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REVIEW

Efficacy and Safety of Acupuncture Combined with Conventional Drug Therapy for the Treatment of Cancer-Induced Bone Pain: A Network Meta-Analysis of Randomized Controlled Trials

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Background: Cancer-induced bone pain (CIBP) involves both nociceptive and neuropathic components, causing significant suffering in cancer patients. Acupuncture has shown beneficial effects on CIBP. However, given the diverse acupuncture techniques, their therapeutic efficacy may vary.

Objective: To evaluate the efficacy and safety of various acupuncture modalities integrated with conventional drug therapy for CIBP.

Methods: Randomized controlled trials (RCTs) of acupuncture combined with conventional analgesics for CIBP were searched across eight Chinese and English databases and clinical trial registries up to September 2024. Two researchers independently performed literature screening, data extraction, and bias assessment. Data were analyzed using Stata 14.0 and R 4.2.3.

Results: Twenty-two RCTs involving 1,738 patients were included, assessing techniques including manual acupuncture (MA), electroacupuncture (EA), moxibustion (MOX), acupoint injection (AI), acupoint catgut embedding (ACE), auricular-plaster therapy (AP), thumbtack needle (TN) and transcutaneous electrical acupoint stimulation (TEAS). The outcomes were assessed across 20 studies for the clinical effective rate, 13 for nausea and vomiting, and 11 for constipation.The results indicated that for the primary outcome of pain relief (as measured by clinical effective rate), TN demonstrated the highest probability of being the most effective acupuncture technique (SUCRA = 75.2%). In terms of mitigating opioid-induced adverse reactions, ACE was most effective for reducing nausea and vomiting (SUCRA = 87.7%), while EA+AP was optimal for alleviating constipation (SUCRA = 93.5%). MA +MOX achieved the best overall balance between efficacy and the incidence of adverse reactions.

Conclusion: Acupuncture combined with conventional drug therapy significantly improves pain relief in CIBP and reduces opioid-related side effects. However, due to methodological limitations and the modest sample sizes of available studies, further high-quality, multicenter trials with larger samples are needed to confirm these findings and inform clinical practice.

Keywords: cancer-induced bone pain, acupuncture, supplementary alternative therapy, network meta-analysis

Key Message

This study evaluated the efficacy of eight acupuncture modalities in managing CIBP. Among the interventions, TN demonstrated superior analgesic effects. For addressing treatment-related complications, ACE showed optimal results in reducing nausea and vomiting, while EA+AP was most effective against constipation. MA+MOX emerged as the optimal therapeutic choice, offering an ideal balance between clinical effectiveness and safety profile for CIBP management.

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Introduction

Cancer remains a major global health challenge, with its incidence continuing to rise annually. According to the latest GLOBOCAN 2024 report,[1] approximately 19.96 million new cancer cases were diagnosed worldwide in 2022, along with an estimated 9.7 million cancer-related deaths. Among the complications associated with advanced malignancies, cancer-induced bone pain (CIBP) is particularly common and burdensome, especially in patients with bone metastases originating from breast, prostate, or lung cancers. CIBP is a complex pathological condition characterized by persistent background pain punctuated by episodic breakthrough pain.[2,3] Its multifactorial pathophysiology involves both nociceptive and neuropathic mechanisms arising from tumor invasion, osteolytic destruction, and sensitization of peripheral and central neurons. Increasing evidence indicates that CIBP is closely associated with central sensitization, neuroinflammation, glial cell activation, and an acidic bone-tumor microenvironment.[4] These alterations, along with structural remodeling of bone and reorganization of sensory nerve fibers, can intensify pain transmission and significantly impair patients'quality of life.[5]

The management of CIBP involves a multimodal approach, including pharmacological, radiotherapeutic, and interventional methods. According to the World Health Organization's analgesic ladder, the standard pharmacological treatments, as outlined by the NCCN guidelines,[6] includes opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvants such as bisphosphonates or denosumab to reduce bone resorption and alleviate pain. In addition, external beam radiotherapy is a common modality to control localized bone pain by targeting metastatic lesions.[7] Despite these advancements, conventional treatments for CIBP have notable limitations. Opioid analgesics while effective for cancer pain are often limited by severe adverse effects including constipation nausea cognitive impairment and dependence that compromise patients quality of life and long term treatment adherence. Most patients experience at least one adverse effect in the early stages of opioid therapy (eg, constipation, nausea, vomiting, etc).[8,9] Additionally, bisphosphonates and denosumab, while effective in reducing skeletal-related events, are limited by delayed onset of action and potential side effects, such as osteonecrosis of the jaw.[7,10] Radiotherapy, though effective, often provides temporary relief, requiring repeat treatments that increase the risk of cumulative toxicity and complications. Poorly controlled chronic CIBP is a key factor contributing to the decline in quality of life and self-confidence among cancer survivors.[11] Studies[12] indicate that the improvements provided by existing treatment methods fall short of meeting the needs of patients and the comprehensive treatment regimen of CIBP needs to be further improved. In this context, multidisciplinary approaches are essential for optimizing pain management of CIBP and improving patient quality of life.

In recent years, acupuncture, a traditional Chinese therapy validated over thousands of years, has gained international recognition and has been incorporated into healthcare systems in countries such as the United States, South Korea, and several European nations. It offers multifaceted mechanisms not only for pain relief but also for mitigating common adverse effects such as nausea, vomiting, and constipation, which are frequently seen in cancer patients receiving conventional treatments. High-quality clinical evidence[13–15] demonstrates that acupuncture can effectively alleviate these adverse effects while enhancing overall treatment tolerance. Its therapeutic efficacy and cost-effectiveness have been highlighted in numerous studies, particularly in its role as a complementary treatment to reduce opioid dependency and associated side effects.[16] International clinical guidelines[6,17] increasingly endorse acupuncture as part of cancer pain management strategies, further proving its importance and clinical value in cancer pain management.

However, acupuncture represents a diverse therapeutic modality, encompassing a range of techniques such as electroacupuncture, which enhances stimulation via electrical current;thumbtack needle (also known as intradermal needle), offering sustained and mild stimulation for longer-term treatment; auricular-plaster therapy, a microsystem approach applying seeds or magnets on ear points; acupoint catgut embedding, involving the implantation of absorbable sutures at acupoints to provide prolonged stimulation; and moxibustion, which utilizes thermal stimulation from burning mugwort to warm and promote Qi and blood circulation. Each method possesses distinct mechanisms, benefits, and clinical indications. Existing meta-analyses primarily focus on comparing combined acupuncture and analgesic efficacy with analgesics alone,[18–20]without evaluating the relative efficacy among different acupuncture methodologies. Network meta-analysis enables simultaneous comparison of multiple interventions, ranking their efficacy and estimating their likelihood of being the most effective. This study aims to identify the optimal acupuncture interventions for CIBP and offer a comprehensive view to inform clinical decision-making.

Materials and Methods

Registration

This study is registered in global system review database PROSPERO (http://www.crd.york.ac.uk/PROSPERO). The registration number is: CRD42024589150. The PRISMA 2020 checklist is shown in Supplementary Table S1.

Search Strategy

The following databases were searched: Four English databases including PubMed, Embase, Cochrane Library (CENTRAL) and Web of Science and four Chinese databases including China National Knowledge Infrastructure (CNKI), VIP database for Chinese Scientific and Technological Periodicals (VIP), WanFang Database for Academic Journals (WanFang) and China Biology Medicine Disc (CBM). Adding to retrieve us clinical trial registry (http://www.clinicaltrials.gov). Existing systematic reviews were examined to identify additional trials. The search language was limited to Chinese and English. The search was limited to Chinese and English publications up to September 30th 2024. The PubMed database search strategy is shown in Table 1. Details of the search strategy are provided in Supplementary Table S2.

Inclusion Criteria

Studies were included if they matched the following criteria:

1. Study type: randomized controlled trial(RCT).
2. Population: Patients who met the diagnostic criteria of primary bone cancer or other types of primary cancer companied by bone metastases. No restrictions were placed on gender, race, or cancer type. Patients diagnosed with CIBP underwent imaging or biopsy procedures. They exhibited clear and localized pain symptoms.
3. Interventions: The control group received conventional analgesic therapy based on the World Health Organization (WHO) three-step analgesic ladder, primarily comprising weak and strong opioid medications.[21] The experimental groups received the same conventional therapy combined with one or more acupuncture modalities—such as manual acupuncture, electroacupuncture, moxibustion, and auricular therapy—used either alone or in combination. Each distinct intervention, including combination therapies, was treated as an independent node in the network meta-analysis.

Table 1 PubMed Database Retrieval Strategy

Number	Search Terms
#1	Bone Neoplasm[MeSH Terms]
#2	Neoplasm, Bone[Title/Abstract] OR Neoplasms, Bone[Title/Abstract] OR Bone Cancer[Title/Abstract] OR Cancer of Bone[Title/Abstract] OR Cancer of the Bone[Title/Abstract] OR cancer-induced bone pain[Title/Abstract] OR bone cancer pain[Title/Abstract] OR bone metastasis pain[Title/Abstract] OR bone metastasis[Title/Abstract
#3	#1 OR #2
#4	"Acupuncture"[MeSH Terms] OR "Acupuncture Therapy"[MeSH Terms] OR "acupuncture, ear"[MeSH Terms] OR "Acupuncture Points"[MeSH Terms] OR "Moxibustion"[MeSH Terms]
#5	"acupuncture"[Title/Abstract] OR "needle"[Title/Abstract] OR "acupunct"[Title/Abstract] OR "Pharmacopuncture"[Title/Abstract] OR "auricular"[Title/Abstract] OR "fire needling"[Title/Abstract] OR "warming needle"[Title/Abstract] OR "electroacupuncture"[Title/Abstract] OR "electro-acupuncture"[Title/Abstract] OR "electric stimulation"[Title/Abstract] OR "acupoint"[Title/Abstract] OR "moxibustion"[Title/Abstract] OR "catgut embedding"[Title/Abstract] OR "acupoint injection"[Title/Abstract]
#6	#4 OR #5
#7	Randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR clinical trial[Publication Type]
#8	(randomized OR randomly OR trial OR randomized controlled trial OR randomised controlled trial OR controlled clinical trial) [All Fields]
#9	#7 OR #8
#10	#3 AND #6 AND #9

4. Outcomes: The primary outcome was the clinical effectiveness rate, defined as the proportion of patients achieving a reduction in pain intensity. Clinical effectiveness was specifically defined as either (1) a ≥50% reduction from baseline in a standardized pain assessment scale (eg, Visual Analogue Scale [VAS] or Numerical Rating Scale [NRS]), or (2) a significant subjective improvement characterized by markedly reduced pain, tolerable pain levels, undisturbed sleep, and the ability to maintain normal daily activities. Secondary outcomes included the incidence of opioid-induced constipation and nausea/vomiting.
5. Each RCT should have a sample size per group of 20 or greater.
6. Literature published from database inception to September 30, 2020, in Chinese or English.

Exclusion Criteria

1. Animal experiments, reviews, expert experience summaries, or case reports;
2. Duplicate publications of the same RCT — in such cases, only the most complete and most recent report was included to avoid overlapping data;
3. Non-randomized studies or those with significantly imbalanced baseline data;
4. Studies with designs, interventions, or reported outcomes inconsistent with the objectives or endpoints of this meta-analysis;
5. Studies with missing key outcome data or data that could not be extracted or synthesized for analysis.

Literature Screening and Data Extraction

For literature screening and management, all records found were imported into EndNote X9 to eliminate duplicates. Two researchers independently screened titles and abstracts during preliminary phase and excluded articles that did not meet the inclusion and exclusion criteria. Full-text screening was performed independently by the same researchers to further assess eligibility based on the criteria.

Data was extracted from the included studies, including (1) basic information: title, author, year; (2) Patient characteristics: age, gender, sample size, course of disease; (3) Intervention measures: acupuncture therapy method, course of treatment, follow-up time; (4) Outcome indicators: primary and secondary outcome indicators. Regarding missing data, attempts were made to contact the authors by Email to obtain said data. Discrepancies were resolved through adjudication by a third investigator.

Risk-of-Bias Assessment

The risk of bias of the final included studies was evaluated according to the Cochrane-recommended Risk of Bias assessment tool.[22] The assessment focused on six key domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Each domain was rated as having a low, unclear, or high risk of bias. Two reviewers independently assessed the bias of the above six aspects, and cross-checked their evaluations. Discrepancies were resolved through adjudication by a third investigator.

Data Statistics and Analysis

Network Diagram

Stata 14.0 software was used to depict network diagrams of different acupuncture and moxibustion related therapeutic interventions. Each treatment was represented by a node and direct comparisons between treatments were made by connecting lines. The node size corresponded to the cumulative number of treatments, with larger nodes signifying a greater number of cases. Similarly, the thickness of the lines connecting the nodes reflected the quantity of studies involved in each comparative analysis.

Network Meta-Analysis

The effect size index was selected based on the type of outcome data. For binary outcomes, the Odds Ratio (OR) was used to measure the effect size, while the Mean Difference (MD) was applied for continuous data, with a 95% confidence interval (CI).

Efficacy data were synthesized and analyzed statistically using Bayesian methods in R version 4.2.3, employing the "Gemtc" package.[23] Network meta-analysis calculations utilized a four-chain simulation with an initial value set at 2.5. The pre-iteration count was set at 50,000, and the main iteration process was conducted for 100,000 iterations with a step size of 1. Convergence of the simulations was assessed using the Potential Scale Reduction Factor (PSRF). A PSRF value between 1 and 1.05 indicated satisfactory convergence, while values outside this range necessitated additional simulations, with the maximum iteration limit capped at 300,000. When closed loops appeared in the network evidence graph, inconsistency was assessed by calculating inconsistency factors (IF) and inconsistency standard deviations (ISD). If the 95% CI of the IF included "0" and the 95% CI of the ISD included "1", the network demonstrated acceptable consistency. A local inconsistency test was also conducted using the point estimate method, with P-values > 0.05 indicating no significant differences between direct and indirect comparisons. In cases of significant inconsistency, sensitivity analyses were performed to identify sources of heterogeneity. If the data demonstrated no significant inconsistency, a consistency model was applied. Interventions were ranked based on the Surface Under the Cumulative Ranking (SUCRA) probability curve, with higher SUCRA values indicating superior intervention efficacy. For outcome indicators derived from more than 10 studies, "comparison-adjusted" funnel plots were constructed to evaluate potential small study effects and publication bias.

Sensitivity Analysis

We performed sensitivity analyses by excluding trials exhibiting substantial overall risk of bias (operationally defined as studies containing >5 domains rated as having unclear risk, based on risk of literature bias of included trials) to evaluate the robustness of outcomes including clinical response rate, incidence of nausea and vomiting and incidence of constipation.

Results

Literature Search

A total of 1,917 studies were retrieved. After the exclusion of 464 duplicate articles, 22 articles were included following the inclusion criteria. All 22 articles are in Chinese. This process of article selection is illustrated in Figure 1.

Features of Literature

All studies included in this analysis were conducted in China, comprising a total of 1,738 cases. The interventions evaluated across these studies comprised of manual acupuncture (MA), electroacupuncture (EA), moxibustion (MOX), acupoint injection (AI), acupoint catgut embedding (ACE), auricular-plaster therapy (AP), thumbtack needle (TN), and transcutaneous electrical acupoint stimulation (TEAS). The control group received conventional analgesic therapy based on the World Health Organization (WHO) three-step analgesic ladder (primarily weak and strong opioid medications).[21] In contrast, the experimental groups received one or more of the aforementioned acupuncture modalities in addition to the same conventional analgesic regimen.

Among the included studies, 17 employed a single intervention method, and 5 utilized combination interventions. Specifically, 8 studies had manual acupuncture as the sole intervention,[24–31] 2 studies had thumbtack needle,[32,33] 2 studies had acupoint catgut embedding,[34,35] another 2 studies had transcutaneous electrical acupoint stimulation,[36,37] and 3 more studies had moxibustion.[38–40] Combination interventions included manual acupuncture with moxibustion in 2 studies,[41,42] electroacupuncture with auricular-plaster therapy in 1 study,[43] manual acupuncture with auricular-plaster therapy in 1 study,[44] and manual acupuncture with acupoint injection in 1.[45] The fundamental characteristics of the literature reviewed are summarized in Table 2.

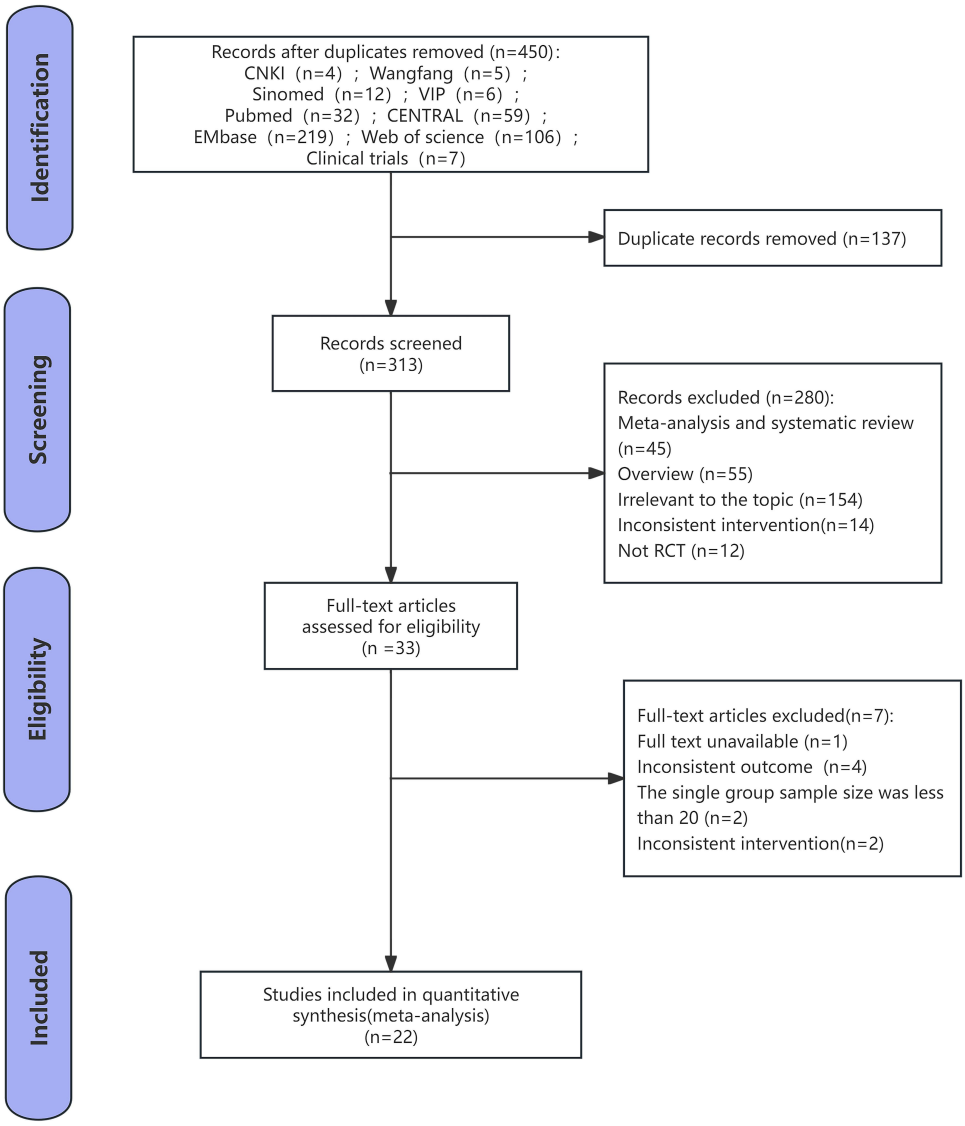

Figure 1 Literature screening process.

Risk of Literature Bias

Using the Cochrane risk of bias assessment tool, we evaluated the 22 included studies and found that all exhibited a moderate to high overall risk of bias. The risk of bias for each trial is shown in Figure 2. In terms of selection bias, all studies reported the use of randomization; 19 described appropriate randomization methods, with 15 using a digital random number table and 3 employing software-based randomization, while 4 failed to specify their procedures. Regarding blinding and detection bias, none of the studies provided detailed descriptions of blinding. Given the particular nature of acupuncture interventions, however, blinding of participants and practitioners is generally difficult to achieve, which may inherently increase the risk of performance and detection bias. For attrition bias, 20 studies reported complete outcome data with no dropouts, while 2 studies had dropout rates of 4.7%;[24,31] none specified how missing data were handled. With respect to reporting bias, only one study reported clinical trial registration and fully disclosed outcome data, while others lacked registration information, making it difficult to assess this domain. Additional potential sources of bias could not be evaluated due to insufficient information. Overall, the methodological quality of the included studies was limited, and the findings of this meta-analysis should therefore be interpreted with caution.

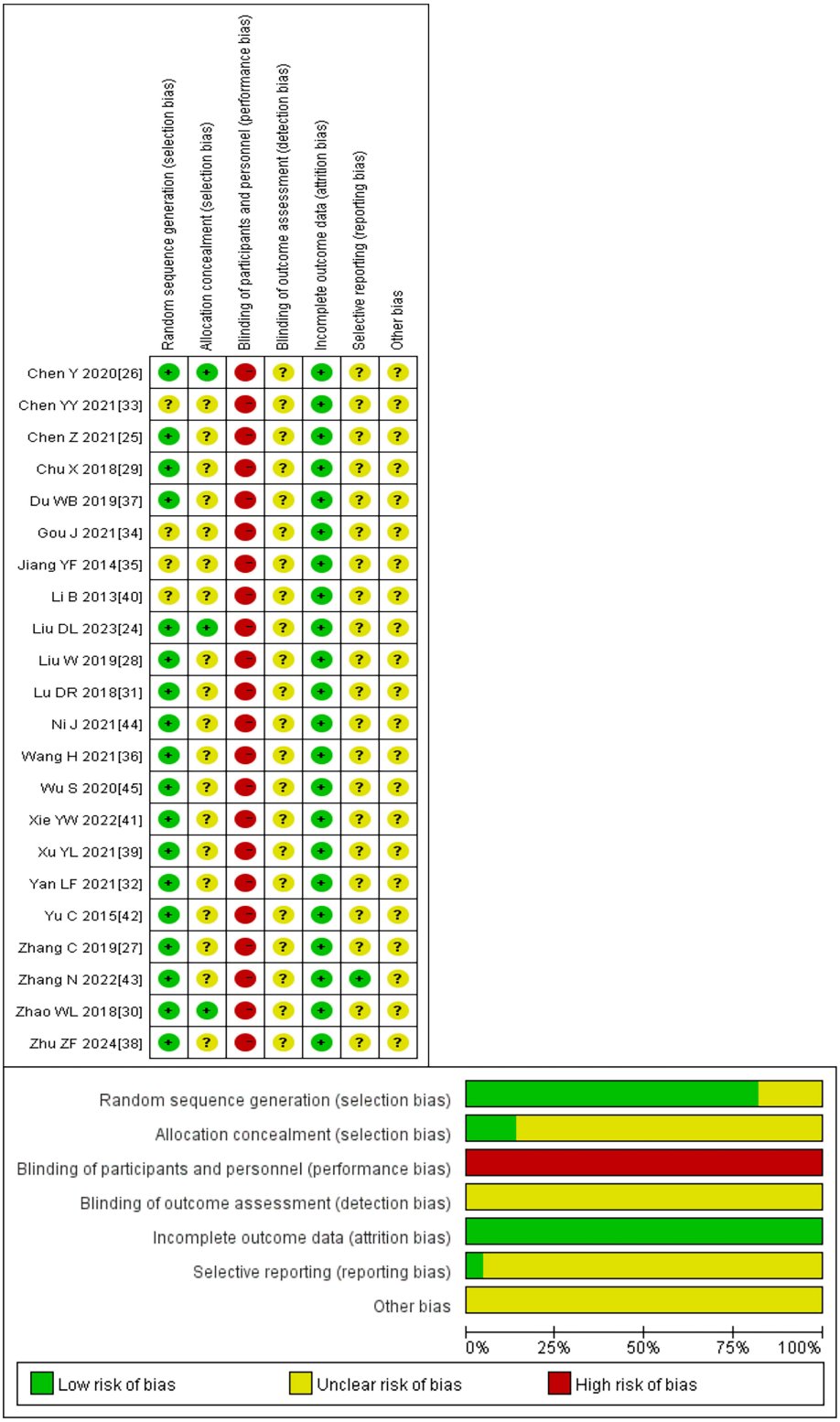

Figure 2 Results of the risk of bias evaluation.

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Table 2 Characteristics of Interventions of Included Studies

Included Studies	Sample (Male/Female)		Age (Years)		Interventions		Type of Cancer (Number of Cases)		Treatment Course	Outcome Indicators
	T	C	T	C	T	C	T	C		
Zhu ZF[38] 2024	30 (15/15)	30 (13/17)	44.52±5.20	44.29±5.04	MOX	UC	Breast cancer 9; pulmonary pain 13; prostate cancer 8	Breast cancer 9; pulmonary pain 11; prostate cancer 10	10d	①
Liu DL[24] 2023	30 (17/13)	30 (16/14)	58.40±12.22	60.30±9.56	MA	UC	Lung cancer 12; Breast cancer 7; Prostate cancer 6; Thyroid cancer 3; Other 2	Lung cancer 13; Breast cancer 8; Prostate cancer 5; Thyroid cancer 4; Other 2	4w	①②③
Zhang N[43] 2022	30 (16/14)	30 (15/15)	57±10	55±9	EA+AP	UC	Colorectal cancer 8; Gastric and esophageal cancers; Lung cancer 7; Other 7	Colorectal cancer 10; Gastric and esophageal cancers; Lung cancer 6; Cholangiocarcinoma 2; 5 Other malignancies	4w	①②③
Xie YW[41] 2022	51 (27/24)	51 (26/25)	64.60±7.38	65.22±9.56	MA+MOX	UC	Multiple myeloma 51	Multiple myeloma 51	4w	①②③
Yan LF[32] 2021	60 (36/24)	60 (38/22)	59.72±15.87	60.44±15.63	TN	UC	Lung cancer 18; Gastric cancer 14; Colorectal cancer 13; Liver cancer 12; Other 3	Lung cancer 20; Gastric cancer 15; Colorectal cancer 11; Liver cancer 10; Other 4	15d	①
Xu YL[39] 2021	50 (25/25)	50 (28/22)	53.12±2.54	55.30±2.98	MOX	UC	Lung cancer 50	Lung cancer 50	10d	①
Wang H[36] 2021	30 (17/13)	30 (16/14)	56.92±11.47	57.21±10.89	TEAS	UC	Lung cancer 30	Lung cancer 30	4w	②
Ni J[44] 2021	40 (30/10)	40 (33/7)	56.28±7.10	53.88±6.23	MA+AP	UC	Lung cancer 40	Lung cancer 40	2w	①②
Gou J[34] 2021	40 (21/19)	40 (22/18)	61.45±16.28	61.62±16.11	ACE	UC	Lung cancer 8; Gastric cancer 9; Breast cancer 7; Prostate cancer 5; Liver cancer 6; Cervical cancer 5	Lung cancer 9; Gastric cancer 8; Breast cancer 8; Prostate cancer 6; Liver cancer 5; Cervical cancer 4	2w	①②③
Chen YY[33] 2021	31 (17/14)	31 (19/12)	60.3±8.2	60.5±8.4	TN	UC	NA	NA	40d	①
Chen Z[25] 2021	54 (28/26)	54 (30/24)	54±5	54±4	MA	UC	Colon cancer 28; Lung cancer 12; Gastric cancer 9; Other 5	Colon cancer 25; Lung cancer 13; Gastric cancer 10; Other 6	1w	①②③
Wu S[45] 2020	80 (53/27)	80 (52/28)	59.28±3.66	58.13±3.46	MA+AI	UC	Lung cancer 80	Lung cancer 80	4w	①②③
Chen Y[26] 2020	90 (NA)	30 (NA)	/	/	MA	UC	Lung cancer 90	Lung cancer 30	10d	①②③
Zhang C[27] 2019	34 (22/12)	34 (20/14)	48.52±6.14	48.86±6.04	MA	UC	Prostate cancer 8; Lung cancer 10; Breast cancer 9; Gastric cancer 7	Prostate cancer 9; Lung cancer 9; Breast cancer 10; Gastric cancer 6	4w	①
Liu W[28] 2019	43 (28/15)	40 (26/14)	63.92±8.47	64.08±8.52	MA	UC	Lung cancer 43	Lung cancer 40	3w	①②③

(*Continued*)

Table 2 (Continued).

Included Studies	Sample (Male/Female)		Age (Years)		Interventions		Type of Cancer (Number of Cases)		Treatment Course	Outcome Indicators
	T	C	T	C	T	C	T	C		
Du WB[37] 2019	24 (16/8)	24 (18/6)	59.1±1.6	58.2±1.6	TEAS	UC	Lung cancer 12; Breast cancer 6; Prostate Cancer 3; Other 3	Lung cancer 10; Breast cancer 6; Prostate Cancer 4; Other 4	4w	②③
Zhao WL[30] 2018	30 (0/30)	30 (0/30)	39.27±10.56	40.00±10.12	MA	UC	Breast cancer 30	Breast cancer 30	8w	①
Lu DR[31] 2018	30 (14/16)	30 (15/15)	62.50±10.06	62.50±10.06	MA	UC	NA	NA	5d	①
Chu X[29] 2018	30 (15/15)	29 (13/16)	61.01±9.81	60.09±9.78	MA	UC	Lung cancer 12; Breast cancer 7; Colorectal 5; Other 6	Lung cancer 13; Breast cancer 6; Colorectal 5; Other 5	1w	①②③
Yu C[42] 2015	34 (34/0)	34 (34/0)	76.8 ± 4.8	77.3 ± 6.0	MA+MOX	UC	Prostate Cancer 34	Prostate Cancer 34	12w	①
Jiang YF[35] 2014	30 (17/13)	30 (16/14)	60.30±3.36	61.47±3.21	ACE	UC	NA	NA	1w	①②③
Li B[40] 2013	30 (17/13)	30 (16/14)	NA	NA	MOX	UC	Lung cancer 11, Breast cancer 6, Prostate Cancer 5, Head and neck neoplasms 7, Gastric cancer 1	Lung cancer 12, Breast cancer 6, Prostate Cancer 4, Head and neck neoplasms 6, Liver cancer 1, Esophageal cancer 1	12w	①

Abbreviations: UC, Usual control; MA, Manual acupuncture; EA, Electro acupuncture; MOX, Moxibustion; AI, Acupoint injection; ACE, Acupoint catgut embedding; AP, Auricular point therapy; TN, Thumbtack needle; TEAS, Transcutaneous electrical acupoint stimulation; T, Treatment Group; C, Control Group; ①, Clinical effective rate; ②, the incidence of nausea and vomiting; ③, the incidence of constipation.

Consistency and Heterogeneity Analysis

Since no closed loop was present in these outcomes, the consistency model was directly applied. The heterogeneity across all outcome indicators was low at the overall level, with I^2 values less than 50%, thus the fixed-effect model was used for analysis.

Results of Network Meta-Analysis

Clinical Effective Rate

The 20 included studies all reported the clinical efficacy rate, with a total sample size of 1826 cases. These studies formed an evidence network diagram comprising 9 intervention nodes and 8 direct comparisons (Figure 3). Among them, manual acupuncture involved the largest sample size, which was 311 cases. There were 7 studies that compared UC with MA, which had the highest frequency of direct comparison. Compared with the use of usual control alone, ACE (OR=0.34,95% CI=[0.12, 0.90]),EA+AP (OR=0.25,95% CI=[0.06, 0.87]),MA (OR=0.24,95% CI=[0.15, 0.39]),MA +AP (OR=0.18,95% CI=[0.02, 0.85]),MOX (OR=0.22,95% CI=[0.09, 0.51]) could improve the clinical effective rate, and the differences between the groups were statistically significant. The SUCRA of different interventions in descending order was as follows: TN>MA+AP>MOX>MA>EA+AP>ACE>MA+MOX>MA+AI>UC, as shown in Table 3 and 4.

Incidence of Nausea and Vomiting

The incidence of nausea and vomiting was reported in 13 of the 22 studies included, and in the evidence network diagram for the incidence of nausea and vomiting, an evidence network diagram containing 8 intervention nodes centered on UC was formed (Figure 4), with a total of 7 pairs of direct comparatives.

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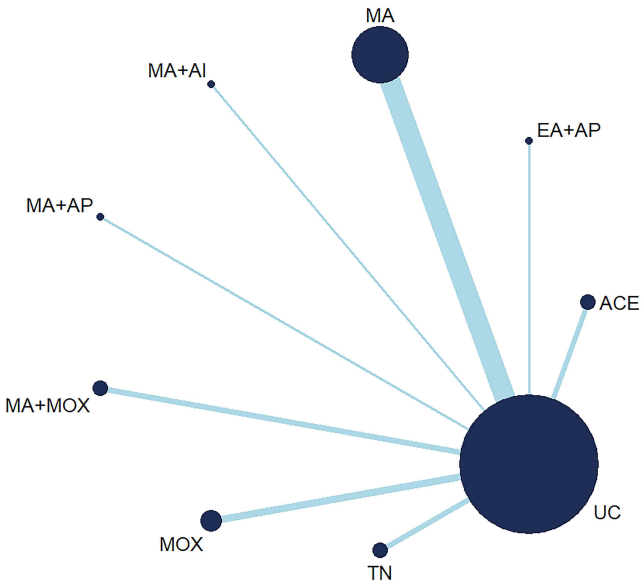

Figure 3 Evidence network diagram of clinical effective rate of different acupuncture therapies against CIBP.

Compared with usual control alone ACE (OR=0.06,95% CI=[0, 0.37]), EA+AP (OR=0.08,95% CI=[0.01, 0.28]) all reduced the incidence of nausea and vomiting, and the differences were statistically significant in all comparisons between the groups. The comparison between the acupuncture and moxibustion groups suggests that ACE (OR=0.11,95% CI=[0, 0.86]),EA+AP (OR=0.15,95% CI=[0.02, 0.68])>MA;EA+AP (OR=0.15,95% CI=[0.02, 0.85]) >TEAS, and the differences were statistically significant in all comparisons between the groups. The SUCRA of different interventions in descending order was as follows: ACE>EA+AP>MA+AP>MA+MOX>TEAS>MA>MA+AI>UC, as shown in Table 5 and 6.

Table 3 League Table of Clinical Effective Rate

ACE								
0.73 (0.13, 3.75)	EA+AP							
0.71 (0.24, 2.23)	0.97 (0.25, 4.42)	MA						
1.55 (0.46, 5.42)	2.12 (0.49, 10.43)	2.18 (0.91, 5.12)	MA+AI					
0.53 (0.06, 3.46)	0.73 (0.07, 6.08)	0.76 (0.09, 3.77)	0.35 (0.04, 1.91)	MA+AP				
1.47 (0.4, 5.52)	2 (0.44, 10.55)	2.06 (0.77, 5.38)	0.95 (0.31, 2.84)	2.74 (0.47, 24.67)	MA+MOX			
0.65 (0.17, 2.47)	0.89 (0.19, 4.68)	0.92 (0.33, 2.41)	0.42 (0.13, 1.28)	1.22 (0.2, 10.89)	0.45 (0.13, 1.47)	MOX		
0.54 (0.11, 2.45)	0.74 (0.12, 4.47)	0.77 (0.19, 2.49)	0.35 (0.08, 1.3)	1.02 (0.13, 10.16)	0.37 (0.08, 1.48)	0.83 (0.18, 3.44)	TN	
2.94 (1.11, 8.33)	4.01 (1.14, 17)	4.14 (2.58, 6.78)	1.9 (0.94, 3.95)	5.45 (1.18, 42.4)	2.01 (0.88, 4.75)	4.49 (1.97, 11.31)	5.36 (1.85, 19.83)	UC

Note: Effect sizes represent summary odds ratios and 95% confidence intervals. Values lower than 1 favour the treatment in the corresponding row, while values higher than 1 favour the treatment in the corresponding column; Grayish-blue shaded cells indicate P<0.05.
Abbreviations: ACE, Acupoint catgut embedding; EA, Electro acupuncture; AP, Auricular-plaster therapy; MA, Manual acupuncture; AI, Acupoint injection; MOX, Moxibustion; TN, Thumbtack needle; UC, Usual control.

Table 4 SUCRA Rank Diagram of Clinical Effective Rate

Treatment	SUCRA	Rank
Thumbtack needle (TN)	75.2	1
Manual acupuncture + Auricular-plaster therapy (MA+AP)	72.3	2
Moxibustion (MOX)	69.0	3
Manual acupuncture (MA)	66.0	4
Electroacupuncture + Auricular-plaster therapy (EA+AP)	62.1	5
Acupoint catgut embedding (ACE)	47.9	6
Manual acupuncture + Moxibustion (MA+MOX)	29.3	7
Manual acupuncture + Acupoint injection (MA+AI)	26.3	8
Usual control (UC)	1.62	9

Incidence of Constipation

11 of the 22 included studies reported on the incidence of constipation, an evidence network diagram containing seven intervention nodes centered on the UC was formed (Figure 5).A total of six pairs of direct comparisons were formed.

Compared with usual control alone, EA+AP (OR=0.05,95% CI=[0.01, 0.18]), TEAS (OR=0.22,95% CI=[0.05, 0.81]) and ACE (OR=0.1,95% CI=[0.02, 0.34]) reduced the incidence of constipation, and the between group the differences were statistically significant in all comparisons. The SUCRA of different interventions in descending order was as follows: EA+AP>ACE>TEAS>MA+MOX>MA>MA+AI>UC, as shown in Table 7 and 8.

Sensitivity Analysis

The sensitivity analysis results are presented in Supplementary Tables S3–S5. After excluding studies[33–35,40] with an overall high risk of bias that employed ACE, TN, and MOX interventions, the ACE category was completely excluded from analysis as both relevant studies were deemed high-risk. The sensitivity analysis indicated that the pooled effect sizes and p-values changed only slightly after these exclusions, and the direction and statistical significance of the results remained consistent. Therefore, excluding these high-risk studies did not materially alter the overall conclusions of this meta-analysis.

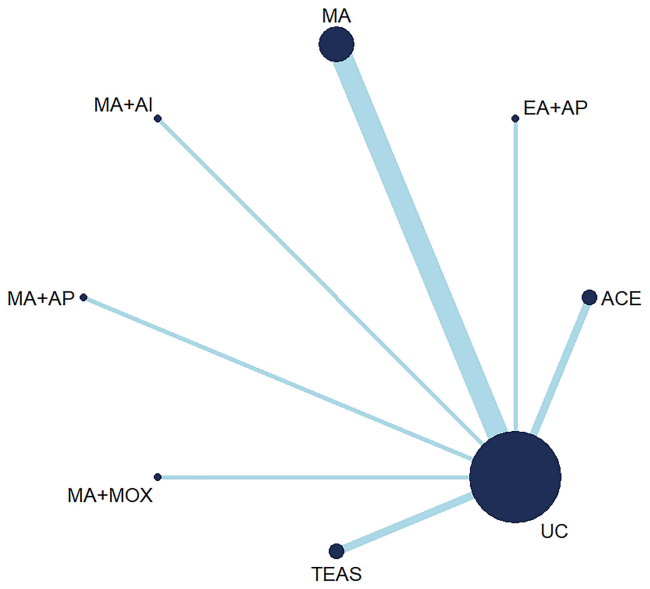

Figure 4 Evidence network diagram of incidence of nausea and vomiting of different acupuncture therapies against CIBP.

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Table 5 League Table of Incidence of Nausea and Vomiting

ACE							
0.74 (0.02, 9.39)	EA+AP						
0.11 (0, 0.86)	0.14 (0.02, 0.68)	MA					
0.05 (0, 1.1)	0.07 (0, 1.04)	0.52 (0.05, 5.7)	MA+AI				
0.31 (0.01, 14.41)	0.43 (0.03, 15.02)	2.95 (0.3, 89.16)	5.96 (0.25, 309.87)	MA+AP			
0.21 (0.01, 2.6)	0.28 (0.03, 2.28)	1.93 (0.42, 11.49)	3.79 (0.27, 59.35)	0.65 (0.02, 9.69)	MA+MOX		
0.11 (0, 1.05)	0.15 (0.02, 0.86)	1.04 (0.28, 3.98)	2.02 (0.17, 25.15)	0.35 (0.01, 4)	0.54 (0.08, 3.04)	TEAS	
0.06 (0, 0.37)	0.08 (0.01, 0.28)	0.52 (0.24, 1.09)	1 (0.1, 9.73)	0.18 (0.01, 1.49)	0.27 (0.05, 1)	0.5 (0.16, 1.41)	UC

Notes: Effect sizes represent summary odds ratios and 95% confidence intervals. Values higher than 1 favour the treatment in the corresponding row, while values lower than 1 favour the treatment in the corresponding column; Grayish-blue shaded cells indicate P<0.05;
Abbreviations: ACE, Acupoint catgut embedding; EA, Electro acupuncture; AP, Auricular-plaster therapy; MA, Manual acupuncture; AI, Acupoint injection; MOX, Moxibustion; TEAS, Transcutaneous electrical acupoint stimulation; UC, Usual control.

Table 6 SUCRA Rank Diagram of Incidence of Nausea and Vomiting

Treatment	SUCRA	Rank
Acupoint catgut embedding (ACE)	87.7	1
Electroacupuncture + Auricular-plaster therapy (EA+AP)	85.1	2
Manual acupuncture + Auricular-plaster therapy (MA+AP)	65.2	3
Manual acupuncture + Moxibustion (MA+MOX)	56.8	4
Transcutaneous electrical acupoint stimulation (TEAS)	37.9	5
Manual acupuncture (MA)	36.7	6
Manual acupuncture + Acupoint injection (MA+AI)	20.3	7
Usual control (UC)	10.2	8

Synthetic Sorting Bubble Diagrams

We used synthetic sorting bubble plots to present a synthesis of the relatively better CIBP interventions in the NMA. The bubble plots suggested that, although ACE exhibited the lowest incidence of nausea and vomiting and MA+AP achieved the highest clinical effective rate, MA+MOX demonstrated the best overall balance when both factors were considered. Meanwhile considering the clinical efficiency and incidence of constipation, MA+MOX was also the best intervention (Figures 6 and 7).

Publication Bias

In this meta-analysis, the visual assessment of the funnel plot revealed a distribution that was not entirely symmetrical, suggesting the possible presence of publication bias or small study effects within the research (Figures 8–10).

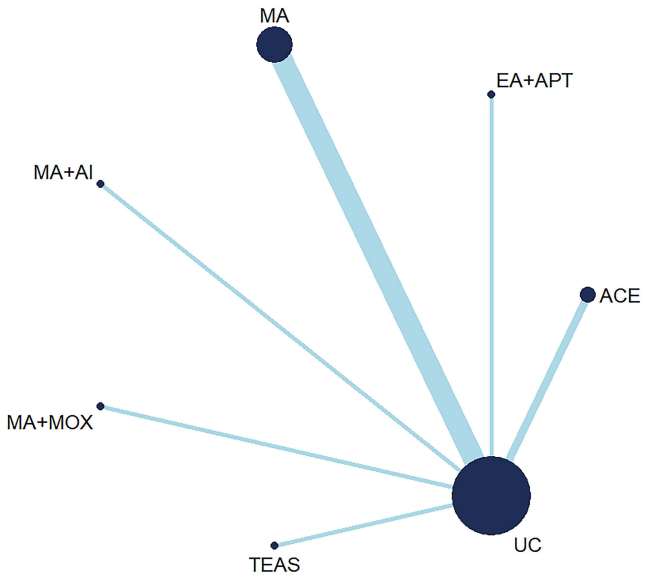

Figure 5 Evidence network diagram of incidence of constipation of different acupuncture therapies against CIBP.

Discussion

Summary and Interpretation of Findings

In this network meta-analysis of acupuncture therapies for cancer-induced bone pain (CIBP), the included studies applied acupuncture in combination with standard pharmacologic treatments. Combination therapy consistently yielded higher clinical response rates and fewer adverse effects than conventional pharmacologic treatment alone, supporting a synergistic role of acupuncture within multimodal pain management. Specifically, our analysis indicated that TN was most likely to improve overall clinical effectiveness, ACE was most effective for mitigating nausea and vomiting, and EA+AP may best reduce constipation. When outcomes were considered collectively, MA+MOX achieved the best balance between pain relief

Table 7 League Table of Incidence of Constipation

ACE						
1.93 (0.25, 13.85)	EA+AP					
0.18 (0.03, 0.86)	0.09 (0.02, 0.45)	MA				
0.09 (0, 4.6)	0.05 (0, 2.49)	0.54 (0.01, 24)	MA+AI			
0.19 (0.03, 0.96)	0.1 (0.02, 0.49)	1.07 (0.29, 4.06)	1.98 (0.04, 86.61)	MA+MOX		
0.43 (0.06, 3.12)	0.23 (0.03, 1.61)	2.48 (0.5, 14.09)	4.61 (0.09, 229.38)	2.31 (0.45, 13.51)	TEAS	
0.1 (0.02, 0.34)	0.05 (0.01, 0.18)	0.54 (0.22, 1.33)	1 (0.02, 38.82)	0.51 (0.19, 1.29)	0.22 (0.05, 0.81)	UC

Notes: Effect sizes represent summary odds ratios and 95% confidence intervals. Values higher than 1 favour the treatment in the corresponding row, while values lower than 1 favour the treatment in the corresponding column; Grayish-blue shaded cells indicate P<0.05.

Abbreviations: ACE, Acupoint catgut embedding; EA, Electro acupuncture; AP, Auricular-plaster therapy; MA, Manual acupuncture; AI, Acupoint injection; MOX, Moxibustion; TEAS, Transcutaneous electrical acupoint stimulation; UC, Usual control.

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Table 8 SUCRA Rank Diagram of Incidence of Constipation

Treatment	SUCRA	Rank
Electroacupuncture + Auricular-plaster therapy (EA+AP)	93.5	1
Acupoint catgut embedding (ACE)	81.9	2
Transcutaneous electrical acupoint stimulation (TEAS)	62.7	3
Manual acupuncture + Moxibustion (MA+MOX)	38.4	4
Manual acupuncture (MA)	36.0	5
Manual acupuncture + Acupoint injection (MA+AI)	26.1	6
Usual control (UC)	11.3	7

and reduction of opioid-related side effects. However, this result must be interpreted with caution, as most included studies were of moderate to high risk of bias, and publication bias could not be excluded. The apparent advantage of MA + MOX may therefore reflect, at least in part, methodological limitations rather than true treatment superiority.

These findings are broadly consistent with previous meta-analyses and systematic reviews suggesting that acupuncture or acupuncture-point stimulation may improve cancer pain and reduce opioid-related side effects, but that the overall certainty of evidence remains low to moderate.[46,47] Likewise, a guideline review highlighted acupuncture as a potential adjunct for cancer pain but emphasized the need for rigorous, well-controlled RCTs to confirm efficacy.[48] Mechanistically, manual acupuncture likely engages endogenous opioid, serotoninergic, and descending inhibitory pathways to modulate nociceptive transmission,[49,50] while moxibustion may provide local anti-inflammatory and neuroimmune regulatory effects through reduction of cytokines such as IL-1β and IL-6.[51] These biological actions could account for the observed additive analgesic benefit when used with pharmacologic therapy. Beyond analgesia, acupuncture also mitigates opioid-related side effects. By modulating the neuroendocrine-immune network and restoring autonomic balance, it helps alleviate nausea, vomiting, and constipation, possibly through regulation of gastrointestinal hormones and enhancement of parasympathetic activity.[52–54] A systematic review further supports the role of moxibustion in relieving these gastrointestinal symptoms among cancer patients.[55] Collectively, these mechanisms provide a biological rationale for the observed benefits of MA + MOX in managing CIBP and its treatment-related adverse effects.

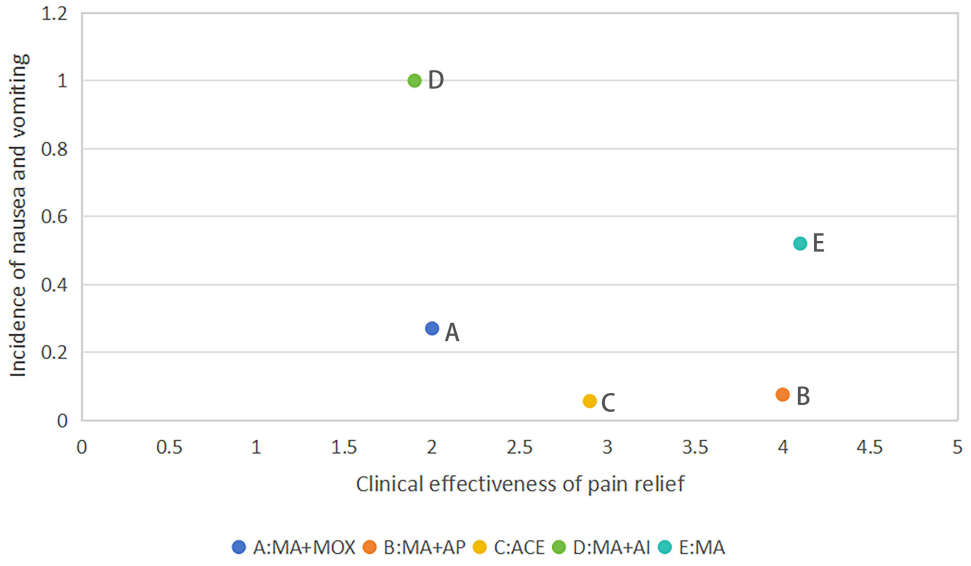

Figure 6 Synthetic sorting bubble diagram plot for the clinical effectiveness of pain relief and incidence of nausea and vomiting.

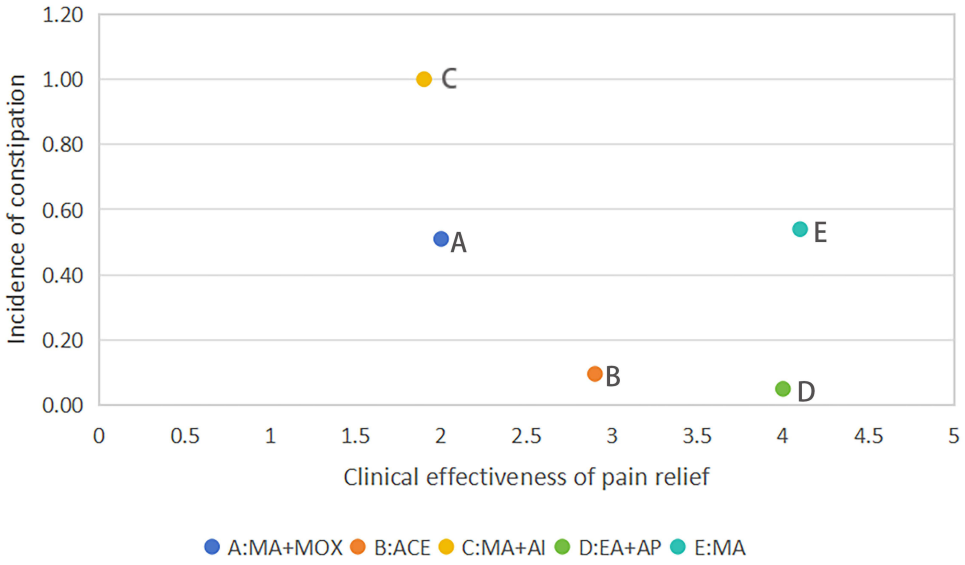

Figure 7 Synthetic sorting bubble diagram plot for the clinical effectiveness of pain relief and incidence of constipation.

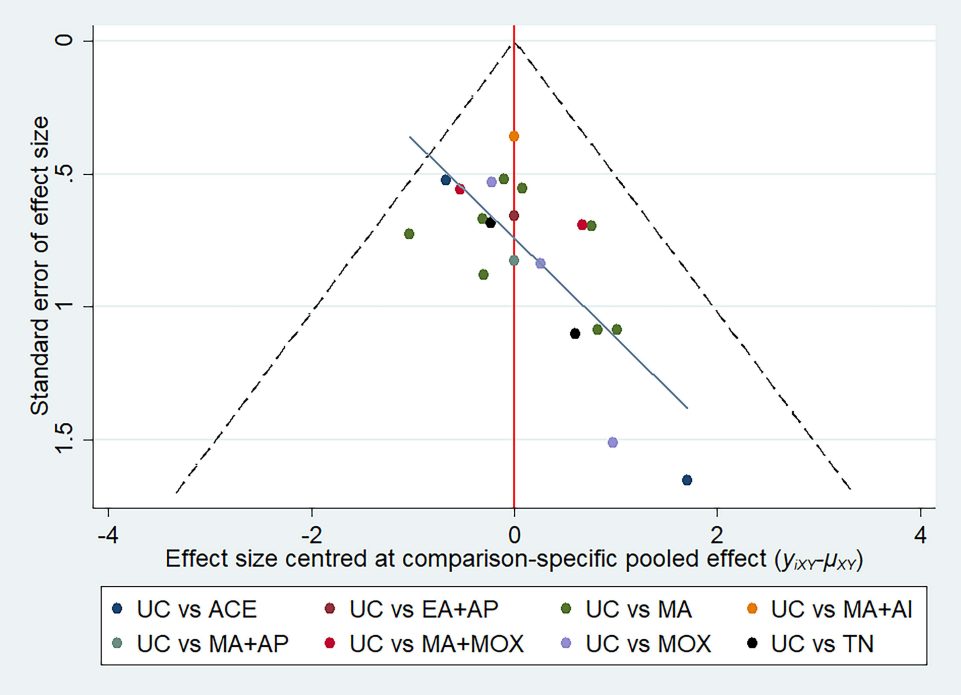

Figure 8 Funnel plots of clinical effective rate.

Implications for Study and Practice

From a clinical standpoint, acupuncture represents a promising adjunctive strategy for managing CIBP, particularly for patients who experience inadequate pain control or intolerable side effects from pharmacological therapy. For individuals requiring opioid analgesics, adjunctive acupuncture may enhance pain relief, reduce adverse effects, and potentially improve functional status without increasing medication burden. In this network meta-analysis incorporating both clinical response rates and incidence of adverse drug reactions, MA+MOX may emerge as the intervention achieving the most favorable balance between efficacy and safety. Sensitivity analyses supported the robustness of this finding, though some interventions (eg, ACE and TN) showed evidence of bias-driven overestimation. Therefore, interventions showing stable

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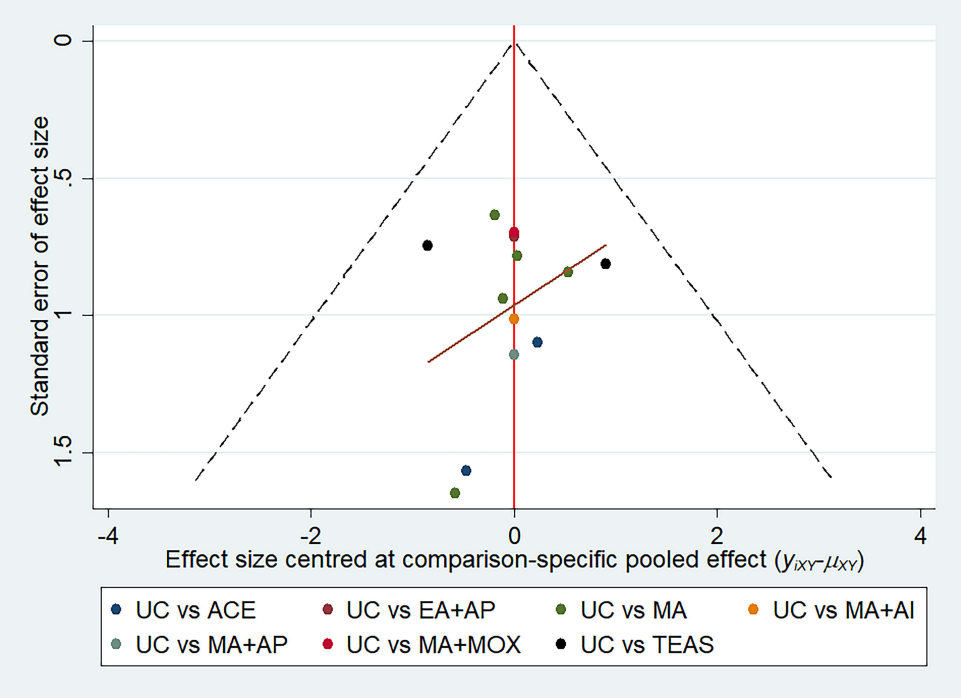

Figure 9 Funnel plots of incidence of nausea and vomiting.

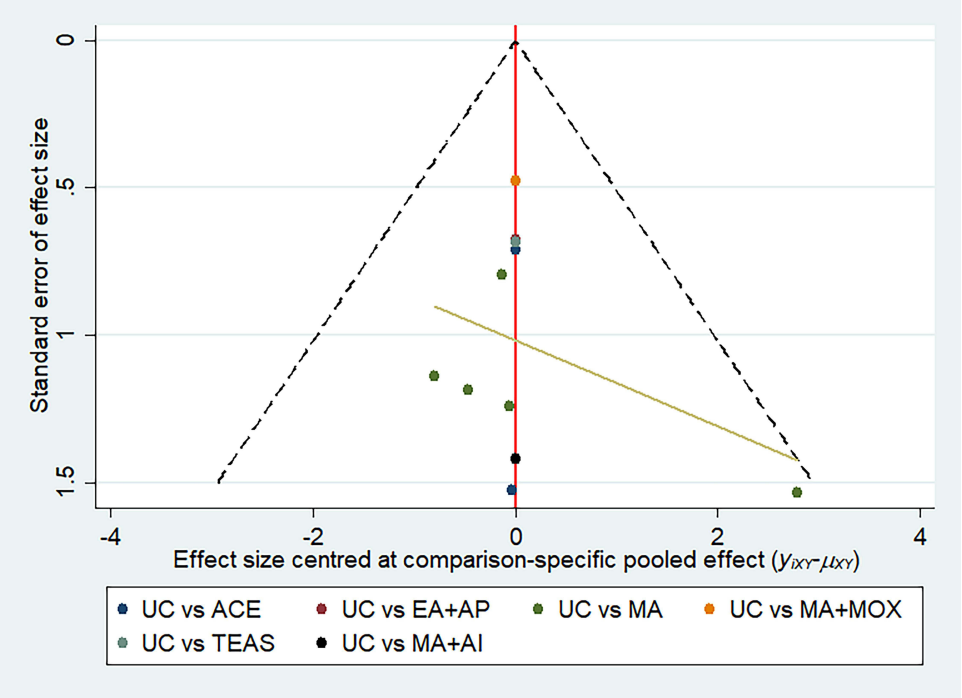

Figure 10 Funnel plots of incidence of constipation.

efficacy after bias adjustment should be prioritized in clinical practice, while results from interventions with substantial bias influence should be interpreted cautiously.

Our analysis of acupoint selection patterns revealed that Zusanli (ST36), Shenshu (BL23), Ashi points, Dazhu (BL11), and Xuanzhong (GB39) were the most frequently used sites. The therapeutic rationale followed two

complementary principles: Ashi points were selected to relieve focal Qi-blood stagnation, while ST36 and BL23 were used to tonify Qi and kidney function, strengthening systemic vitality and bone integrity. This dual strategy of local de-obstruction and systemic reinforcement provides a traditional yet evidence-informed framework for optimizing acupuncture protocols in CIBP management.

Regarding the selection of outcome measures, this study used the clinical effectiveness rate as the primary endpoint rather than direct pain score reduction. While standardized scales such as the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) are more quantitative, only a limited subset of trials reported comparable data. The "clinical effectiveness rate" remains a commonly used and clinically meaningful indicator in acupuncture research. Nevertheless, this approach may obscure finer distinctions in pain intensity, and future research should integrate standardized pain scales to improve precision. For secondary outcomes, nausea/vomiting and constipation were selected as representative indicators of opioid-related side effects, reflecting acupuncture's potential to provide complementary benefits beyond analgesia. Although 14 of the 22 included RCTs reported quality-of-life (QoL) assessments, they used heterogeneous tools (EORTC QLQ-C30, KPS, ECOG, SF-36), precluding meaningful pooled analysis. The lack of uniform QoL instruments remains a key barrier to evidence synthesis. Future trials should adopt standardized and widely accepted QoL scales and develop a core outcome set encompassing both subjective and objective indicators. Such harmonization would substantially enhance the reliability and clinical applicability of meta-analyses in this field.

In summary, our findings support the role of acupuncture as an adjunctive modality that can both enhance analgesia and mitigate treatment-related burden. Clinicians should select specific acupuncture protocols based on pain severity, opioid tolerance, patient preference, and treatment goals, while acknowledging that current evidence remains preliminary and requires confirmation through rigorous trials. Future research should employ rigorous trial designs with transparent randomization, appropriate blinding, and prospective registration, ensuring methodological consistency and greater confidence in clinical recommendations.

Strengths and Limitations of the Study

This study is, to our knowledge, the first network meta-analysis to comprehensively compare the relative efficacy and safety of multiple acupuncture therapies for cancer-induced bone pain (CIBP). By integrating direct and indirect evidence, it provides a comparative framework for identifying potentially optimal acupuncture interventions and offers clinically relevant insights for multimodal pain management. The inclusion of both clinical effectiveness and opioid-related adverse effects as dual endpoints strengthens its practical relevance, reflecting both symptom relief and tolerability. Furthermore, sensitivity analyses were conducted to ensure the robustness of the findings and to identify potential bias-driven overestimations.

However, several limitations should be considered. First, all included studies were conducted in China and published in Chinese journals, which may limit generalizability and introduce publication or language bias. Most trials were single-center studies with small sample sizes and incomplete reporting of randomization, allocation concealment, and blinding, leading to moderate certainty of evidence. Second, the primary endpoint, clinical effectiveness rate, though widely used, may not fully capture subtle gradations in pain relief. Only a subset of studies reported standardized pain scores (VAS or NRS), and the limited availability of comparable data prevented their inclusion in the network meta-analysis.Future studies should report direct pain scores using standardized scales such as the VAS or NRS to enhance comparability across trials. Likewise, data on quality of life (QoL) were inconsistently reported using heterogeneous scales, preventing meta-analytic synthesis. Future studies should prioritize standardized, validated, and comparable pain and QoL assessment tools to allow for more nuanced evaluation of treatment effects. Third, in most studies, acupuncture was combined with pharmacologic treatments, but details regarding drug types, dosages, and duration were often insufficient. This limitation prevents a clear understanding of whether acupuncture reduced opioid requirements or improved drug tolerance. Although MA+MOX appeared to achieve the best balance between analgesic efficacy and reduction of opioid-related side effects, the lack of detailed pharmacologic information across studies precludes identifying the optimal drug-acupuncture combination. Future trials should systematically document and analyze changes in analgesic dosage to clarify the potential opioid-sparing effects of acupuncture. Furthermore, the short follow-up duration of most studies limits conclusions regarding the long-term sustainability of analgesic benefits and side-effect reduction. Economic evaluations were also lacking, preventing assessment of acupuncture's cost-effectiveness compared with standard care.

Despite these limitations, this study provides valuable preliminary comparative evidence for clinical decision-making. It underscores acupuncture's potential as an adjunctive therapy within comprehensive cancer pain management, especially for patients who experience suboptimal relief or intolerable adverse reactions from pharmacologic therapy alone. To advance the field, future research should focus on large-scale, multicenter, rigorously designed RCTs with standardized reporting, consistent outcome measures, and transparent methodology to strengthen the evidence base for acupuncture in CIBP.

Conclusion

Based on this network meta-analysis, the eight acupuncture therapies exhibited varying degrees of analgesic efficacy in the management of cancer-induced bone pain (CIBP). Among them, manual acupuncture combined with moxibustion (MA +MOX) may provide a potentially favorable balance between pain relief and reduction of opioid-related adverse effects. These findings suggest, but do not confirm, that acupuncture could serve as a supportive adjunct to pharmacologic therapy in enhancing analgesia and improving tolerability. Treatment selection should be individualized according to patients' pain severity, opioid tolerance, and treatment preferences. Given the moderate methodological quality, high risk of bias, and limited generalizability of existing studies, these results should be viewed as exploratory and interpreted with caution. Future large-scale, multicenter randomized controlled trials with rigorous designs and standardized pain and quality-of-life measures are required to verify these findings and better define the role of acupuncture within evidence-based CIBP management.

Abbreviations

UC, Usual control; MA: Manual acupuncture; EA, Electroacupuncture; MOX, Moxibustion; AI, Acupoint injection; ACE, Acupoint catgut embedding; AP, Auricular point therapy; TN, Thumbtack needle; TEAS, Transcutaneous electrical acupoint stimulation.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Declarations

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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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