# Efficacy and safety of bloodletting puncture and cupping in postherpetic neuralgia: A systematic review and meta-analysis

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**Abstract.** The present study aimed to evaluate the efficacy and safety of bloodletting puncture and cupping (BLP-C) in postherpetic neuralgia (PHN) and to provide guidance for clinical treatment. Randomized controlled trials (RCTs) of BLP-C therapy in PHN were systematically searched in eight databases from inception to September 2022. Literature screening, data extraction and quality assessment were performed by two independent researchers. Dichotomous and continuous variables were pooled using the risk ratio (RR) and weighted mean difference (WMD), respectively. A total of 13 studies involving 1,129 patients with PHN (571 in the experimental group and 558 in the control group) were included in the present meta-analysis. Overall efficacy (RR=1.21, 95% CI: 1.15 to 1.28, P<0.00001), VAS score (WMD=-1.10, 95% CI: -1.31 to -0.90, P<0.00001) and PSQI score (WMD=-2.42, 95% CI: -2.87 to -1.96, P<0.0001) were significantly different between the BLP-C group and Western medicine group. Furthermore, subgroup analysis demonstrated that BLP-C alone or combined with other traditional Chinese medicines was more effective than Western medicine in PHN. A total of four RCTs mentioned adverse reactions, most of which were in the Western medicine group and were relieved after treatment discontinuation. In conclusion, BLP-C is superior to Western medicine in relieving pain and improving the sleep quality of patients with PHN with a lower incidence of adverse effects.

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*Abbreviations:* BLP-C, blood-letting puncture and cupping; PHN, postherpetic neuralgia; TCM, Traditional Chinese Medicine; RR, risk ratio; VAS, visual analogue scale; PSQI, Pittsburgh sleep quality index

*Key words:* postherpetic neuralgia, blood-letting puncture, cupping, Traditional Chinese Medicine, systematic review, meta-analysis

## Introduction

Postherpetic neuralgia (PHN) is a common type of neuropathic pain that persists for >3 months after a rash heals from acute herpes zoster (HZ) (1,2). PHN typically manifests as spontaneous pain, hyperalgesia and allodynia that last for several months or even a lifetime and seriously affects the physical and mental health of patients (3). PHN is the most common complication of HZ that mainly affects patients >50 years of age (4), and its incidence increases with age.

PHN is difficult to treat and pharmacological therapy is currently the primary treatment for PHN (5). Pregabalin, gabapentin and tricyclic antidepressants are first-line therapeutic drugs recommended for PHN (6). Since long-term medication is needed, adverse effects such as dizziness, drowsiness, dry mouth and edema are often observed in patients with PHN. Opioids, including tramadol, morphine and oxycodone, should generally be considered for PHN with severe pain after consultation with a specialist, and should only be prescribed with appropriate goals followed by close monitoring (2). However, these Western medical practices have only achieved mild successes in pain alleviation. Numerous patients with PHN still respond poorly to pharmacological treatments such as gabapentinoids (7). Therefore, an effective and safe therapy for PHN is urgently needed.

Studies have found that bloodletting puncture and cupping (BLP-C) may effectively reduce pain in patients with PHN with fewer or no adverse effects on physical health. BLP-C is a Traditional Chinese Medicine (TCM) treatment modality based on the meridian theory, which has an important role in the field of complementary and alternative medicine. BLP stimulates the acupoints on the patient's body to promote blood circulation, remove blood stasis and dredge the meridians, thereby relieving pain. Cupping uses the heat of combustion to achieve suction (negative pressure) inside a glass cup, which is then applied to specific parts of the body. This suction induces congestion or hemostasis at selected acupoints (8), resulting in therapeutic effects such as promoting skin blood flow (9), increasing the pain threshold, improving local anaerobic metabolism (10), attenuating inflammation and regulating

cellular immune responses (11). In clinical practice, BLP-C has been found to be moderately effective in the management of PHN. However, there is currently no comprehensive systematic review and meta-analysis that quantitatively assessed the efficacy of BLP-C in the treatment of PHN. Therefore, the present meta-analysis aimed to assess the efficacy and safety of BLP-C in PHN patients by performing a data synthesis from randomized-controlled trials (RCTs) and to provide a reliable reference for clinical decision-making.

## Materials and methods

*Registration*. The protocol of this review has been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) on October 24th, 2022 (no. CRD42022367056).

*Search strategies*. Relevant RCTs were searched in the China National Knowledge Infrastructure (CNKI; https://www.cnki.net), Wanfang (www.wanfangpaper.net), CQVIP (http://www.cqvip.com), SinoMed (http://www.sinomed.ac.cn), Cochrane Library (https://www.cochranelibrary.com/?contentLanguage=eng), PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://www.webofscience.com/wos) and Embase (https://www.embase.com) databases from inception to September 2022 without any language restrictions. The title, abstract and full text of the studies were reviewed and screened independently by two investigators (WK and YL) to determine eligibility for inclusion in the meta-analysis. Any disagreement was resolved by a third investigator (CX).

The relevant studies were searched using subject and entry terms. Chinese databases were searched using Chinese (Mandarin) search terms 'Ci Luo Ba Guan' (BLP-C) and 'Dai Zhuang Pao Zhen Hou Yi Shen Jing Tong/Dai Zhuang Pao Zhen Hou Yi Liu Shen Jing Tong' (PHN). English databases were searched by the English search terms 'acupuncture', 'blood-letting', 'pricking', 'cupping', 'postherpetic neuralgia' and 'PHN'. The search strategy for PubMed is outlined in Table SI.

*Eligibility criteria*. The inclusion criteria for the present study were as follows: i) Participants: Patients medically diagnosed with PHN, regardless of ethnicity, nationality or course of the disease; ii) interventions and controls: Intervention in the treatment group included BLP-C therapy or BLP-C combined with other TCM therapies. Intervention in the control group was conventional Western medicine therapy; iii) outcomes: Overall efficacy [efficacy=(cured + markedly improved + improved)/total number of cases in each group x100%], visual analogue scale (VAS) score (12) and Pittsburgh sleep quality index (PSQI) (13); iv) study type: RCT. The exclusion criteria for this study were as follows: i) Participants: Patients diagnosed with a special type of HZ, such as HZ ophthalmicus, HZ sacralis or incomplete HZ; ii) study type: Studies that did not describe outcome measures in detail or had an inaccessible full text.

*Literature screening and data extraction*. Literature screening and data extraction were performed independently by two investigators (WK and YL). Any disagreement was resolved by a third investigator (XC). Data were extracted according to a pre-designed Excel 2019 data extraction form, including basic literature information, study type, basic subject information, interventions for the treatment group and control group, intervention time, outcome measures, safety evaluation and other observational measures.

*Quality assessment*. The quality of the articles was assessed independently by two investigators (WK and YL) using the Cochrane risk of bias (RoB) tool (methods.cochrane.org). The RoB tool assesses risk of bias in 7 domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluation, incomplete outcome data, selective reporting and other biases. The possible answers for each domain are Yes (+); Not clear (?) and No (-). Yes (+) indicates a low risk of bias for the respective domain; Not clear (?) indicates an unclear or uncertain risk of bias for the respective domain; No (-) indicates a high risk of bias for the respective domain.

*Data synthesis and statistical analysis*. The collected data were processed and analyzed by RevMan 5.4 (Cochrane Collaboration) and StataSE15 (StataCorp LP). Dichotomous and continuous variables were pooled using the risk ratio (RR) and weighted mean difference (WMD), respectively. Heterogeneity was evaluated using the $I^2$ statistic and was considered absent when $P>0.1$ and $I^2 \leq 50\%$. The meta-analysis was conducted using a fixed-effects or random-effects model and the presence of bias among studies for different interventions was judged using a funnel plot. A fixed-effects model was used when the studies were assumed to be homogeneous, while a random-effects model was used when there was heterogeneity among the studies.

## Results

*Literature search*. A total of 671 records were initially identified through database searching, of which 381 were duplicates. After a preliminary review of titles and abstracts, 177 records were excluded for not meeting the inclusion criteria. Of the remaining 113 records, 67 were excluded due to the lack of outcomes of interest, 13 were excluded due to no available data and 20 were excluded due to abstract-only access. Finally, a total of 13 RCTs involving 1,129 patients with PHN were included (14-26). The process of study search and selection is illustrated in Fig. 1.

*Characteristics of included studies*. A total of 13 RCTs were included in the present review (14-26), all of which were conducted in China and published in Chinese. Basic information on the included RCTs is provided in Table I.

*Participants*. The 13 RCTs (14-26) involved 1,129 patients with PHN, including 574 males and 555 females. Except for the 4 patients who dropped out from one study (22), all remaining patients were included in the statistical analysis.

*Interventions in the treatment group*. As indicated in Table I, among the 13 included RCTs (14-26), BLP-C was the intervention in three studies (15,19,22), BLP-C combined with acupuncture was used in five studies (16,18,21,23,24), BLP-C combined with TCM was used in two studies (20,26) and

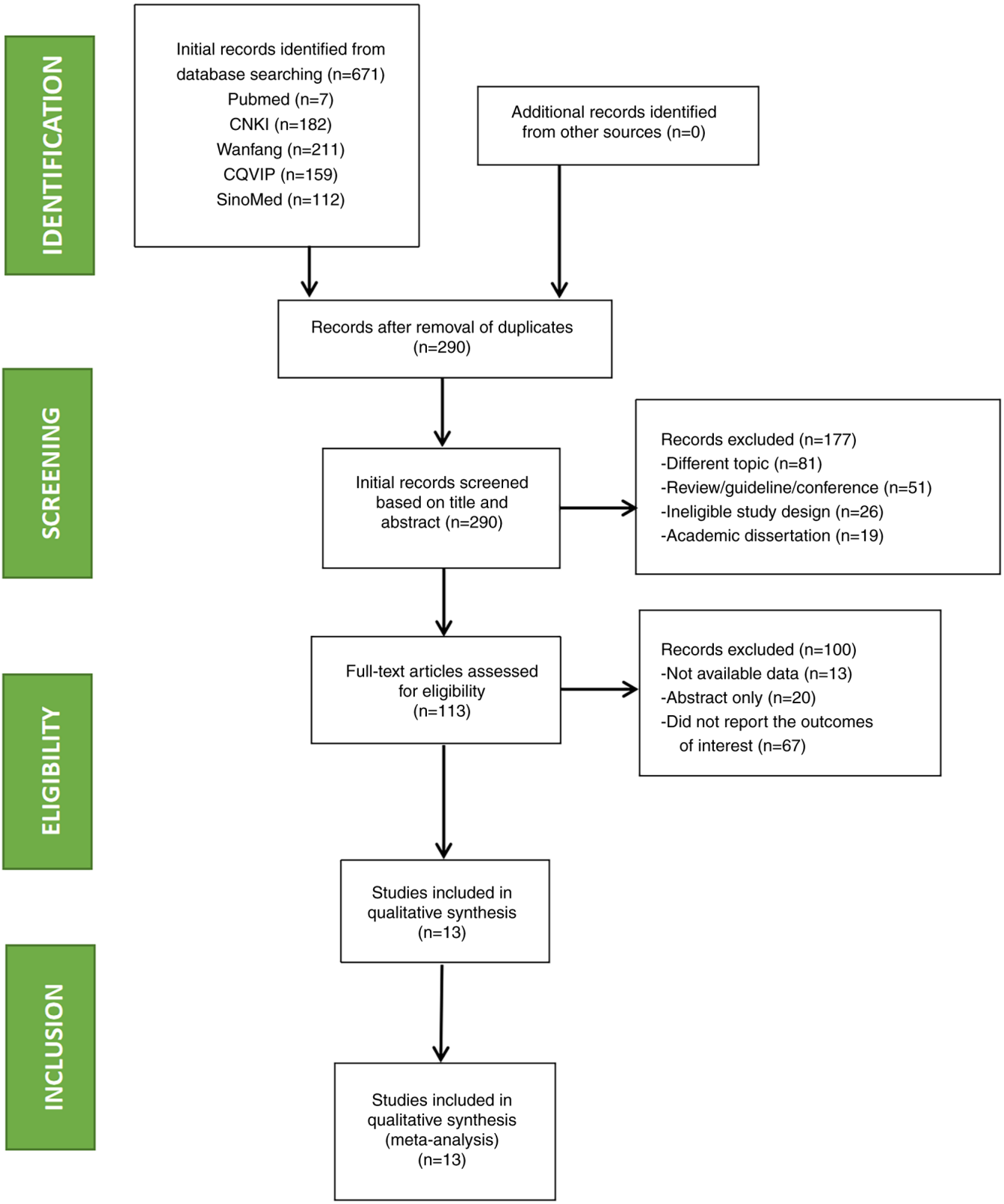


Figure 1. Flowchart of literature screening. CNKI, China National Knowledge Infrastructure.

BLP-C combined with acupuncture and TCM were used in three studies (14,17,25).

The specific characteristics of the included BLP-C studies are listed in Table I. In all of the 13 studies included, Ashi Xue had been selected as the puncture site for BLP-C (14-26).

*Interventions in the control group*. Western medicine was used as the intervention for the control group. Pregabalin was used in five studies (15,16,16,19,21), carbamazepine was used in two studies (14,26), gabapentin was used in two studies (22,24) and ibuprofen was used in one study (20). In

Table I. Basic characteristics of included studies.

| Author, year | Number of cases (Exp/Ctr) | Age, years (Exp/Ctr) | Duration of disease, months (Exp/Ctr) | Intervention (Exp/Ctr) | Course of treatment, days | Operating point | Outcome indicators | (Refs.) |
|---|---|---|---|---|---|---|---|---|
| Gao, 2019 | 30/30 | 71.78±7.53/73.16±7.34 | 20.04±1.68/13.56±15.00 | PC+A+TCM/Carbamazepine | 14 | Ashi Xue | ①②④⑦ | (14) |
| Liu, 2019 | 40/40 | 50.25±10.17/50.18±10.38 | / | PC/Pregabalin | 30 | Ashi Xue | ①②③ | (15) |
| Lu, 2019 | 30/30 | 66.50±2.69/69.90±2.52 | 9.38±2.87/10.16±2.38 | PC+A/Pregabalin | 10 | Ashi Xue | ①②③④ | (16) |
| Ma, 2014 | 68/68 | 56.4±0.00/51.3±0.00 | / | PC+A+TCM/VitB1 | 30 | Ashi Xue | ①②③⑤ | (17) |
| Tang, 2019 | 30/30 | 59.5±10.30/61.67±8.20 | / | PC+A/Pregabalin | 14 | Ashi Xue | ①②③⑥ | (18) |
| Tian, 2013 | 32/32 | 61.00/61.00 | 4.00/4.00 | PC/Pregabalin | 16 | Ashi Xue | ③⑧ | (19) |
| Wang, 2016 | 49/40 | 58.26±2.16/57.26±2.21 | 4.02±0.43/4.00±0.44 | PC+TCM/Ibuprofen | 84 | Ashi Xue | ①②③⑤ | (20) |
| Wang, 2019 | 39/39 | 58.30±3.20/59.10±2.80 | 4.20±1.30/4.00±1.40 | PC+A/Pregabalin | 10 | Ashi Xue | ①②③④ | (21) |
| Wang, 2020 | 35/35 | 58.60/57.80 | 2.09±0.34/2.06±0.32 | PC/Gabapentin | 16 | Ashi Xue | ①②③⑦⑧ | (22) |
| Wen, 2015 | 25/25 | 45.00±20.00/45.00±21.00 | / | PC+A/Carbamazepine, Mecobalamin, VitB1 | 14 | Ashi Xue | ①②③⑥ | (23) |
| Xing, 2019 | 36/36 | 68.25±7.42/67.94±6.39 | 3.23±1.05/3.47±0.74 | PC+A/Gabapentin | 22 | Ashi Xue | ①②③ | (24) |
| Yu 2018, | 115/115 | 42.41±5.19/43.26±5.28 | 7.98±2.27/7.94±2.30 | PC+A+TCM/Paracetamol, Codeine | 12 | Ashi Xue | ①②③⑤ | (25) |
| Zhao, 2013 | 42/38 | 54.26±0.00/51.72±0.00 | 6.12±0.00/6.28±0.00 | PC+TCM/Carbamazepine | 21 | Ashi Xue | ①②③⑤ | (26) |

①, Overall effective rate ②, cure rate ③, VAS score; ④, Pittsburgh sleep quality index; ⑤, incidence of adverse reactions; ⑥, recurrence rate; ⑦, start time of pain relief; ⑧, serological indicators (SP, IL-6); ⑨ McGill score. Exp, experimental group; Ctr, control group; TCM, Traditional Chinese Medicine; PC, blood-letting puncture and cupping; A, acupuncture.

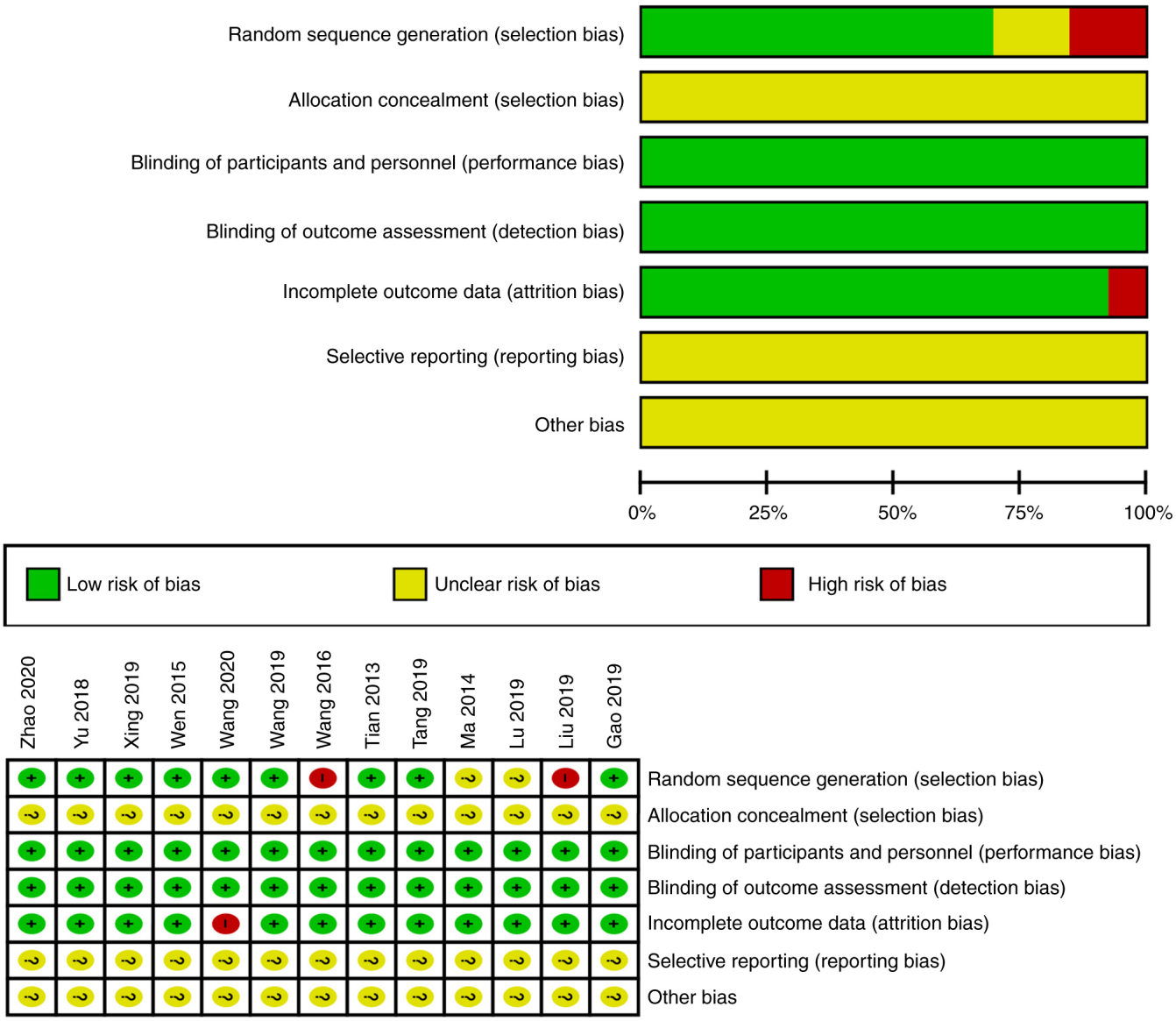


Figure 2. Quality assessment of included studies.

the other three studies (17,20,25), different combinations of two or three Western medicines (acetaminophen, codeine, mecobalamin, vitamin B1, Fenbid and carbamazepine) were used. The duration of intervention in the control group was the same as that in the treatment group.

*Efficacy assessment*. The overall efficacy was reported in 12 of the 13 eligible studies (14-26), the VAS score was reported by 12 studies (15-26), the PSQI was reported by 3 studies (14,16,21), the incidence of adverse reactions was reported by 4 studies (17,20,25,26) and the recurrence rate was reported by 2 studies (18,23). In addition, serum levels of pain-related factors, namely substance P and IL-6, were reported by two studies (19,22).

*Quality assessment of included studies*. Among the 13 included studies, the random sequence generation method was used in 11 studies (14,15,18-26), the random number table method was adopted in nine studies (14,18,19,21-26), random grouping was conducted according to the visit time in one study (20), random grouping was conducted according to the admission time in one study (15), and the term 'random' was mentioned in the remaining two studies (16,17) without describing the random grouping method. BLP-C was used as the intervention in these studies. Allocation concealment and blinding are not feasible for BLP-C because the traces left by the procedure are usually visible and may last for several days. Therefore, it is difficult to carry out the masking process and impossible to use any blinding methods. However, the patients showed good compliance and the non-blinding method was unlikely to affect the results. Follow-up at three months (18) and one year (23) were respectively mentioned in two studies (18,23) and the recurrence rate was statistically analyzed. One study (22) reported four cases of dropout and provided explanations. The outcome data were complete in the other 12 studies (14-21,23-26) and no dropout cases were reported. Baseline characteristics were comparable among the 13 studies (14-26), but selective reporting and other bias were unclear. The quality assessment results of the 13 studies (14-26) are summarized in Fig. 2.

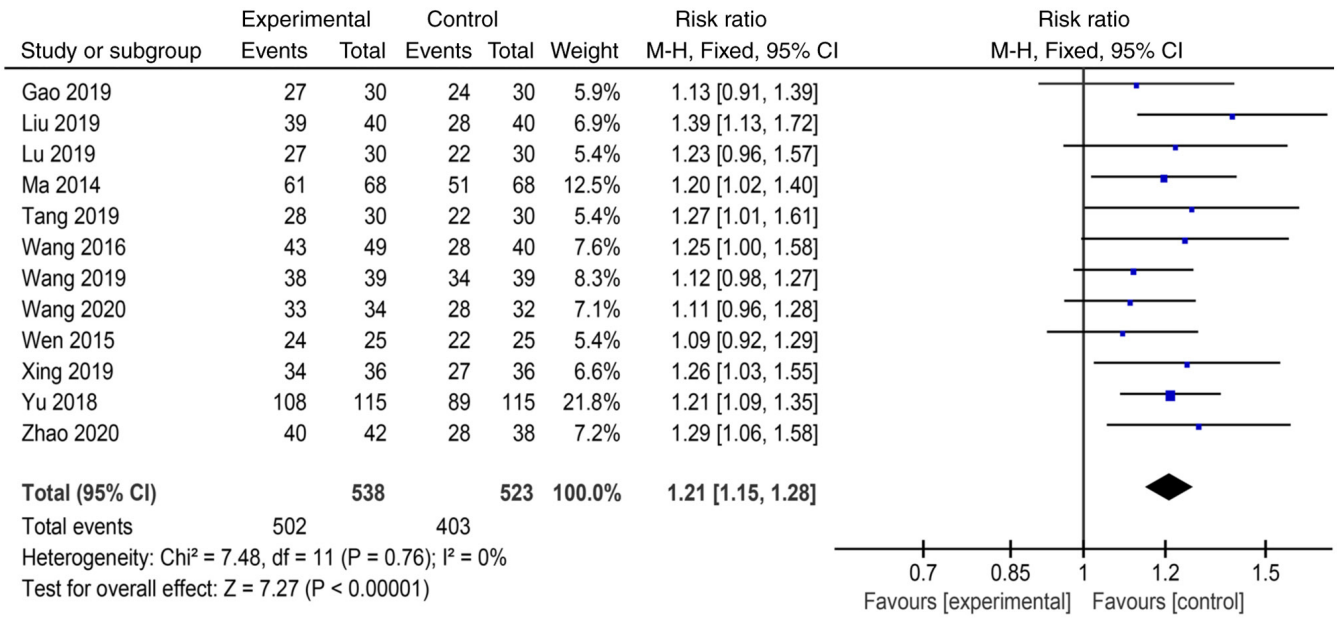


Figure 3. Forest plot of overall efficacy of blood-letting puncture and cupping in postherpetic neuralgia. M-H, Mantel-Haentzel; df, degrees of freedom.

*Meta-analysis*

*Overall efficacy*. The overall treatment efficacy in the experimental and control groups was reported in 12 studies. There were 1,061 patients, including 538 in the experimental group and 523 in the control group. Heterogeneity was low among the studies (P=0.76, $I^2$=0%). The results showed that the overall efficacy was significantly higher in the experimental group (including BLP-C alone and BLP-C + acupuncture or TCM) than in the control group (drug treatments) [RR=1.21, 95% CI: 1.15-1.28, P<0.00001] (Fig. 3). There was low publication bias in the results (Fig. 4).

*VAS score*. Post-treatment VAS scores were reported in 12 studies (15-26). VAS scores were decreased after intervention and were significantly different between the experimental group and control group (WMD=-2.31, 95% CI: -2.42-2.31, P<0.00001] (Fig. 5). However, there was high heterogeneity among the studies (P<0.00001, $I^2$=97%). Therefore, a subgroup analysis was conducted according to different interventions.

As shown in Fig. 6, three studies (15,19,22) compared BLP-C vs. Western medicine (Fig. 6A). Furthermore, seven studies (16,18,20,21,23,24,26) compared BLP-C plus acupuncture or TCM vs. Western medicine (Fig. 6C). In addition, two studies (17,25) compared BLP-C plus acupuncture and TCM vs. Western medicine. BLP-C was superior to pharmacological therapy in relieving pain in all three subgroups; however, there was high heterogeneity among the studies ($I^2$=85%, P=0.002, Fig. 6A; $I^2$=94%, P<0.00001, Fig. 6D). Thus, a sensitivity analysis was further conducted. As shown in Fig. 6B, heterogeneity was decreased upon removal of the study by Liu (15) ($I^2$=0%, P=0.62), but VAS scores were still significantly different between the BLP-C plus acupuncture and TCM group and the pharmacological therapy group. It was suspected that the observed heterogeneity may be attributed to variations in the duration of treatment and the specific Western medicines employed in the control group across the included studies. The differences in the duration of treatment may have influenced the treatment outcomes and given rise to heterogeneity. Each study may have adopted a different duration or frequency of treatment, leading to variations in patient response and overall treatment effects.

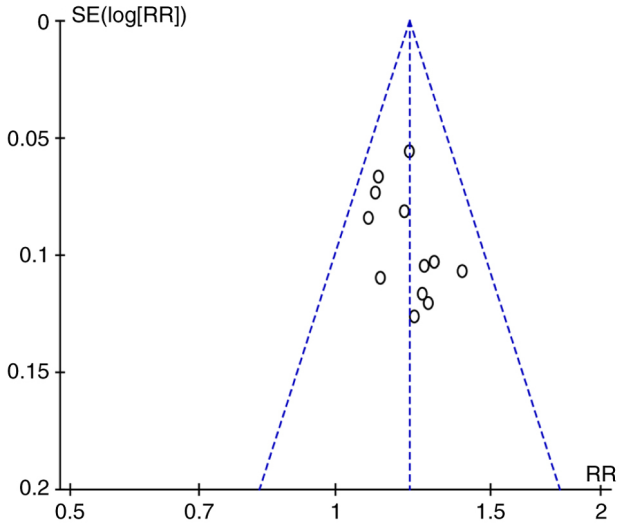


Figure 4. Funnel plot of overall efficacy of blood-letting puncture and cupping in postherpetic neuralgia. SE, standard error; RR, risk ratio.

*PSQI*. The PSQI was reported by three studies (14,16,21). PSQI scores were decreased after intervention in both groups and were significantly lower in the experimental group than in the control group (WMD=-2.42, 95% CI: -2.87 to -1.96, P<0.00001, Fig. 7), which suggests that BLP-C is superior to Western medicine in improving sleep quality. However, PSQI scores were only reported by 3 RCTs with a small sample size. Therefore, further investigations are warranted to confirm this conclusion.

*Safety*. Adverse reactions were mostly caused by drugs, which resolved after treatment discontinuation. Of the 13

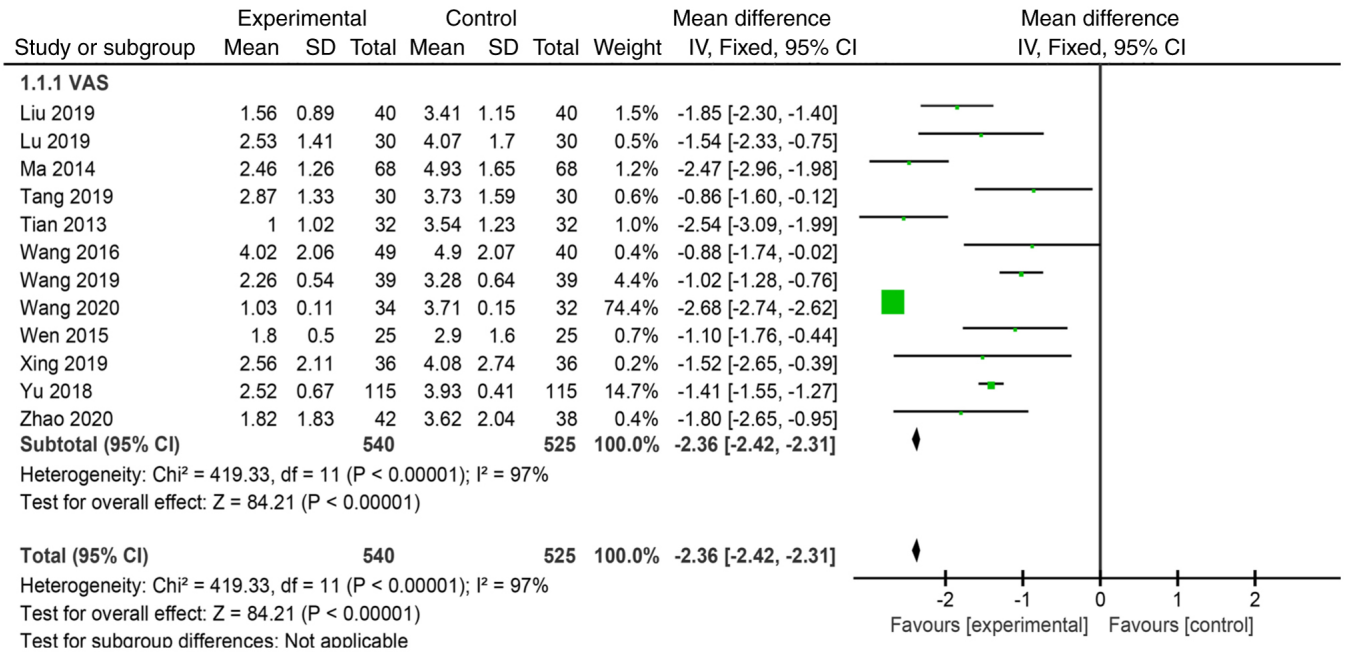


Figure 5. Forest plot of VAS score after blood-letting puncture and cupping in postherpetic neuralgia; VAS, visual analog scale; IV, inverse variance; SD, standard deviation; df, degrees of freedom.

studies included, 3 studies (17,25,26) reported stomach discomfort in the pharmacological therapy group, including 2 cases receiving vitamin B1 injection, mecobalamin and Fenbid (n=30) (17), 4 cases receiving paracetamol and codeine (n=12) (25) and 2 cases receiving carbamazepine (n=12) (26). Furthermore, one study reported 11 cases of adverse reactions of the nervous system in the control group (paracetamol and codeine, n=12) (25). Conversely, only 4 cases (17,25) of adverse reactions were reported in the BLP-C group (Table SII).

## Discussion

The present systematic review and meta-analysis were performed on 13 RCTs (14-26) published between 2013 and 2020. The findings showed that the BLP-C group had a better VAS score, PSQI score and safety profile than the Western medicine group. VAS and PSQI scores were used as outcome measures to quantify improvements in pain and sleep disorders, which are the most common symptoms of PHN. In addition, two studies (14,22) reported the start time of pain relief and the results showed that the BLP-C group had earlier pain relief than the Western medicine group. The duration of disease in the experimental group was 20.04±1.68 and 4.00±0.00 months, respectively, which indicates that BLP-C may be more effective for both a short and long disease duration.

The pathogenesis of PHN is highly complex and involves both peripheral and central sensitization, which makes treatment challenging (27). There is compelling evidence from skin biopsies, along with subcutaneous and cutaneous drug challenges, showing that the peripheral afferents may be a significant pain generator in a subset of patients with PHN (28). Furthermore, a previous clinical trial indicated that inhibiting inflammation of locally injured nerves may help reduce the intensity of pain in patients with PHN (29). These findings suggest that inhibiting peripheral nociceptor stimulations and inflammatory responses may contribute to PHN pain.

Patients with PHN are often troubled by debilitating pain of various sensations (e.g., burning pain or paroxysmal severe pain) in the region of damaged innervation. The current meta-analysis results indicated that the analgesic effect of BLP-C was superior to that of Western medicine. BLP-C combines both acupuncture and cupping to treat the painful area. After the cupping site is disinfected, it is punctured by a three-edged needle to release blood, henceforth blood-letting. Cupping is then performed at the bloodletting site, and the negative pressure inside the glass jar creates suction on the local skin and thus induces bleeding at the puncture site. It was recently reported that BLP-C may improve hemorheological abnormalities and local microcirculation, reduce proinflammatory factors and eliminate nerve root edema (30). Hence, BLP-C of the painful region of the skin may modulate the inflammatory microenvironment of the affected side of cases with PHN, effectively reduce the transmission of peripheral noxious stimuli to the spinal cord and inhibit the establishment of central sensitization, thereby successfully reducing pain.

Elderly individuals with a weakened immune system are most susceptible to PHN and related symptoms. It was shown that BLP-C therapy is closely related to endocrine and immunological regulation (31). Thus, controlling the activity of the immune and endocrine systems may be the therapeutic mechanism of BLP-C in PHN. Human nerve endings can release 'endorphin-like chemicals' when the acupoint is stimulated, increasing the pain threshold and decreasing susceptibility to pain (32). Signals triggered by the needles during BLP-C may reach the brain and induce the release of several central neurotransmitters, including acetylcholine, morphine and

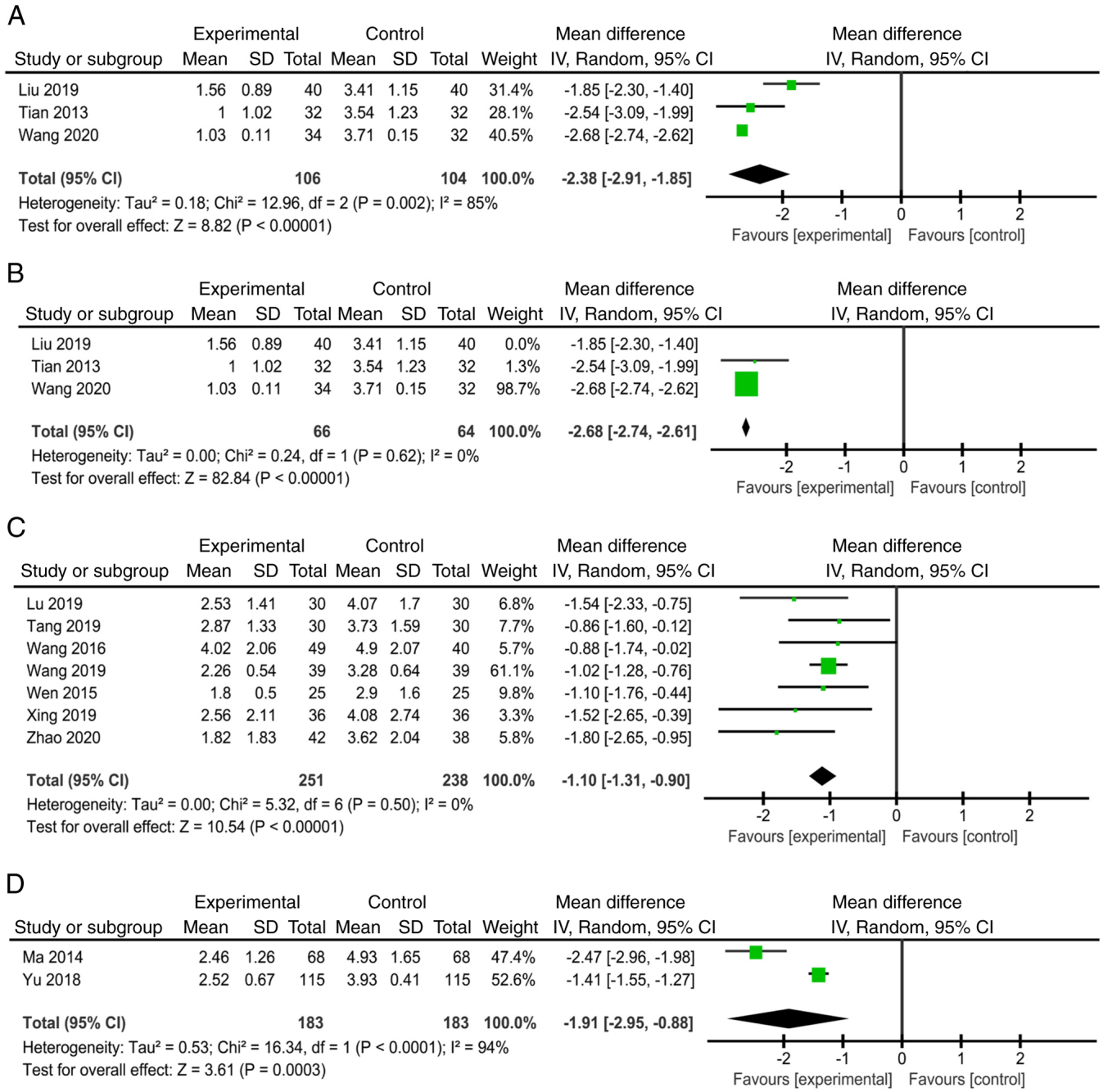


Figure 6. Forest plot of VAS score after BLP-C in PHN (subgroup analysis). (A) BLP-C. (B) BLP-C (after sensitivity analysis). (C) BLP-C combined with acupuncture or TCM. (D) BLP-C combined with acupuncture and TCM. BLP-C, blood-letting puncture and cupping; PHN, postherpetic neuralgia; TCM, Traditional Chinese Medicine; VAS, visual analog scale; IV, inverse variance; SD, standard deviation; df, degrees of freedom.

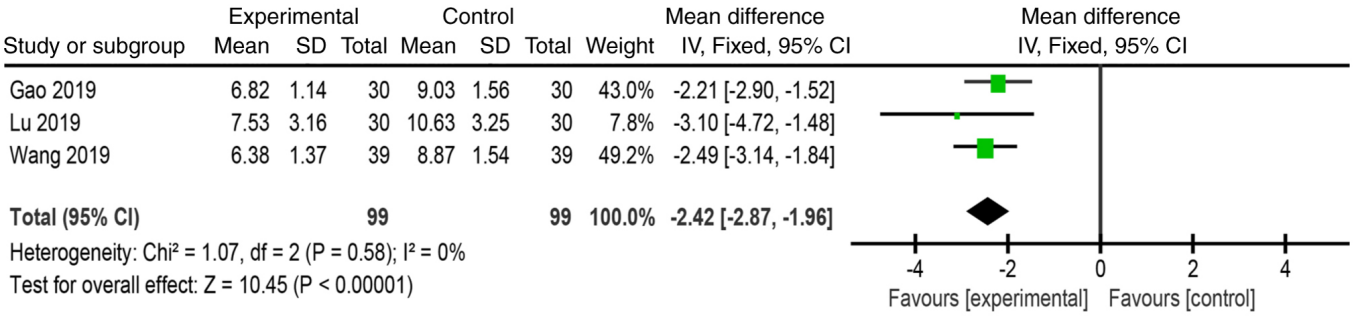


Figure 7. Forest plot of Pittsburgh sleep quality index score after blood-letting puncture and cupping in postherpetic neuralgia. IV, inverse variance; SD, standard deviation; df, degrees of freedom.

5-hydroxytryptamine, thereby enhancing the analgesic effects (33). Cupping after puncture may help discharge blood stasis and dredge the meridians and Qi, which can effectively improve the local blood circulation and maintain nutritional supply.

BLP-C exerts neuromodulatory effects by controlling the release of neurotransmitters, such as endorphin (34) and substance P (19,22). The present meta-analysis showed that the serum level of substance P is decreased after treatment. Substance P can induce the accumulation of pain-causing and inflammatory substances, thereby leading to neurogenic inflammation and persistent or worsening pain. BLP-C may lead to higher oxygen saturation (35), which can remove oxidants, reduce oxidative stress and damage caused by free radicals, and protect cells and tissues. These effects are all associated with pain relief and the improvement of sleep quality. In addition, it was shown that substance P can influence sleep physiology through neurokinin receptors (36). Andersen *et al* (37) revealed that a certain dose of substance P led to decreased sleep efficiency and increased sleep onset latency.

PHN is often accompanied by sleep disorders (38). In addition to the improvement of pain, BLP-C is also better than Western medicine in improving sleep quality. There is a bidirectional relationship between sleep disturbance and pain (39). Chronic pain can interfere with sleep depth and continuity, as well as reduce sleep duration and quality (40). Furthermore, decreased sleep quality can increase pain sensitivity and severity (41). On the other hand, pain in patients with PHN often occurs in the chest, back, waist and abdomen (2). Compression of certain body parts during sleep may aggravate the patients' pain perception, increase their physiological stress response and thus affect their sleep quality. Altogether, this suggests that BLP-C may improve sleep quality by reducing pain.

The findings of the present review support that BLP-C is a safe and effective treatment for PHN. Western medicines generally have hepatorenal toxicity and elderly patients are less likely to tolerate long-term medication. Compared with Western medicine, BLP-C is performed directly on the skin and does not cause hepatorenal toxicity, which makes this treatment approach favorable for patients with weak gastrointestinal function or renal insufficiency. Collectively, the present results demonstrated that BLP-C is a promising complementary and alternative therapy for addressing pain and sleep loss in patients with PHN, particularly in those who are elderly and have poor liver and renal functions.

Although the literature on BLP-C treatment for PHN was comprehensively reviewed for the present study, certain limitations remain. First, the studies included in the present meta-analysis were of medium quality and there may be biases in the results due to language restriction. Furthermore, the subjectivity of assessors may have introduced bias. Finally, the duration of treatment varied among studies, which in turn may affect the accuracy of the results. Further studies with better design or higher quality are warranted to confirm the present findings.

In conclusion, the present systematic review showed that BLP-C is an effective therapy for reducing pain intensity and improving sleep quality in patients with PHN. The therapeutic effects of BLP-C are mediated through multiple targets and pathways, whereas Western medicine usually addresses a single target, which may explain the superior efficacy of BLP-C compared with Western medicine. Therefore, BLP-C is an effective external therapy worthy of further application in the treatment of PHN. Due to the limited quantity and quality of the included studies, more high-quality studies are needed to ascertain these findings.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Authors' contributions**

KW and CX conceived and designed the study and set the direction of the manuscript. WK and LX performed the literature search and KW made the final decision regarding study inclusion. WK and LX prepared the original manuscript, as well as figures and tables. YL and ZG analyzed the study data. SL visualized the study data. CX and KW reviewed and proofread the manuscript. All authors contributed to editorial changes to the manuscript. All authors have read and approved the final version of the manuscript. CX and KW have checked and approved the authenticity of the raw data.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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