. (34)	TCM	Y	NA	13	EX-HN1, GV 29, PC 6 (bilateral), KI 3 (bilateral), ST 40 (bilateral), and LR 3 (bilateral)	15 mm	NR	Manual	NR	Diameter and length: 0.35 mm & 25 mmNeedle brand: Hwato	20	Frequency: five times per week Duration: 12 weeks	NA	NR	Y	Y	Y
Xu et al. (33)	TCM	Y	NA	8	GV 20, EX-HN 1, GV 24, GB 20 (bilateral)	12.5-30 mm	Deqi	Electronic	NR	Diameter and length: 0.30 mm & 40 mmNeedle brand: Zhongyan-Electroacupuncture apparatus: 6805C	24	Frequency: three times per week Duration: 56 days	NA	NR	NR	Y	Y
Liu (35)	TCM	Y	NA	14	EX-HN 1, GB 20 (bilateral), GB 39 (bilateral), BL 23 (bilateral), KI3 (bilateral), HT 7 (bilateral)	7.5-25mm	Deqi	Electronic	20 min	Diameter and length: NRNeedle brand: NR-Electroacupuncture apparatus: G6805-II	30	Frequency: each day Duration: 30 days	NA	NR	NR	NR	Y
Du (36)	TCM	Y	NA	18	GV 24, GV 14, GV 23, GV 29, GV 16, GV 15, EX-HN 1, KI3 (bilateral), KI4 (bilateral), ST 36 (bilateral), GB 39 (bilateral)	15-40 mm	Deqi	Manual	40 min	Diameter and length: 0.30 mm & 25/40 mmNeedle brand: Tianxie-Electroacupuncture apparatus: 6805C	48	Frequency: six times per week Duration: 56 days	Y	NR	NR	Y	Y
Zhu et al. (37)	TCM	Y	NA	4	GV 24, GV 14, GB 39 (bilateral)	≤50 mm	Deqi	Warm	30 min	Diameter and length: 0.3 mm & 25/40 mmNeedle brand: Hwato	56	Frequency: six times per week Duration: 56 days	Y	NR	NR	NR	Y

(Continued)

TABLE 2 (Continued)

| Study	Acupuncture rationale			Details of needling							Treatment regimen		Other components		Practitioner	Comparator interventions	
	1a	1b	1c	2a	2b	2c	2d	2e	2f	2g	3a	3b	4a	4b	5	6a	6b
Zhu et al. (38)	TCM	Y	NA	3	GV 24, CV 4, GV 4	25 mm	Deqi	Warm	30 min	Diameter and length: 0.3 mm & 50 mmNeedle brand: Hwato	60	Frequency: six times per week Duration: 70 days	NA	NR	NR	NR	Y
Zhao et al. (39)	TCM	Y	NA	8	GV 20, EX-HN 1, GV 24, GB 20 (bilateral)	15-25 mm	Deqi	Electronic	30 min	Diameter and length: 0.3 mm & 25/40 mmNeedle brand: Hwato-Electroacupuncture apparatus: G6805-II	24	Frequency: three times per week Duration: 56 days	Y	Y	NR	Y	Y
Liu (40)	TCM	Y	NA	9	GV 20, GB 20 (bilateral), BL 23(bilateral), GB 39 (bilateral), KI3 (bilateral)	13-25 mm	Deqi	Electronic	NR	Diameter and length: 0.35 mm & 25 mmNeedle brand: Shenlong-Electroacupuncture apparatus: G6805-II	30	Frequency: each day Duration: 30 days	NA	NR	NR	Y	Y
Jin (41)	TCM	Y	NA	10	EX-HN 1, GB 20 (bilateral), BL 23(bilateral), KI3 (bilateral)	13-25 mm	Deqi	Electronic	20 min	Diameter and length: 0.30 mm & 40 mmNeedle brand: Hwato-Electroacupuncture apparatus: G6805-II	45	Frequency: each day Duration: 45 days	NA	NR	NR	Y	Y
Wang (42)	TCM	Y	NA	12	GV 20, EX-HN 1, GV 24, GB 20 (bilateral), BL 23(bilateral), KI3 (bilateral)	25 mm	Deqi	Manual	30 min	Diameter and length: 0.38 mm & 25-65 mmNeedle brand: Hwato	28	Frequency: each day Duration: 28 days	NA	NR	NR	Y	Y

1a, Style of acupuncture; 1b, Reasoning for the treatment provided; 1c, Extent to which treatment was varied; 2a, Number of needle insertions per subject per session; 2b, Names of points used; 2c, Depth of insertion; 2d, Response sought; 2e, Needle stimulation; 2f, Needle retention time; 2g, Needle type; 3a, Number of treatment sessions; 3b, Frequency and duration of treatment sessions; 4a, Details of other interventions administered to the acupuncture group; 4b, Setting and context of treatment; 5, Description of participating acupuncturists; 6a, Rationale for the control or comparator; 6b, A precise description of the control or comparator; TCM, traditional Chinese medicine; NA, not applied; NR, not recorded; Y, Yes; &, and.

FIGURE 2
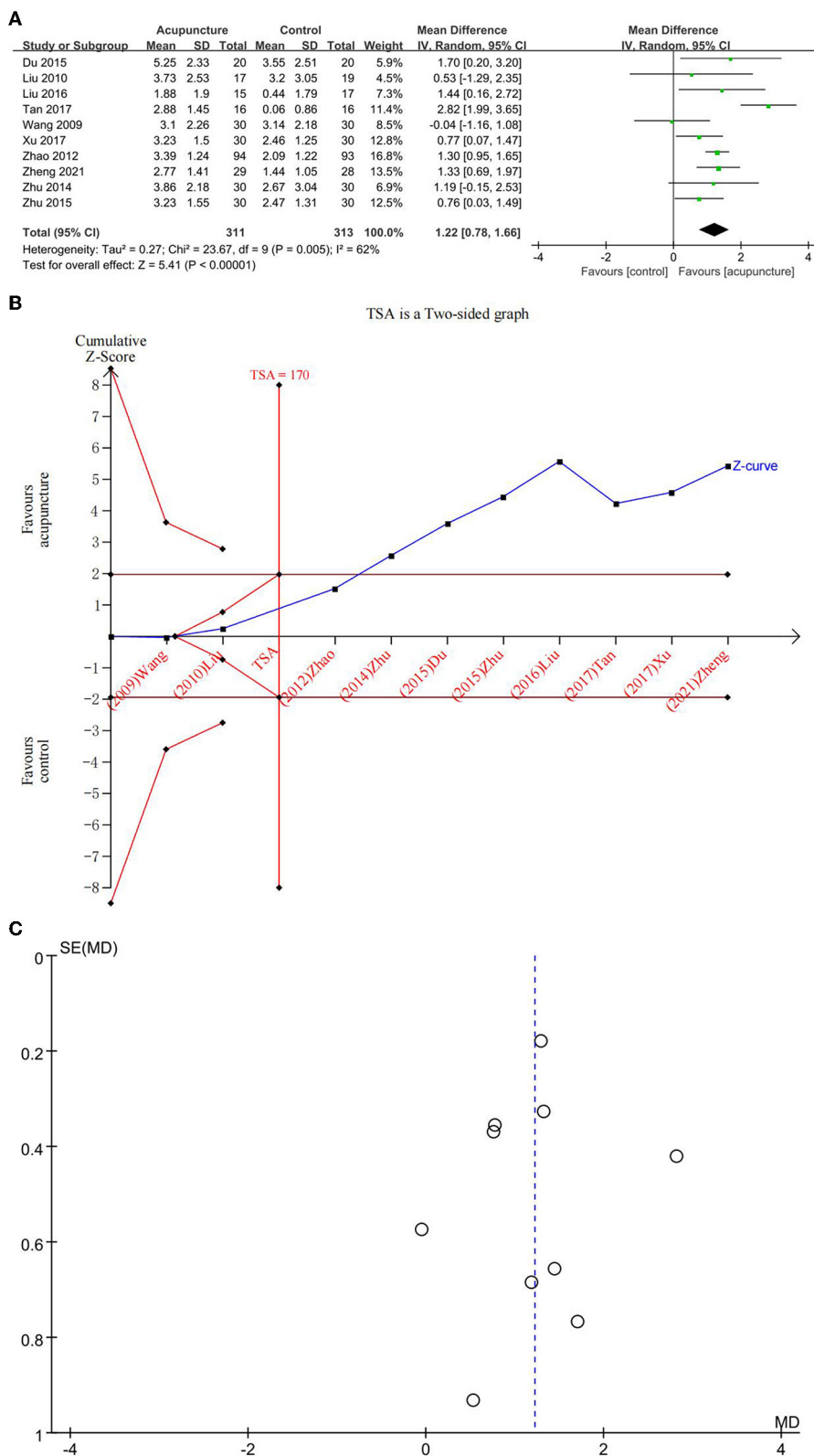**(A)** Risk of bias graph and **(B)** Risk of bias summary.
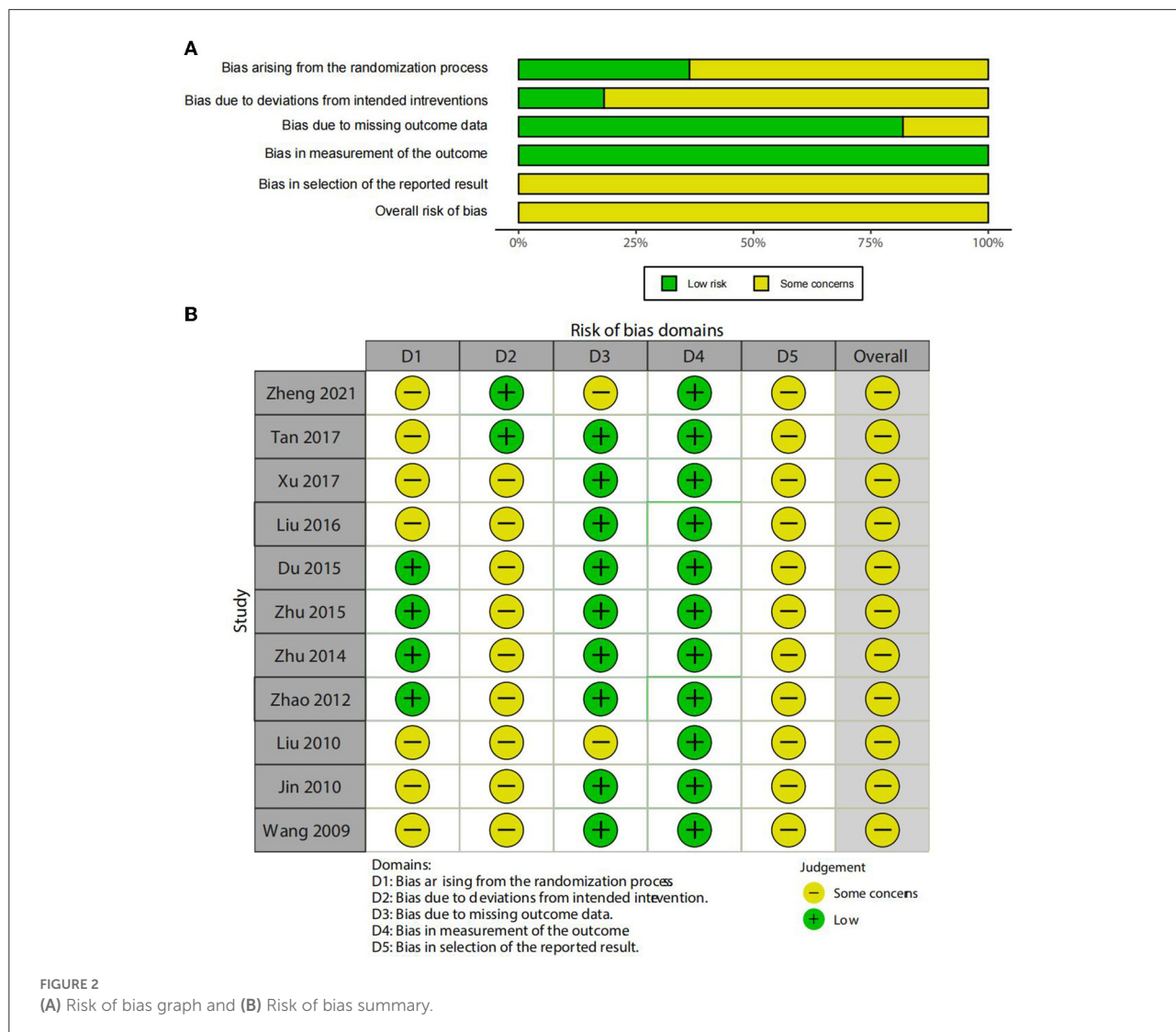
difference between acupuncture and comparator interventions was statistically significant (MD = 1.22; 95% CI: 0.47, 1.97). Due to major heterogeneity ($I^2 = 79\%$, $p = 0.001$), a random-effects model was used. In a comparison between acupuncture and the comparator intervention, TSA revealed that the cumulative Z-curve had crossed an RIS boundary (RIS = 263), indicating that the sample size was competent to determine whether acupuncture treatment was superior to comparator interventions in improving MoCA on MCI (Figure 4B). As displayed in Figure 4C, the funnel plot manifested a low ROB of publication. The GRADE approach evaluated that the quality of evidence regarding MoCA improvement was "low" (Table 3).

Because control groups (CM and SA) were different, a subgroup analysis was implemented. The heterogeneity was significantly reduced ($I^2 = 59\%$, $p = 0.004$). The results of MA found statistical differences between acupuncture and CM (MD = 0.93, 95% CI: 0.29, 1.56) as well as between acupuncture and SA (MD = 2.19, 95% CI: 1.51, 2.87). These findings

demonstrated that acupuncture increased MoCA scores better than CM and SA.

Secondary outcome: Improvement in MF

Two studies explored the beneficial effects of acupuncture on MF in subjects with MCI using a clinical memory scale (CMS) (Figure 5A). There was no statistical difference between acupuncture and the comparator intervention (CM) (MD = 6.05; 95% CI: −1.33, 13.44). Due to low heterogeneity ($I^2 = 34\%$, $p = 0.22$), a fixed-effects model was used. In the comparison between acupuncture and CM, TSA investigated that the cumulative Z-curve had not crossed the RIS boundary (RIS = 258), indicating that the sample size was insufficient to determine whether acupuncture treatment was equal to comparator interventions in improving CMS on MCI (Figure 5B). The GRADE approach evaluated that the quality of evidence regarding CMS improvement was "low" (Table 3).

A

Study or Subgroup	Acupuncture Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Du 2015	5.25	2.33	20	3.55	2.51	20	5.9%	1.70 [0.20, 3.20]
Liu 2010	3.73	2.53	17	3.2	3.05	19	4.5%	0.53 [-1.29, 2.35]
Liu 2016	1.88	1.9	15	0.44	1.79	17	7.3%	1.44 [0.16, 2.72]
Tan 2017	2.88	1.45	16	0.06	0.86	16	11.4%	2.82 [1.99, 3.65]
Wang 2009	3.1	2.26	30	3.14	2.18	30	8.5%	-0.04 [-1.16, 1.08]
Xu 2017	3.23	1.5	30	2.46	1.25	30	12.8%	0.77 [0.07, 1.47]
Zhao 2012	3.39	1.24	94	2.09	1.22	93	16.8%	1.30 [0.95, 1.65]
Zheng 2021	2.77	1.41	29	1.44	1.05	28	13.5%	1.33 [0.69, 1.97]
Zhu 2014	3.86	2.18	30	2.67	3.04	30	6.9%	1.19 [-0.15, 2.53]
Zhu 2015	3.23	1.55	30	2.47	1.31	30	12.5%	0.76 [0.03, 1.49]
Total (95% CI)			**311**			**313**	**100.0%**	**1.22 [0.78, 1.66]**

Heterogeneity: Tau² = 0.27; Chi² = 23.67, df = 9 (P = 0.005); I² = 62%
Test for overall effect: Z = 5.41 (P < 0.00001)

B

C

FIGURE 3
(A) Forest plot of improvement of Mini-Mental State Examination (MMSE); **(B)** trial sequential analysis of improvement of MMSE; and **(C)** a funnel plot of improvement of MMSE.

TABLE 3 Quality of evidence included RCTs by Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Outcomes	Included RCTs (patients)	Relative effect (95% CI)	Quality assessment								Quality of evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose response	All plausible confounding	
MMSE	10 (592)	MD 1.22 (0.78, 1.66)	Serious①	Serious②	Not serious	Not serious	Undetected	Undetected	Undetected	Undetected	Low
MoCA	7 (339)	MD 1.22 (0.47, 1.97)	Serious①	Serious②	Not serious	Not serious	Undetected	Undetected	Undetected	Undetected	Low
CMS	2 (62)	MD 6.05 (−1.33, 13.44)	Serious①	Not serious	Not serious	Serious③	Undetected	Undetected	Undetected	Undetected	Low
ADL	2 (120)	MD 3.19 (−4.53, 10.90)	Serious①	Serious②	Not serious	Serious③	Undetected	Undetected	Undetected	Undetected	Critically Low

① Most information is from the moderate risk studies, and there are major limitations; ② The size and direction of the effect size, the overlap of the confidence interval (CI) is small, the P-value of the heterogeneity test is small, and the combined results of I² value are large; ③ The sample is insufficient.

Secondary outcome: Improvement in ADL

Two studies explored the beneficial effects of acupuncture on ADL in subjects with MCI using the ADL scale (Figure 6A). There was no statistical difference between acupuncture and the comparator intervention (CM) (MD = 3.19; 95% CI: −4.53, 10.90). Due to major heterogeneity ($I^2 = 78\%$, $p = 0.03$), a random-effects model was used. In the comparison between acupuncture and comparator intervention, TSA investigated that the cumulative Z-curve had not crossed the RIS boundary (RIS = 1,512), indicating that the sample size was insufficient to determine whether acupuncture treatment was equal to the comparator intervention in improving ADL on MCI (Figure 6B). The GRADE approach evaluated that the quality of evidence regarding ADL improvement was "critically low" (Table 3).
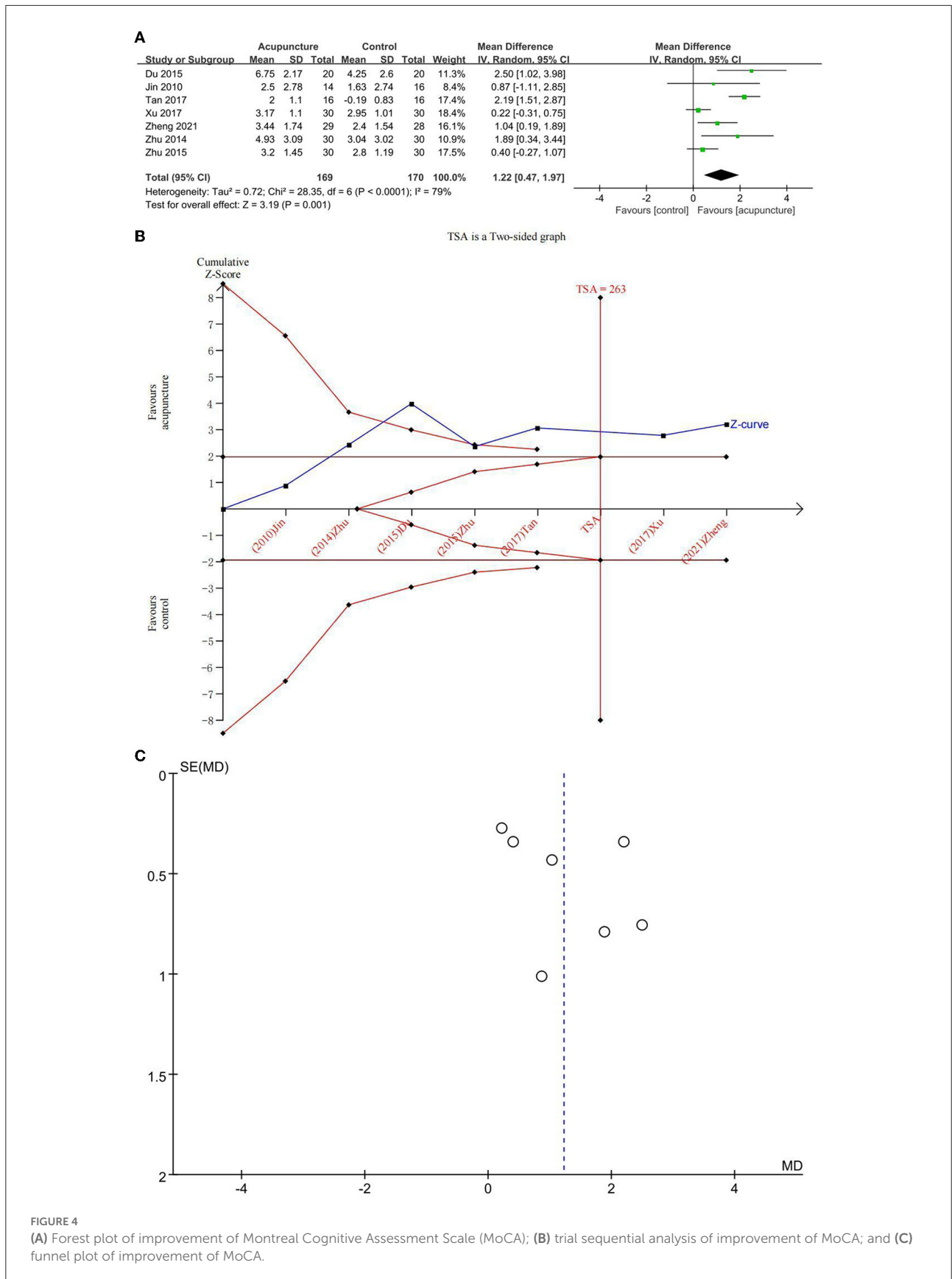
Quality of evidence

The GRADE approach was employed to measure the quality of evidence from 11 RCTs (Table 3). The analysis assessed the four outcome measurements: MMSE improvement, MoCA improvement, CMS improvement, and ADL improvement. Overall, pieces of evidence were ranked from low to critically low in quality. The results indicated that none of the outcomes had high-quality evidence, two (1/2, 50%) had low-quality evidence, and the other two (1/2, 50%) had critically low-quality evidence. The ROB and inconsistency were the main reasons for low-quality evidence.
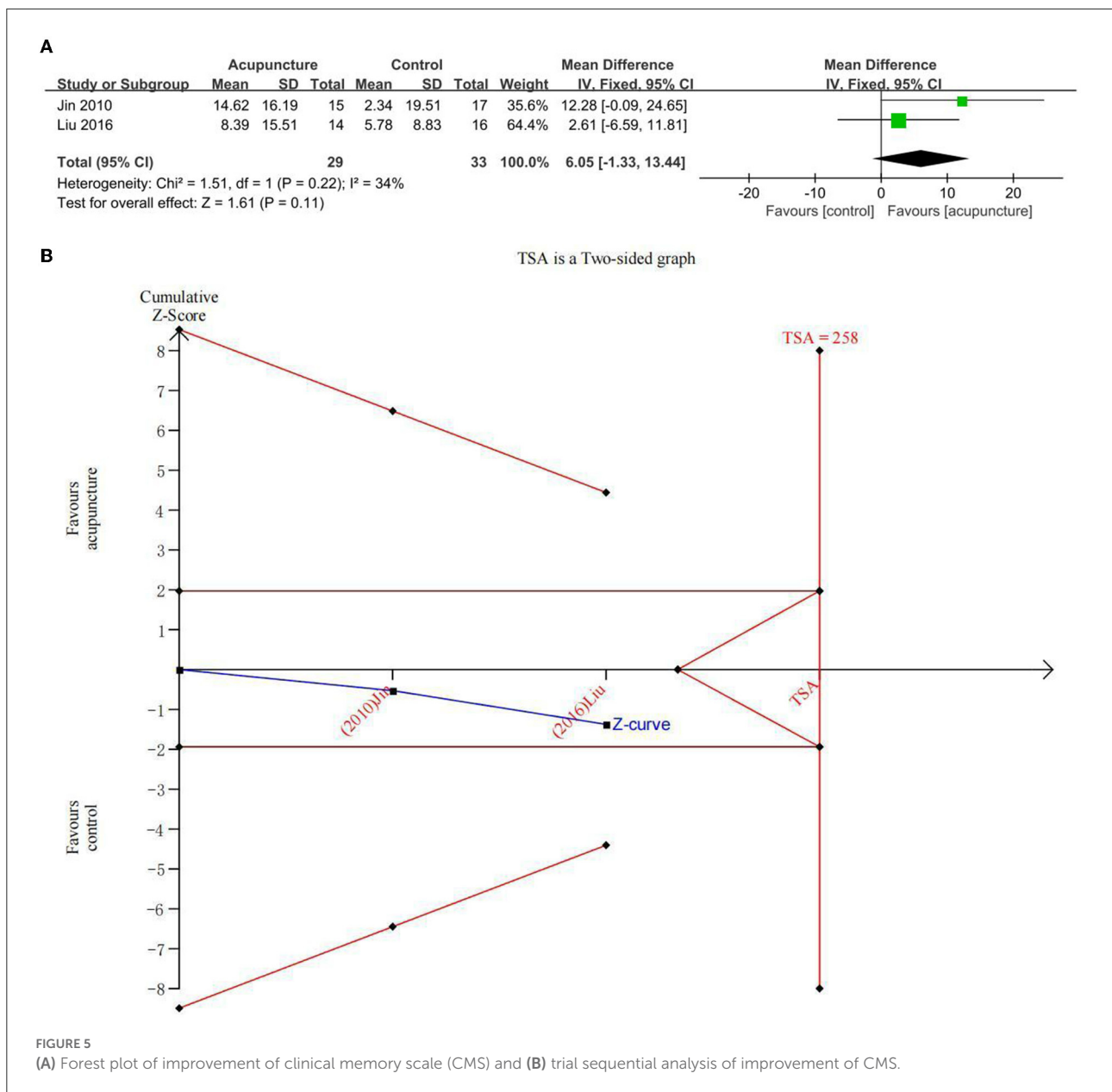
Discussion

Mild cognitive impairment, a vital stage between normal aging and dementia, is one of the key health issues for sufferers, families, and society of an aging population worldwide. In recent years, acupuncture has been widely applied for the treatment of MCI. However, previous studies (13, 16, 17, 44) have reported that more carefully designed studies are needed to confirm the efficacy of acupuncture for MCI; its effectiveness is uncertain because it is unknown whether the sample size is sufficient and the quality of the evidence is high. This review includes 11 studies with 602 participants to summarize and analyze the findings of acupuncture for MCI.

Summary of main findings

All RCTs had moderate methodological quality, as determined by the ROB 2.0 approach. These articles compared acupuncture with controls (including CM and SA). This MA

A

Study or Subgroup	Acupuncture Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Du 2015	6.75	2.17	20	4.25	2.6	20	11.3%	2.50 [1.02, 3.98]
Jin 2010	2.5	2.78	14	1.63	2.74	16	8.4%	0.87 [-1.11, 2.85]
Tan 2017	2	1.1	16	-0.19	0.83	16	17.4%	2.19 [1.51, 2.87]
Xu 2017	3.17	1.1	30	2.95	1.01	30	18.4%	0.22 [-0.31, 0.75]
Zheng 2021	3.44	1.74	29	2.4	1.54	28	16.1%	1.04 [0.19, 1.89]
Zhu 2014	4.93	3.09	30	3.04	3.02	30	10.9%	1.89 [0.34, 3.44]
Zhu 2015	3.2	1.45	30	2.8	1.19	30	17.5%	0.40 [-0.27, 1.07]
Total (95% CI)			**169**			**170**	**100.0%**	**1.22 [0.47, 1.97]**

Heterogeneity: Tau² = 0.72; Chi² = 28.35, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 3.19 (P = 0.001)

B

C

FIGURE 4
(A) Forest plot of improvement of Montreal Cognitive Assessment Scale (MoCA); **(B)** trial sequential analysis of improvement of MoCA; and **(C)** funnel plot of improvement of MoCA.

FIGURE 5

(A) Forest plot of improvement of clinical memory scale (CMS) and **(B)** trial sequential analysis of improvement of CMS.
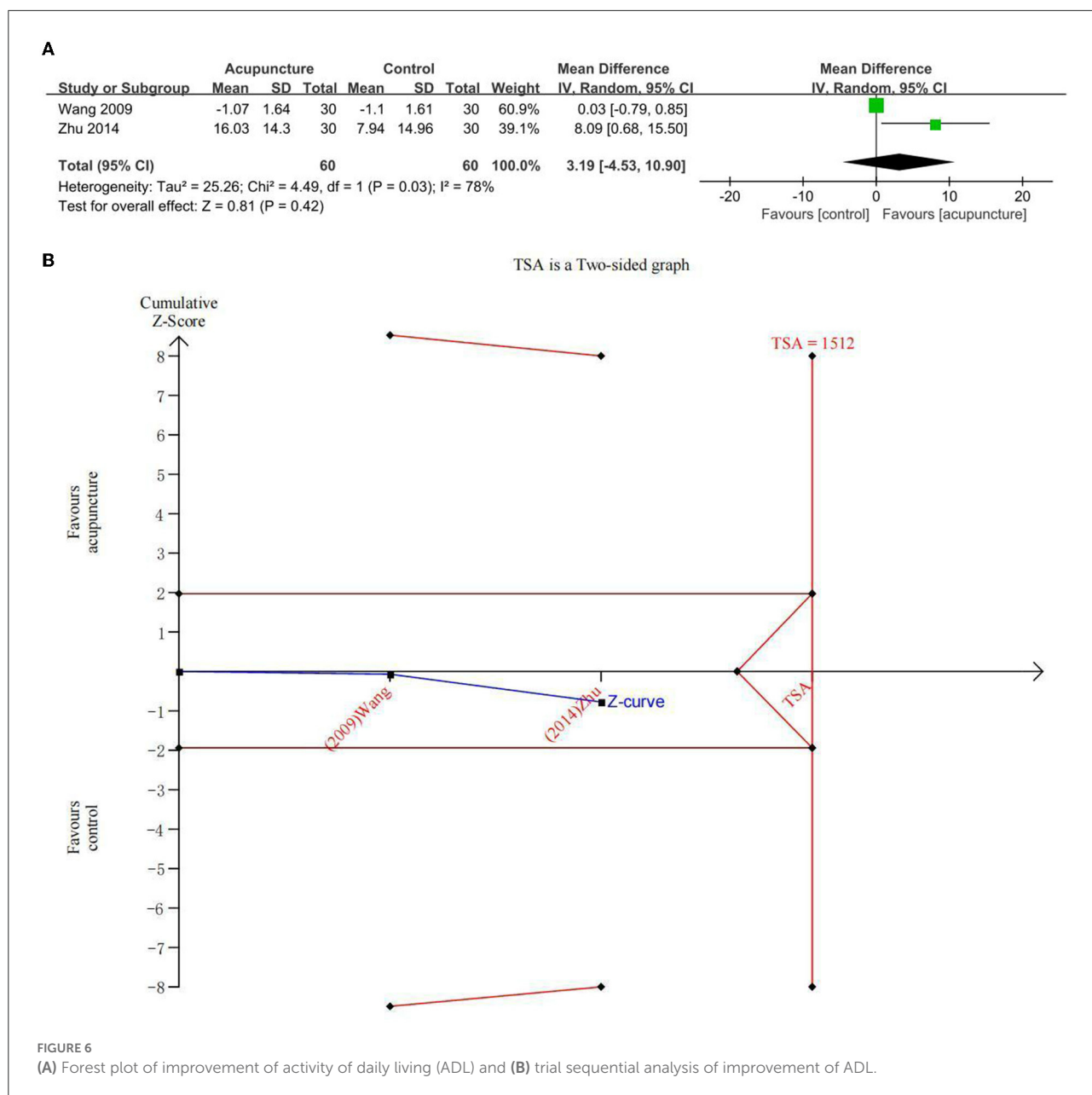
included four outcomes (improvement in MMSE, MoCA, CMS, and ADL) and illustrated the following results. For instance, for improving OCF, acupuncture demonstrated statistically significant differences in improving MMSE and MoCA scores; in subgroup analyses, acupuncture significantly improved in comparison with CM and SA. Meanwhile, TSA analysis demonstrated sufficient information size; however, pieces of evidence were ranked as low. Regarding CMS and ADL, we found no differences between acupuncture and CM in MA; TSA showed that the amount of information was insufficient and the quality of evidence was ranked as critically low.

Strengths and limitations

To our knowledge, this study is the first MA with TSA to certify acupuncture therapy for improving OCF, MF, and the activities of daily living with MCI. Meanwhile, we used ICC to measure the consistency of investigators. TSA was used to provide the required sample size and a conclusive result by maximizing the use of extracted data in the included trials. The GRADE approach was applied to evaluate the quality of evidence from the included RCTs. As a result, our findings might provide credible evidence, which may guide clinical treatment decisions and health policies on MCI. Nonetheless,

FIGURE 6
(A) Forest plot of improvement of activity of daily living (ADL) and **(B)** trial sequential analysis of improvement of ADL.

the following shortcomings should be considered. A significant limitation of this study is the low quality of evidence of the included RCTs. Meanwhile, the characteristics of the subjects and acupuncture methods of the included studies were insufficiently homogeneous. Furthermore, all included studies were carried out in China, which might potentially contribute to bias. Additionally, acupuncture has a long-term effect (45–49); however, no studies had a follow-up period, which is needed to illuminate the long-term effect of acupuncture on MCI.

Implications for clinical practice

Diagnostic and Statistical Manual of Mental Disorders (DSM) and Petersen's criteria are clinically and frequently applied for the diagnosis of MCI. Nevertheless, the Jak/Bondi diagnosis criteria are suggested to be better than the two due to their individual phenotype and accurate diagnosis. In detail, acupuncture utilizes a variety of acupoints. However, the most frequently applied acupoints are GV 20 and EX-HN1, the response sought is Deqi, the commonly used needle stimulation

is electroacupuncture, the needle type used is Hwato (0.35 and 25/40 mm), and the main frequency is daily. Despite the flaws of MA, all included RCTs demonstrated that acupuncture improved OCF in managing MCI. According to therapeutic effects, it should be considered in clinical practice when clinical decision-makers consider a selection. In addition, based on existing findings, acupuncture therapy is not inferior to CM in improving MF and ADL, thus, for patients who have MCI and are either unresponsive to CM or poly-pharmacy, acupuncture therapy should be administered.

Implications for future research

The findings of this study have a number of important implications for further research. First, the methodological quality of the included trials is moderate due to the problems with the randomization process, deviations from the intended interventions, and the selection of the reported results. Therefore, the randomized design, blinded method, and others of future RCTs may conform discreetly to the Cochrane ROB 2.0 tool. Meanwhile, this study collected and summarized acupuncture details according to STRICTA, and we found that most of the included RCTs neglected the details of other components, practitioner, and comparator interventions. As a result, STRICTA and Consolidated Standards of Reporting Trials (CONSORT) (50) should be considered as the standard criteria for future RCTs using acupuncture therapy. Moreover, TSA analysis indicated that the sample size was adequate in terms of acupuncture improving OCF; nevertheless, due to the limited quality of evidence, future high-quality research on this aspect should be implemented. Meanwhile, in this study, acupuncture can play a pivotal role in improving global cognitive function. To the best of our knowledge, the global cognitive function has been divided into memory, verbal, executive functions and so on. However, evidence for the efficacy of acupuncture on these specific cognitive functions is very scarce. Thus, the efficacy of acupuncture for certain MCI symptoms needs to be confirmed in the future. In addition, evidence for the improvement of ADL with acupuncture in patients with MCI needs to be explored in the future. Additionally, this study shows the short-term efficacy of acupuncture; however, the long-term efficacy of acupuncture for MCI remains unclear due to the paucity of follow-up studies. Therefore, future studies should expand the sample size, increase the study period, and extend a follow-up period to assess long-term sustained efficacy. Finally, the potential mechanisms of acupuncture for MCI should be studied further.

Conclusion

According to the existing research, the use of acupuncture in the treatment of patients with MCI demonstrated promising efficacy. However, due to low-quality evidence, further studies are still required to confirm the findings in the following years.

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

Conceptualization: ZY, LZ, and FL. Methodology, software, and writing—original draft preparation: ZY, YL, and CJ. Study selection and data extraction: MX and ZC. Quality assessment: XZ and CJ. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1091125/full#supplementary-material

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