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Wet cupping with rehabilitation training for upper-limb poststroke spasticity: A systematic review and meta-analysis of randomized controlled trials

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A R T I C L E I N F O

Keywords:
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Rehabilitation
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A B S T R A C T

Background: Upper-limb poststroke spasticity (PSS) negatively impacts on patients' quality of life. An increasing number of clinical trials have indicated that wet cupping with rehabilitation training is conductive to alleviate spastic muscle tone, thereby to improve upper-limb function. However, related evidence base is insufficient. This study systematically investigates the efficacy and safety of wet cupping with rehabilitation training on stroke patients with upper-limb spasticity.

Methods: Eight separate databases and two clinical trial registries were searched from their inception to December 6, 2022. Two reviewers extracted the data and assessed the quality of the literature, independently. The mean difference (MD) or risk ratio (RR) were used as measure of effect size in meta-analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used for the certainty of evidence.

Results: Eight randomized controlled trials (RCTs) were quantified for meta-analysis. The results indicated that in comparison with the control group, wet cupping with rehabilitation training was more effective in reducing modified Ashworth scale score (MD = −0.60, 95% CI: −0.74, −0.46; $P < 0.00001$) and the integral electromyography value of biceps muscle (MD = −4.71, 95% CI: −6.74, −2.67; $P < 0.00001$), but improving effective rate (RR = 1.28, 95% CI: 1.15, 1.41; $P < 0.00001$), Fugl-Myer Assessment score (MD = 4.84, 95% CI: 3.05, 6.64; $P < 0.00001$) as well as Barthel Index score (MD = 6.38, 95% CI: 2.20, 10.57; $P = 0.003$). However, no significant difference was found regarding the integral electromyography value of triceps muscle between groups (MD = 1.72, 95% CI: −2.05, 5.48; $P = 0.37$).

Conclusion: Wet cupping with rehabilitation training should be included in a comprehensive therapeutic regimen for stroke patients with upper-limb spasticity. However, these results need to be further verified by more RCTs with rigorous design and large sample size.

1. Introduction

As population aging becomes more conspicuous worldwide, stroke has been a huge public health challenge attributable to the

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second-leading cause of both death and disability globally [1,2]. More than one-quarter of stroke survivors will develop poststroke spasticity (PSS), particularly with upper-limb involvement, which impairs arm functional activity and patients' social participation [3,4]. The direct cost of care provision associated with PSS has risen fourfold compared with those without spasticity, bringing a heavy financial burden to the family and society [5].

At present, a wide range of antispastic regimens are available, and are sorted into pharmacological and nonpharmacological interventions [6]. Pharmacological interventions mainly refer to baclofen either taken orally or injected intrathecally. Although it was found that the use of baclofen is favorable to muscle hypertonia reduction, certain adverse events, such as long-term intake of baclofen inducing general muscle weakness, hepatorenal damage and paranesthesia, remain problematic. Nonpharmacological interventions include but are not limited to physiotherapy and surgery as well as complementary and alternative medicine such as acupuncture, traditional Chinese exercise, and cupping therapy. However, the long-term treatment duration and relatively low efficiency of physiotherapy and surgery-related high risks and expensive medical costs decrease patients' preference and compliance [6–8]. Thus, a better therapeutic regimen for upper-limb PSS is highly expected.

Cupping therapy is a commonly used traditional Chinese medicine nursing practice that normally utilizes flaming heating power to induce negative pressure inside the cup and make it easily attachable to the selected area to then produce hyperemia or hemostasis purposefully [9]. With the merits of noninvasive characteristics, relatively shorter treatment duration, fewer acupoint selections and lower treatment costs compared to acupuncture [10], cupping therapy has increased worldwide, especially among athletes with muscle discomfort [11,12]. Cupping is dry or wet, which depends on whether there is a need for the expulsion of blood. Wet cupping, also named blood pricking and cupping, is commonly used for PSS and other motor impairments (e.g., joint immobilization) [13,14]. Wet cupping has shown superior efficacy to dry cupping because it removes stagnant blood and toxins that are deemed the source of disease, whereas dry cupping works merely by diluting and redistributing pathogenic substances [15]. Although the antispastic mechanisms of wet cupping remain obscure, previous studies have indicated that wet cupping helps to suppress the inflammatory response and oxidative stress [16,17], restore blood supply to the skin and muscle [18] and alleviate stiffness in deep muscles [19], which potentially favors relaxation of muscle hypertonia and reconstruction of motor ability.

Rehabilitation is a process that integrates and coordinates the application of medical, social, educational, and vocational methods to alleviate physical, mental, and social impairments in disabled individuals and thereby to improve their quality of life [20]. Currently, rehabilitation strategies for PSS management are gradually developing. Previous research has indicated changes within peripheral muscle properties after stroke, including shortened and stiffer muscle tissues or an increased proportion of type I muscle fibers [21,22]. Notably, these alterations could be soothed by specific rehabilitation training (stretching) to prevent excessive muscle contracture and lessen spasticity as well as related pain [23,24]. In addition, other rehabilitation regimens, such as robot-assisted training, weight-supported treadmill training and task-oriented training, have also shown positive effects on spasticity alleviation [25]. These regimens are therefore widely used as an adjunct therapy for stoke with spasticity. Recently, poststroke rehabilitation has been developed by combining wet cupping and rehabilitation training. Increasing clinical evidence shows that such a combination has better antispastic effects than rehabilitation training alone or other combined therapies based on rehabilitation training [26–33]; however, relevant evidence is still insufficient.

Given the role of wet cupping with rehabilitation training in the management of upper-limb PSS, a critical systematic review and meta-analysis was designed to examine the efficacy and safety of this combination. Comparing wet cupping with rehabilitation training to wet cupping/rehabilitation training alone or other combinations (e.g., rehabilitation with baclofen). If we found a valid evidence base, then it might serve as a meaningful inspiration for practitioners to incorporate such a combination of the two therapies into the clinical management of upper-limb PSS and may provide patients with a safer, more effective, and more economical therapeutic option.

2. Methods

The protocol of this systematic review and meta-analysis has been registered at PROSPERO (registration ID: CRD42023394812). This review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34] and the Cochrane Handbook [35].

2.1. Criteria for inclusion and exclusion

The inclusion criteria were developed according to PICOS principles:

P, patients with upper-limb PSS would be enrolled (as diagnosed using any recognized diagnostic criteria); and no limitations to the age, gender, region, race, type of stroke, cause of disease and disease duration.

I, the intervention in the experimental group was wet cupping with rehabilitation training (i.e., combined with another therapy based on the treatment of the control group).

C, the control group received wet cupping or rehabilitation training alone or other combined therapies based on rehabilitation.

O, the primary outcome indicator was upper-limb spasticity. The effective rate (ER), scales used to assess upper-limb motor function and activity daily living, the integral electromyography (iEMG) value and adverse events were employed as the secondary outcome indicators.

S, the study design included randomized controlled trials (RCTs).

The exclusion criteria were as follows: (1) non-RCTs; (2) no definite diagnostic criteria or upper-limb spasticity caused by reasons other than stroke, such as brain traumatic injury, spinal cord injury or tumor; (3) no common interventions between the experimental and control groups; (4) incomplete outcome data; (5) duplicate publications; and (6) full text was not available.

2.2. Literature searches

Eight databases were searched from their inception to December 6, 2022, including PubMed, Embase, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure Database, *Wanfang* Database, Chinese Scientific Journals Database and Chinese Biomedical Literature Database. Meanwhile, we manually searched the Chinese Clinical Trials Registry and the US Health Ongoing Trials Registry (www.%20ClinicalTrials.%20gov) to identify potentially eligible trials. Two reviewers independently identified the gray literature and reference list of eligible studies. There was no restriction on language. Search terms were related to stroke, spasticity and cupping therapy or wet cupping. The complete search strategy is available in the **Supplementary file**.

2.3. Literature screening and data extraction

Two reviewers (TYS and STS) independently performed literature screening and crosschecked the outcomes from eligible articles that met the above requirements. Disagreements were evaluated by a third reviewer (JXW). The corresponding author was contacted by email if the required information was incomplete or obscure.

Characteristics of enrolled studies were extracted via predesigned data checklists, including article title, author information, publication year, country/region, participants' characteristics, sample size, details of interventions (e.g., modes, frequency, and duration), and reported outcomes. After extraction, two reviewers crosschecked again to ensure the accuracy of the included data.

2.4. Outcome measures

It is known that PSS negatively impacts the flexors of the upper limbs and the extensors of the lower limbs, while the incidence of upper-limb spasticity is much higher than that of lower-limb spasticity, presenting as a marked increase in muscle tone during movement [3]. Spasticity limits voluntary and coordinated movement of the upper limb and thereby impairs patients' motor functions, particularly fine motor function, which ultimately decreases their daily life abilities, such as dressing, bathing, and eating. Clinically, the modified Ashworth scale (MAS) is the most used scale for spasticity assessment, and the Fugl-Meyer Assessment (FMA) and Barth Index (BI) are frequently applied for the evaluation of motor function and activities of daily living, respectively [36]. The primary outcome indicator was the MAS, with higher scores indicating serious spasticity (range 0–4 points). The secondary outcome indicators include the ER; adverse events; the FMA, which covers five domains, of which assessment of motor function mainly includes mobility, coordination, and reflex action of the shoulder, elbow, wrist, and hand, with high scores indicating improved motor function (range 0–100 points). Likewise, the BI outcome includes higher scores indicating less disability (range 0–100 points). In addition, given that most outcome indicators (e.g., MAS, FMA, BI) are relatively subjective, and considering that there is still a lack of exploration of antispastic mechanisms, the iEMG value, with higher scores indicating worse spasticity, was also involved. All included studies were required to report the primary outcome.

2.5. Risk of bias assessment of the included studies

The quality of the included studies was evaluated by two trained reviewers using the Cochrane Collaboration risk of bias tool. This study checked for selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias [37]. Conflicts were resolved by discussion or negotiation with the third reviewer. Each item in the included study was then rated as "low risk", "high risk", or "unclear". RevMan 5.4 software was employed to create the risk of bias summary and graph.

2.6. Data analysis

Data synthesis was performed using Revman 5.4 software between reviewers. The risk ratio (RR) with a 95% confidence interval (CI) was calculated for dichotomous data, while the mean difference (MD) or standard mean difference (SMD) with 95% CI was calculated for continuous data. If the reported outcomes were measured by the same scale, MD was used to synthesize the effect size; otherwise, SMD was implemented. The combined result of multiple studies was considered statistically significant at the $P < 0.05$ level. MAS data were calculated as continuous data. Heterogeneity was assessed by the chi-square test and I^2 statistic. When $I^2 \leq 50\%$ and $P \geq 0.1$, the fixed-effects model was used for data synthesis; otherwise, the random-effects model was used.

Subgroup analysis and sensitivity analysis were expected to explore the source of heterogeneity [38]. Depending on the data permitted, we conducted subgroup analysis based on the following aspects that may lead to heterogeneity: (1) treatment mode; (2) treatment frequency (twice or three times a week); and (3) total duration of treatment (two weeks, four weeks or twelve weeks). Sensitivity analysis was performed to test the robustness of the results by excluding studies one by one. If the number of included studies was less than 10, publication bias tests were not required [39].

2.7. Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used for the certainty of evidence [40], and GRADE profiler 3.6 software was used for the evidence summary. The evidence of RCTs was the highest quality, and each outcome was assessed in terms of five factors that may reduce the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence was then classified as "high", "moderate", "low" or "very low".

3. Results

3.1. Search results

A total of 437 records were identified, of which 64 duplicates were removed, resulting in 373 unique records. By initial screening of the titles and abstracts, 349 irrelevant studies were excluded. Among the remaining 24 studies, eight studies met the eligibility criteria

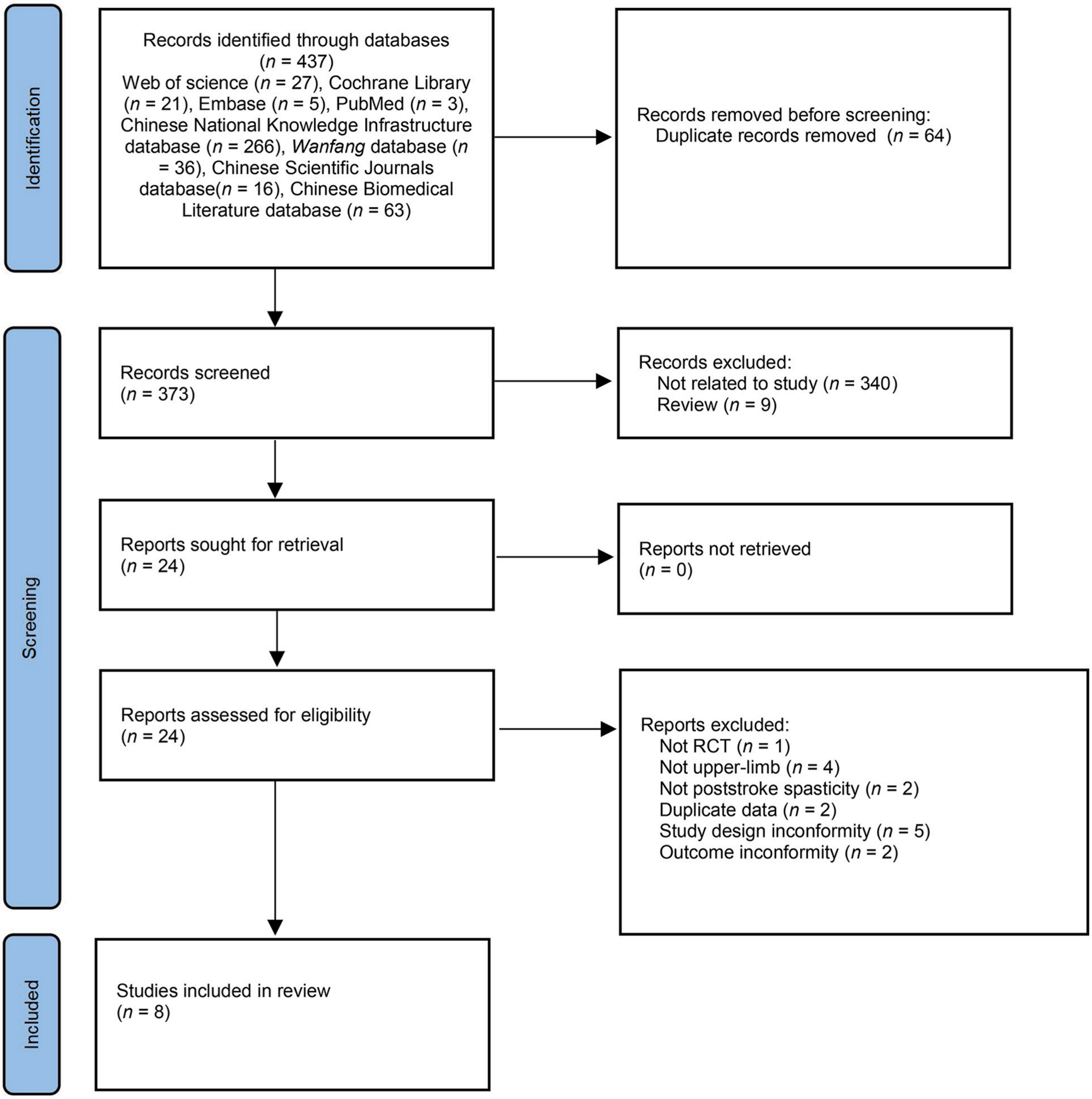

Fig. 1. Flow diagram of literature screening.

Table 1
The characteristics of included studies.

Study ID	Time	Sample size		Type of stroke	Age of patients	Outcomes	Treatment		Treatment duration	Treatment frequency	Stimulating points
		E	C				E	C			
Wet cupping + rehabilitation training vs. rehabilitation training alone											
Cheng ZQ [26]	2022	30	30	Ischemic stroke, hemorrhagic stroke	60.97 ± 9.53	①②③④⑤	Wet cupping + rehabilitation training	Rehabilitation training	Four weeks	Three times a week	Positive reaction points (tender points) on the biceps muscle
Li YY [27]	2019	48	48	Ischemic stroke	63.90 ± 10.00	①③⑥⑦	Wet cupping + rehabilitation training	Rehabilitation training	Twelve weeks	Three times a week	Positive reaction points on the biceps muscle
Wet cupping + rehabilitation training vs. rehabilitation training with other interventions											
Zhan ZL [28]	2018	52	51	Ischemic stroke, hemorrhagic stroke	56.42 ± 6.18	①②③⑥	Wet cupping + rehabilitation training + Acupuncture	Rehabilitation training + Acupuncture	Four weeks	Three times a week	Positive reaction points + acupoints mainly surrounding the affected joints (e.g., LI15-*Jianyu*, SJ14-*Jianliao*, SI9-*Jianzhen*, LI11-*Quchi*, SI10-*Tianjing*, SJ5-*Waiguan*, LI4-*Hegu*)
Xi ML [29]	2018	30	30	Ischemic stroke, hemorrhagic stroke	59.50 ± 7.95	①②③	Wet cupping + rehabilitation training + Acupuncture	Rehabilitation training + Acupuncture	Two weeks	Three times a week	Positive reaction points + acupoints mainly surrounding the affected joints (e.g., LI4-*Hegu*, LI11-*Quchi*, LI15-*Jianyu*, SJ14-*Jianliao*)
Ma XH [30]	2021	30	30	Ischemic stroke, hemorrhagic stroke	62.45 ± 6.78	①②③	Wet cupping + rehabilitation training	Rehabilitation training + baclofen	Four weeks	Twice a week	Positive reaction points on the biceps muscle
Huang ZQ [31]	2018	30	30	Ischemic stroke, hemorrhagic stroke	59.50 ± 7.48	①②③④⑤	Wet cupping + rehabilitation training	Rehabilitation training + baclofen	Four weeks	Twice a week	Positive reaction points on the biceps muscle
Li N [32]	2018	29	29	Ischemic stroke, hemorrhagic stroke	63.90 ± 10.60	①③	Wet cupping + rehabilitation training	Rehabilitation training + baclofen	Four weeks	Twice a week	Positive reaction points on the biceps muscle
Chen JY [33]	2017	43	43	Ischemic stroke, hemorrhagic stroke	60.80 ± 7.00	①②③④⑤	Wet cupping + rehabilitation training	Rehabilitation training + baclofen	Four weeks	Twice a week	Positive reaction points on the biceps muscle

Note: E, experimental group; C, control group; ① modified Ashworth scale (MAS); ② effective rate (ER); ③ Fugl-Myer Assessment (FMA); ④ integral electromyography (iEMG) value of biceps muscle; ⑤ iEMG value of triceps muscle; ⑥ Barthel Index (BI); ⑦ adverse events.

and were finally included after assessing the full text [26–33]. The literature screening process is shown in the PRISMA flow diagram (Fig. 1).

3.2. Study characteristics

A total of eight RCTs published from 2017 to 2022 were included, involving 583 patients with upper-limb PSS (292 in the experimental group and 291 in the control group). The average age of the patients ranged from 40 to 80, and the duration of stroke ranged from one to six months. Seven studies set no restriction on the stroke type [26,28–33], whereas in one study, only ischemic stroke was enrolled [27]. All studies were observed at pre- and posttreatment time points. No long-term follow-up was performed [26–33]. One study mentioned adverse events [27]. Another study reported shedding data primarily due to poor patient compliance or reoccurrence of stroke, including four cases in the control group and three in the other group [28]. The included studies involved comparisons of wet cupping with rehabilitation training versus rehabilitation training alone [26,27] and wet cupping with rehabilitation training versus rehabilitation training with acupuncture [28,29] or baclofen [30–33].

The positive reaction point (tender point) is most used in wet cupping treatment. Generally, with the point as the center, the skin was quickly pricked (approximately 5–10 times) by a tiny needle to a depth of 2–4 mm. Then, a cup was attached, and blood was discharged (no more than 10 ml per time). Although rehabilitation training was highly valued during the treatment of upper-limb spasticity, the rehabilitation strategies varied, mainly including muscle stretching, anti-spasticity position, active or passive exercise training, and the Bobath concept. Of note, muscle stretching was the most used among these eight studies. The treatment frequency was set at twice a week in four studies [30–33] and three times in the rest [26–29]. For treatment duration, one study lasted two weeks [29], six studies lasted four weeks [26,28,30–33], and one study lasted twelve weeks [27]. All studies were compared with the

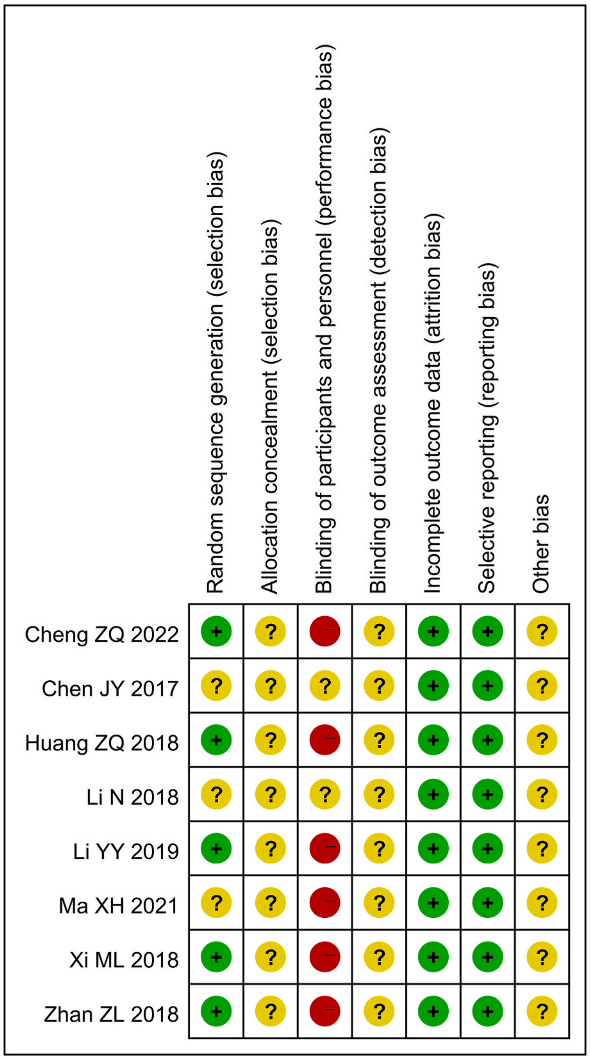

Fig. 2. Risk of bias summary. Judgments about the risk of bias for each item of the included studies are shown.

baseline information of the patient [26–33] and found no significant differences. Detailed information on the included studies is presented in Table 1.

3.3. Risk of bias of included studies

The results of the risk of bias assessment are presented in Figs. 2 and 3. Random sequence generation was mentioned in all included studies, of which five studies used random numerical tables [26–29,31], but the rest did not mention the details of randomization [30, 32,33]. Additionally, the blinding of participants and personnel was hard to implement, attributable to the characteristics of the intervention (wet cupping and rehabilitation). In the eight studies [26–33], the predetermined outcome indicators within the methodology section were completely reported in the results section, hinting at no selective reports. One of the studies reported the shedding data and potential causes, which had no impact on the final outcome [28]. The data outcomes of all studies were complete [26–33]. The side of allocation concealment, blinding of outcome assessment and other biases were unclear. Thus, most of the included studies were unclear or high risk of bias.

3.4. Primary outcomes

3.4.1. Effect on the MAS

All enrolled studies with 583 patients used the MAS to evaluate the degree of upper-limb PSS pre- and posttreatment. High heterogeneity was found among the studies ($I^2 = 57\%$, $P = 0.02$). Thus, a random-effects model was used. The results of the meta-analysis revealed that compared with the control group, wet cupping with rehabilitation training was more effective in decreasing the MAS score (MD = −0.60, 95% CI: −0.74, −0.46; $P < 0.00001$) (Fig. 4).

3.4.2. Subgroup analysis

Due to high heterogeneity among the eight studies, we conducted a subgroup analysis to explore the source of heterogeneity and examined whether the results were influenced by combination mode, treatment frequency, or treatment duration.

In terms of combination mode, we found that wet cupping with rehabilitation training (MD = −0.40, 95% CI: −0.77, −0.03; $P = 0.04$), wet cupping with rehabilitation training and acupuncture (MD = −0.36, 95% CI: −0.56, −0.16; $P = 0.0006$) and wet cupping with rehabilitation training (MD = −0.73, 95% CI: −0.83, −0.62; $P < 0.00001$) were superior to rehabilitation training alone, rehabilitation training with acupuncture, and rehabilitation training with baclofen for treating upper-limb PSS, respectively.

Regarding the treatment frequency, low heterogeneity was found within the subgroups (both are $I^2 = 0\%$, $P > 0.1$), indicating that the differences in treatment frequency might be the source of heterogeneity between studies. We found that wet cupping with rehabilitation training surpassed the control group in reducing the MAS score of the upper limb when the treatment frequency was set at two (MD = −0.73, 95% CI: −0.83, −0.62; $P < 0.00001$) or three times a week (MD = −0.38, 95% CI: −0.54, −0.22; $P < 0.00001$).

For the treatment duration, we found no significant difference between the subgroups during the two-week intervention (MD = −0.52, 95% CI: −1.15, 0.11; $P = 0.10$). However, with the extension of treatment duration, i.e., four weeks of treatment (MD = −0.60, 95% CI: −0.77, −0.43; $P < 0.00001$) and twelve weeks of treatment (MD = −0.58, 95% CI: −0.92, −0.24; $P = 0.0007$), the experimental group exerted better effects in reducing the MAS score than the control group. The results of subgroup analyses are summarized in Table 2, and related forest plots are presented in the **Supplementary file**.

3.4.3. Sensitivity analysis

Sensitivity analysis was performed to recombine the data by excluding each of the included studies one by one. The outcome indicator included eight studies, and after excluding one of them, the combined results of the remaining studies were all statistically significant. The original pooled results were barely impacted by a single study (**Supplementary file**). Sensitivity analysis could partly mean that the result was stable.

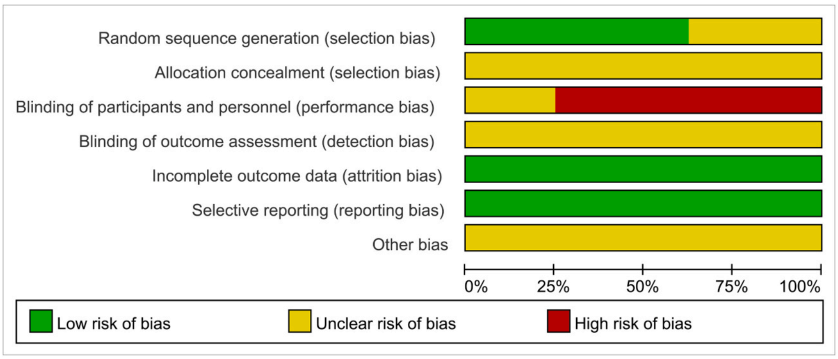

Fig. 3. Risk of bias graph. Judgments of the risk of bias percentage of the included studies are shown.

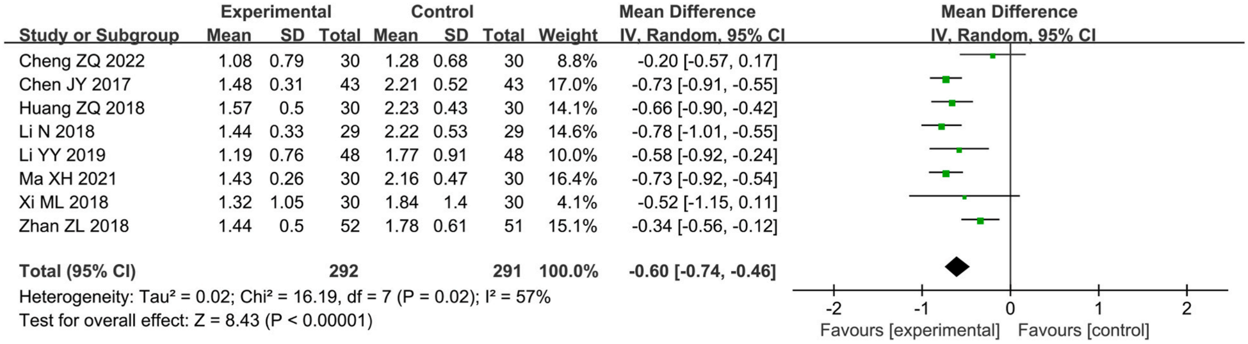

Fig. 4. The forest plot of effect on MAS score. MAS: modified Ashworth scale.

Table 2
Subgroup analysis of MAS.

Subgroups	No. of studies	Effect size (95% CI)	*P*-value	I^2	*P*-heterogeneity
Combination mode					
Wet cupping with rehabilitation training vs. rehabilitation training alone	2	−0.40 (−0.77, −0.03)	0.04	55%	0.14
Wet cupping with rehabilitation training and acupuncture vs. rehabilitation training with acupuncture	2	−0.36 (−0.56, −0.16)	0.0006	0%	0.59
Wet cupping with rehabilitation training vs. rehabilitation training with baclofen	4	−0.73 (−0.83, −0.62)	<0.00001	0%	0.91
Treatment frequency					
Twice a week	4	−0.73 (−0.83, −0.62)	<0.00001	0%	0.91
Three times a week	4	−0.38 (−0.54, −0.22)	<0.00001	0%	0.46
Treatment durations					
Two weeks	1	−0.52 (−1.15, 0.11)	0.10	/	/
Four weeks	6	−0.60 (−0.77, −0.43)	<0.00001	69%	0.007
Twelve weeks	1	−0.58 (−0.92, −0.24)	0.0007	/	/

Note: CI, confidence interval.

3.5. Secondary outcomes

3.5.1. Effect on the ER

Six studies calculated the ER of wet cupping with rehabilitation training for upper-limb PSS in 429 patients. A fixed-effects model was employed because no statistically significant heterogeneity existed among the studies ($I^2 = 0\%$, $P = 0.96$). The results indicated that compared with the control group, wet cupping with rehabilitation training could effectively improve the ER of upper-limb PSS (RR = 1.28, 95% CI: 1.15, 1.41; $P < 0.00001$) (Fig. 5).

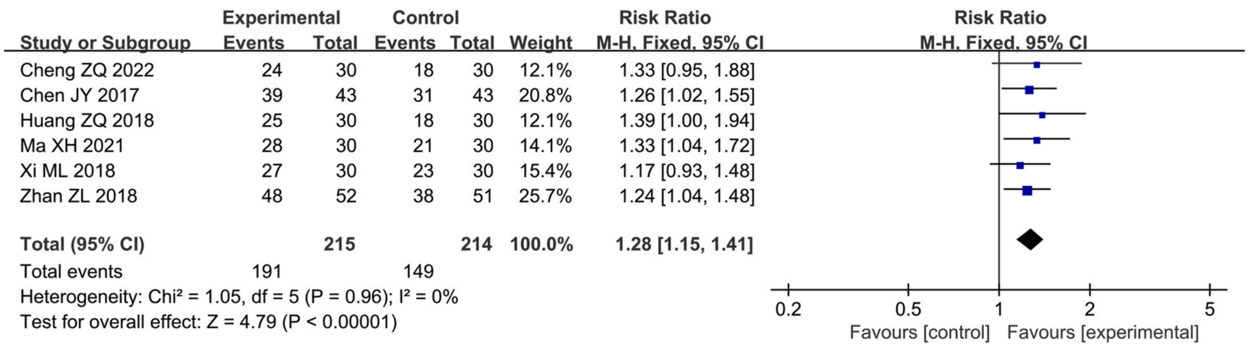

Fig. 5. The forest plot of effect on ER. ER: effective rate.

3.5.2. *Effect on the FMA*

All enrolled studies reported the FMA outcome, of which one study was excluded [32] because it evaluated the whole-limb FMA. Seven studies with 525 patients were thus analyzed and presented with low heterogeneity ($I^2 = 32\%$, $P = 0.18$). The results revealed that wet cupping with rehabilitation training was superior to the control group in increasing FMA scores of the upper limb (MD = 4.84, 95% CI: 3.05, 6.64; $P < 0.00001$) (Fig. 6).

Subgroup analysis of FMA by combination mode demonstrated that wet cupping with rehabilitation training (MD = 7.14, 95% CI: 1.42, 12.86; $P = 0.01$), wet cupping with rehabilitation training and acupuncture (MD = 3.19, 95% CI: 1.23, 5.15; $P = 0.001$) and wet cupping with rehabilitation training (MD = 5.20, 95% CI: 2.18, 8.23; $P = 0.0007$) were more effective than rehabilitation training alone, rehabilitation training with acupuncture, and rehabilitation training with baclofen in improving motor functions of the upper limb, respectively (Fig. 6).

3.5.3. *Effect on the BI*

The results showed that wet cupping with rehabilitation training could effectively improve activities of daily living that were assessed by BI compared to the control group (MD = 6.38, 95% CI: 2.20, 10.57; $P = 0.003$) (Fig. 7).

3.5.4. *Effects on the iEMG of the upper limb*

Wet cupping with rehabilitation training effectively reduced the iEMG value of the biceps muscle (MD = −4.71, 95% CI: −6.74, −2.67; $P < 0.00001$) (Fig. 8), indicating that flexor spasticity was relieved. However, it had no effect on the iEMG value of the triceps muscle (MD = 1.72, 95% CI: −2.05, 5.48; $P = 0.37$) (Fig. 9).

3.5.5. *Adverse events*

Only one study reported wet cupping-related adverse events in the management of upper-limb PSS [27]. Two patients reported mild subcutaneous ecchymosis at the site of wet cupping, which was absorbed gradually within one week and had no impact on daily life in patients.

3.5.6. *Sensitivity analysis of secondary outcomes*

Sensitivity analysis of ER and FMA showed that none of the studies confounded the result significantly; thus, the result seemed to be robust (**Supplementary file**).

3.6. *Evidence evaluation*

The certainty of the evidence was evaluated, and the results showed that "ER" and "FMA" were rated as moderate quality evidence because of the risk of bias. Three outcomes were rated as low-quality evidence: "MAS" due to the risk of bias and inconsistency and "BI" and "iEMG value of biceps muscle" due to the risk of bias and imprecision. The iEMG value of triceps muscle was rated as very low-quality evidence. A summary of the results of the GRADE classification is shown in Table 3.

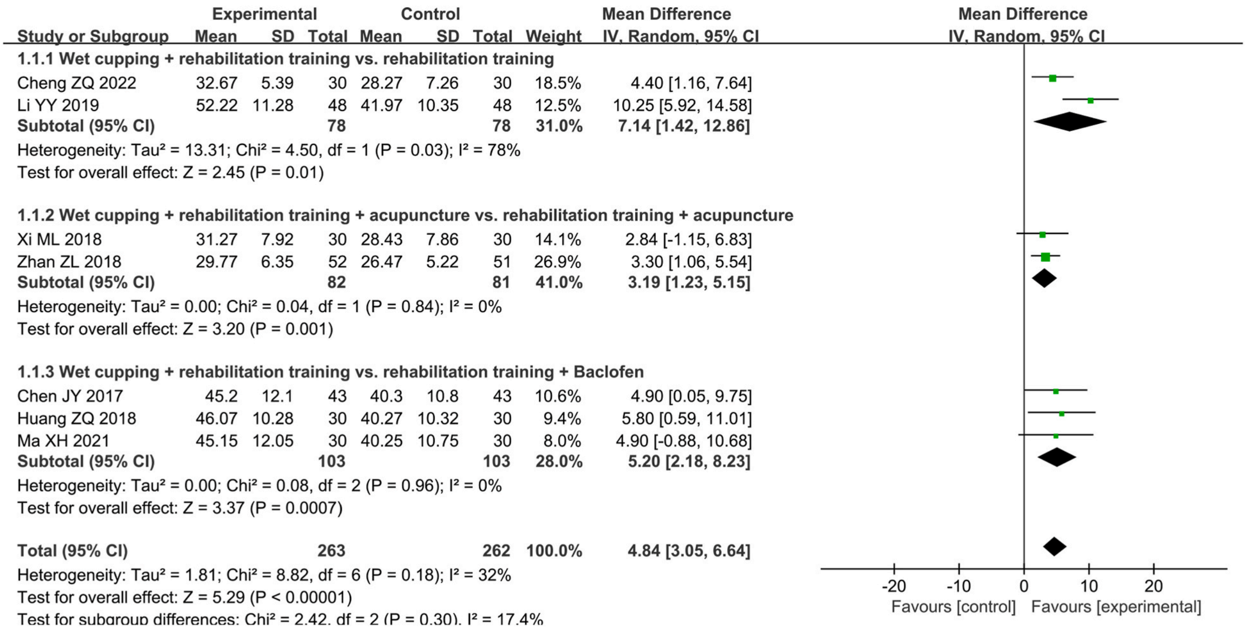

Fig. 6. The forest plot of subgroup analysis of FMA score. FMA: Fugl-Myer Assessment.

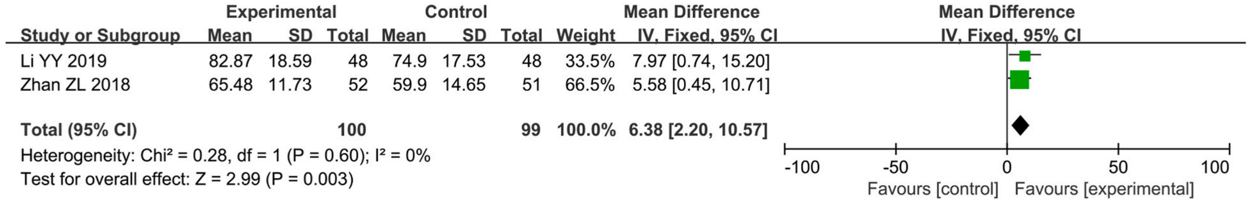

Fig. 7. The forest plot of effect on BI score. BI: Barthel Index.

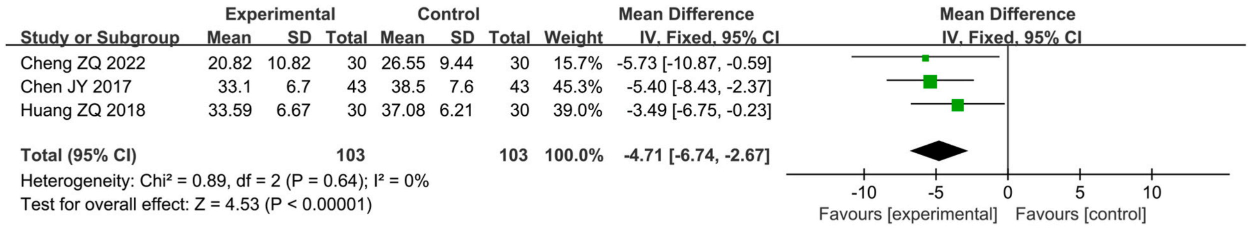

Fig. 8. The forest plot of effect on the iEMG value of biceps muscle. iEMG: integral electromyography.

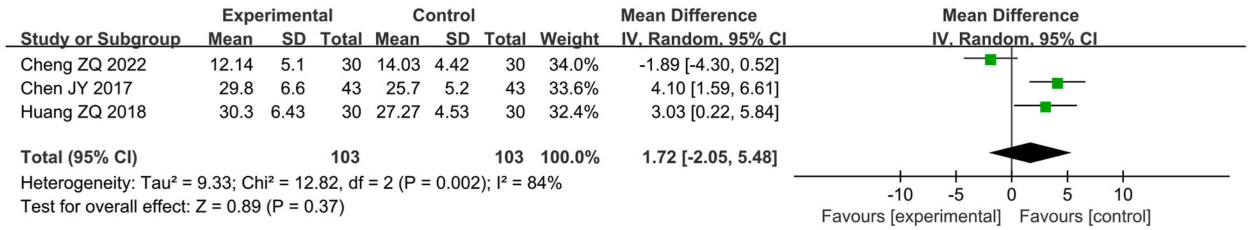

Fig. 9. The forest plot of effect on the iEMG value of triceps muscle. iEMG: integral electromyography.

4. Discussion

4.1. Summary of evidence

Although an increasing number of clinical trials have advocated the preferable effects of wet cupping with rehabilitation training for upper-limb PSS, little is known about the best combination mode, the timing, the frequency and the duration of treatment and etc. Thus, eight RCTs from 437 studies that met the inclusion criteria were analyzed in this systematic review and meta-analysis, aiming to provide new evidence-based insights for practitioners to incorporate such combination into clinical settings.

This systematic review and meta-analysis indicated that wet cupping with rehabilitation training as a part of a comprehensive therapeutic protocol could effectively alleviate upper-limb spasticity (MAS, iEMG value of biceps muscle) and improve motor function (FMA) and patients' quality of life (BI). Subgroup analysis indicated that treatment sessions held two or three times a week for at least four weeks potentially enhanced antispastic effects. Notwithstanding, the above results should be treated with caution due to relatively lower evidence quality, moderate to very low certainty of evidence, which is may be attributed to the high risk of bias of the included studies and the inconsistency and imprecision of the results.

4.2. Finding and theoretical basis

Although the pathogenesis of PSS is not fully understood, recent studies have indicated that the plausible primary mechanism for PSS is weakened inhibitory control from the lateral reticulospinal tract to the spinal stretch reflex. Alternatively, the secondary factors are alterations within the intraspinal network process (e.g., spontaneous/subthreshold discharging of spinal motoneurons) and the peripheral muscle properties (e.g., increased proportion of connective tissue but decreased amount and shortened length of sarcomeres) [41,42]. In traditional Chinese medicine, PSS belongs to the category of meridian-tendon disorders, and the pathological mechanism is disturbance or stagnation of qi and blood, with pathogenic factors lingering in the meridian-tendon, or dystrophy of muscle and tendon, and presenting a series of motor impairments [43]. For the acupoint selection of wet cupping, normally, *Dushu* (BL16), *Geshu* (BL17), *Xuehai* (SP10) and *Ashi* points are used alternatively for the removal of stagnant blood and pathogenic factors. In particular, the *Ashi* point is regarded as the primary stimulating point for muscle disorders and pain syndrome, which is, to a great degree, similar to the tender point used in the enrolled studies. Tender points originate from the theory of soft tissue and muscles. They

Table 3
GRADE classification for evidence evaluation.

outcomes	No. of studies	Quality assessment						No. of patients		Effect size (95% CI)		Certainty of the evidence (GRADE)
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	E	C	RR	MD	
MAS	8	RCTs	Serious[1]	Serious[2]	No serious	No serious	None	292	291	–	−0.60 (−0.74, −0.46)	⊕⊕◯◯ Low
ER	6	RCTs	Serious[1]	No serious	No serious	No serious	None	215	214	1.28 (1.15, 1.41)	–	⊕⊕⊕◯ Moderate
FMA	7	RCTs	Serious[1]	No serious	No serious	No serious	None	263	262	–	4.84 (3.05, 6.64)	⊕⊕⊕◯ Moderate
BI	2	RCTs	Serious[1]	No serious	No serious	Serious[3]	None	100	99	–	6.38 (2.20, 10.57)	⊕⊕◯◯ Low
iEMG value of biceps muscle	3	RCTs	Serious[1]	No serious	No serious	Serious[3]	None	103	103	–	−4.71 (−6.74, −2.67)	⊕⊕◯◯ Low
iEMG value of triceps muscle	3	RCTs	Serious[1]	Very serious[2]	No serious	Serious[3]	None	103	103	–	1.72 (−2.05, 5.48)	⊕◯◯◯ very low

Note: E, experimental group; C, control group; CI, confidence interval; RR, risk ratio; MD, mean difference; modified Ashworth scale; ER, effective rate; FMA, Fugl-Myer Assessment; iEMG, integral electromyography; BI, Barthel Index; RCTs, randomized controlled trials; [1] Lack of blinding; [2] I^2 value of the combined results was large and high heterogeneity; [3] Small sample size and the confidence intervals were wide.

are within the muscular attachments linked to the skeleton and are sensitive to palpation, and characterized by the presence of taut bands and the generation of a referral pattern of pain [44]. It was found that intervention at tender points might contribute to alterations in muscle properties [45] and thereby alleviate muscle tone.

Subgroup analysis indicated that the antispastic effect of combination therapy (wet cupping with rehabilitation training) was superior to that of a single therapy (rehabilitation training alone), which was consistent with previous views [20,46]. Moreover, different combination modes, for instance, the basic intervention (rehabilitation training) in conjunction with acupuncture or baclofen, may lead to different outcomes. The reason, of course, is multifaceted. Previous acupuncture studies have focused mainly on the regulation of the central nervous system, which can be summarized as follows: increasing microcirculation of the peri-infarct cortex, reconstructing the balance between interhemispheric inhibition, and facilitating the balance between excitatory and inhibitory neurotransmitters [36]. Given that the changes in peripheral muscle properties are considered the secondary mechanism of PSS, as well as the positive effects of wet cupping on the adjustment of peripheral muscles [18,19], these mechanism studies partially explain why the antispastic effect of wet cupping with acupuncture is better than acupuncture alone, based on their mutual modulations to the central and peripheral aspects. Likewise, subgroup analysis also indicated that based on rehabilitation training, the antispastic effect of wet cupping seemed better than that of baclofen. As reported, the dosage of baclofen needs to increase gradually over time to achieve a sustained effect on hypertonia reduction [47]. However, a long duration of baclofen consumption may lead to drug resistance and derivative adverse events [48]. In comparison, wet cupping acts directly on the affected muscle, with the merits of fewer adverse events and more targetability, which ultimately produces favorable regulations on the peripheral muscles. Although no definite conclusions can be drawn regarding the relatively limited evidence base, this combination mode might provide noteworthy insight for the management of upper-limb PSS.

Subgroup analysis indicated that wet cupping with rehabilitation training two or three times a week was superior to rehabilitation training alone or other combinations. However, twice a week intervention appears to be more effective than three times in relieving upper-limb spasticity. A possible explanation is that relatively strong and frequent stimulation in a short span tends to cause pain sensitivity and treatment tolerance [49], which in turn aggravates the degree of spasticity. In addition, our results supported the view that longer treatment durations (e.g., four or twelve weeks) may be linked with better antispastic effects, largely attributed to the cumulative effect of the intervention.

In this review, we analyzed the heterogeneity for outcome indicators with high heterogeneity. Through subgroup analyses of MAS, we found that the difference in intervention frequency may be a source of heterogeneity, with lower heterogeneity within each subgroup after grouping. Other indicators presented low heterogeneity and stability in sensitivity analysis, supporting the hypothesis that wet cupping and rehabilitation training yielded more improvements in treatment efficacy (elevated ER), upper-limb motor function (increased FMA score) and activities of daily living (increased BI score) in stroke patients than rehabilitation training alone or other combinations. The iEMG value was obviously decreased in the biceps muscle rather than the triceps, indicating that the muscle tone of the flexor of the upper limb was decreased. Alleviation of muscle tone is conducive to reconstructing the balance between the agonist and antagonist muscles and thereby favors the coordination of motor function and daily life activities. In addition, only one study mentioned wet cupping-related adverse events—subcutaneous ecchymosis, which was absorbed after one week and had no impact on the patient's daily life [27].

4.3. Limitations of review

This study also has some limitations. First, the overall quality of the included studies was not optimal, and methodological heterogeneity may exist, possibly caused by no description of allocation concealment and difficult implementation of blinding during the experimental phase. Second, certain differences exist among the included studies, including the treatment frequency, the duration and the differences in combination mode (nonuniform control groups), which in turn lead to clinical heterogeneity and difficult comparisons. Third, relatively subjective assessment methods (e.g., MAS-based spasticity evaluation criteria) as well as the absence of long-term follow-up to some extent limit the certainty of the results. There was no comparison between wet cupping with rehabilitation and wet cupping in the included studies. Setting wet cupping alone as the control group in future studies may provide more chances to verify the differences in clinical efficacy between combined therapy and single therapy. All included studies were conducted in China, which means that the research ethnicity and region were single. These underlying problems, to a certain extent, hinder us from systematically and objectively assessing the true efficacy of wet cupping with rehabilitation for upper-limb PSS. Thus, more rigorous study designs, such as sham control, standardized treatment protocol and long-term follow-up, are urgently needed in the years ahead.

4.4. Implications for practice and research

To the best of our knowledge, this systematic review and meta-analysis is the first to comprehensively evaluate the effectiveness and safety of wet cupping with rehabilitation training on upper-limb PSS, aiming to provide an evidence-based foundation and noteworthy insight for practitioners to consider this combined therapy as an adjunctive therapy for improvements in spasticity and motor ability. Of note, the determination of the treatment regimen should depend on the patient's condition. For patients with mild to moderate motor impairments, active trainings such as weight-supported treadmill training or task-oriented training are particularly recommended [25], whereas passive trainings, e.g., muscle stretching and robot-assisted training, are more suitable for those with severe motor impairments who cannot perform tasks by themselves and can also be flexibly combined with wet cupping. The selection point for wet cupping is supposed to be more comprehensive, which means that not only the local point (tender/Ashi point) but also the remote point based on meridian theory should be considered. In addition, other important indicators should be considered in future research, e.g., quality-adjusted life year (a common unit of measurement in health valuation) and patient-reported outcome measures, which may increase international comparisons and contribute to optimizing treatment regimens. More importantly, the use of valid and reliable assessment tools, such as iEMG and shear wave elastography [50], will provide more substantial evidence for the anti-spastic effect of this combination from the aspect of peripheral muscular changes.

5. Conclusion

Wet cupping with rehabilitation training should be included in a comprehensive therapeutic protocol for stroke patients who suffer from upper-limb spasticity. However, due to the high risk of bias and heterogeneity of the involved studies, the antispastic efficacy of this combination needs further verification.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

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Ethics statement

Review or approval by an ethics committee was not needed and informed consent was not required for this study because this work consisted of an examination of publicly available documents.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20623.

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