Digital Chinese Medicine

External application of traditional Chinese medicine in combination with three-step analgesic ladder therapy for cancer-induced bone pain: a systematic review and meta-analysis

Fei WANG[a], Guihua LAI[b], Fang ZHOU[a], Duorui NIE[a], Xiongtao CHENG[a], Yue WANG[a], Jianxiong CAO[c*]

a. Graduate School, Hunan University of Chinese Medicine, Changsha, Hunan 410208, China

b. Department of Rehabilitation, The First Affiliated Hospital of University of South China, Hengyang, Hunan 421001, China

c. Department of Oncology, The First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan 410007, China

ARTICLE INFO

Article history
Received 11 October 2024
Accepted 20 January 2025
Available online 25 March 2025

Keywords
External application of traditional Chinese medicine (EA-TCM)
Three-step analgesic ladder therapy
Cancer-induced bone pain (CIBP)
Systematic review
Meta-analysis

ABSTRACT

Objective To systematically evaluate the overall efficacy of external application of traditional Chinese medicine (EA-TCM) in combination with oral three-step analgesic ladder therapy for patients suffering from cancer-induced bone pain (CIBP).

Methods We conducted a literature search of randomized controlled trials on the combination of EA-TCM and three-step analgesic ladder therapy for CIBP across ten databases and two registration systems. It included four Chinese databases [Chinese Biomedical Literature Database (SinoMed), China National Knowledge Infrastructure (CNKI), Wanfang Database, and China Science and Technology Journal Database (VIP)], six English databases (Scopus, Embase, Web of Science, PubMed, Cochrane Library, and OpenGrey), and two registration systems (Chinese Clinical Trial Registry and ClinicalTrials.gov). The timeframe for the literature search extended from the inception of each database to December 31, 2023. Meta-analysis was performed using RevMan (v5.4.1), and the outcome indicators (pain relief rate, analgesic duration, quality of life, pain intensity, breakthrough pain frequency, and adverse reactions) were graded using GRADE profiler (v3.6).

Results According to the established inclusion and exclusion criteria, a total of 43 studies was deemed eligible, involving 3 142 participants with CIBP. The results of meta-analysis showed that compared with oral three-step analgesic ladder therapy alone, the combined therapy of EA-TCM and three-step analgesic ladder has a significant improvement in pain relief rate [risk ratio (RR) = 1.32, 95% confidence interval (CI): 1.24 to 1.41, $P < 0.000\ 01$], analgesic duration [mean difference (MD) = 1.33, 95% CI: 0.97 to 1.69, $P < 0.000\ 01$], and quality of life (MD = 5.66, 95% CI: 4.88 to 6.44, $P < 0.000\ 01$). Furthermore, the combined therapy significantly reduced pain intensity (MD = – 1.00, 95% CI: – 1.19 to – 0.80, $P < 0.000\ 01$), breakthrough pain frequency (MD = – 0.43, 95% CI: – 0.51 to – 0.36, $P < 0.000\ 01$), and adverse reactions (RR = 0.60, 95% CI: 0.53 to 0.68, $P < 0.000\ 01$) in CIBP patients. Based on the GRADE assessment, the level of evidence varied from low to moderate.

Conclusion EA-TCM combined with the three-step analgesic ladder therapy can effectively alleviate pain symptoms in patients with CIBP and improve their quality of life. Additionally, the EA-TCM can effectively reduce the incidence of adverse reactions associated with three-step analgesic therapy.

*Corresponding author: Jianxiong CAO, E-mail: 003998@hnucm.edu.cn.

Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmed.2025.03.006

Citation: WANG F, LAI GH, ZHOU F, et al. External application of traditional Chinese medicine in combination with three-step analgesic ladder therapy for cancer-induced bone pain: a systematic review and meta-analysis. Digital Chinese Medicine, 2025, 8(1): 59-75.

1 Introduction

With the increasing incidence of cancer, there is also a corresponding rise in the incidence of cancer-induced bone pain (CIBP). CIBP is a persistent chronic condition primarily characterized by a continuous dull ache, often accompanied by unendurable breakthrough pain, commonly associated with primary bone tumors or bone metastases. Research data show that up to 85% of patients with advanced malignancies experience cancerous bone pain [1, 2]. Failure to manage CIBP effectively and promptly can lead to symptoms such as anxiety, depression, and sleep disturbance in patients. Poor long-term control significantly diminishes their quality of life. Patients with serious cancerous bone pain may even develop suicidal tendencies, posing a serious threat to their lives and health [3, 4]. The need for prolonged medication among CIBP patients imposes a heavy burden on both their patients' families and socio-economy.

Three-step analgesic ladder, recommended by the World Health Organization (WHO), serves as a guideline for managing CIBP including nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, strong opioids, and adjunctive analgesics. NSAIDs are often used as combination therapy in patients with CIBP. However, prolonged use of NSAIDs fails to enhance pain management and instead increases the potential for drug-related toxicity, including the risk of cardiovascular and gastrointestinal diseases [5]. Weak opioids are not frequently used in the management of CIBP due to their limited analgesic efficacy and they are easily replaced by low-dose morphine in clinical practice [6]. Strong opioids are the primary treatment option for patients experiencing severe CIBP. Nevertheless, studies indicate that continued use of strong opioids is linked to adverse effects, including hepatic toxicity, renal impairment, gastrointestinal disturbances, dizziness, drowsiness, drug dependence, and drug addiction, which have limited their clinical application to some extent [7, 8]. To date, more than 50% of patients with CIBP continue to struggle with inadequate pain relief despite undergoing various treatment modalities [9]. Therefore, effectively controlling CIBP while reducing side effects is of significant clinical importance.

External application of traditional Chinese medicine (EA-TCM) has a long history in the treatment of CIBP, and the integration of pain relief with antitumor effects can be effectively incorporated into the clinical management of CIBP. EA-TCM involves applying medicinal substances to the skin, enabling the drug to directly reach the affected area. This method minimizes gastrointestinal irritation through transdermal absorption and enhances local drug concentration, thereby quickly alleviating pain without notable side effects [10, 11]. The mechanisms of EA-TCM is quite complex. It is postulated that potential mechanisms may include the stimulatory and regulatory effects of the herbs on the corresponding meridians and acupoints, as well as the local or systemic pharmacological effects subsequent to drug absorption.

CIBP is a complex type of pain where a single pain relief method often fails to achieve the desired therapeutic outcome. By combining EA-TCM with three-step analgesic ladder therapy, a multimodal pain relief strategy can be employed to alleviate pain through different mechanisms and improve the analgesic efficacy. However, no systematic evaluation exists for their combined efficacy. This study aims to comprehensively assess the combined efficacy of EA-TCM and oral three-step analgesic ladder therapy in the treatment of CIBP through meta-analysis, thereby providing a basis for clinical treatment.

2 Data and methods

2.1 Research protocol and registration

We formally registered the meta-analysis protocol on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY), with the registration No. INPLASY202180004. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

2.2 Search strategy

Two researchers independently conducted a literature search across ten common databases, including four Chinese-language databases: Chinese Biomedical Literature Database (SinoMed), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), as well as six English-language databases: Scopus, Embase, Web of Science, PubMed, Cochrane Library, and OpenGrey. Additionally, we searched the Chinese Clinical Trial Registry (https://www.chictr.org.cn) and the ClinicalTrials.gov (https://clinicaltrials.gov) for studies on EA-TCM in the treatment of CIBP. The search strategy was customized to the unique features of each database. For instance, CNKI was searched using pertinent subject headings. The search string was constructed as follows: (subject = “external treatment” OR “external use” OR “external application” OR “powder” OR “paste” OR “cream” OR “patch” OR “traditional Chinese medicine” OR “Chinese medicine” OR “TCM”) AND (subject = “bone cancer pain” OR “cancer-induced bone pain” OR “bone metastatic cancer pain” OR “bone metastatic pain” OR “bone metastases”) AND (subject = “clinical” OR “random”). The timeframe for the literature search extended from the inception of each database to December 31, 2023. For details of the search strategy, please refer to Supplementary Table S1.

2.3 Study selection and data extraction

2.3.1 Inclusion criteria We adhered rigorously to the (participants, intervention, control, outcome, and study design) PICOS methodology specified by PRISMA guidelines to establish inclusion criteria as follows. (i) Patients with primary or secondary bone tumors, characterized by definitive lesions ascertained through radiological imaging and exhibiting pain symptoms at the lesion site. (ii) The combination therapy group is defined as the group that received EA-TCM with oral three-step analgesic ladder therapy. (iii) The control group refers to the group that was administered oral three-step analgesic ladder therapy alone or with an external placebo. (iv) The studies included in our analysis must incorporated at least one clinical metric: pain relief rate, pain intensity, breakthrough pain frequency, analgesic duration, quality of life assessment, or the incidence of adverse effects (e.g., nausea, vomiting, constipation, drowsiness). (v) Only randomized controlled trials (RCTs) that investigated the efficacy of EA-TCM combined with oral three-step analgesic ladder therapy for CIBP management were included in this review.

2.3.2 Exclusion criteria Studies were excluded: (i) if patients suffered from other types of pain besides CIBP, such as trauma-related pain and post-surgical pain; if the combination therapy group received interventions in addition to EA-TCM and oral three-step analgesic ladder therapy, while the control group did not undergo these additional interventions; (ii) if the study was in the form of a case report, literature review, duplicate publication, experimental study, conference abstract, or theoretical discussion; (iii) if the literature could not be obtained by contacting the authors.

2.3.3 Literature screening and data extraction Two researchers independently screened the literature based on the inclusion and exclusion criteria. Subsequently, two researchers separately extracted the relevant data. The information collected encompassed the first author's name, publication date, title of the article, randomization method, baseline characteristics (including gender, average age, types of cancer, pain severity, and number of cases), diagnostic criteria, treatment protocols, outcome indicators (including pain relief rate, pain intensity, breakthrough pain frequency, analgesic duration, quality of life assessment, nausea, vomiting, constipation, and drowsiness), and the duration of treatment. In cases of disagreement during the screening process, a third researcher was consulted for resolution.

2.4 Evaluation of risk of bias and quality assessment

Two researchers independently evaluated the methodological quality of the included studies utilizing the Cochrane Risk of Bias Tool. This comprehensive assessment categorized the potential risks into three distinct levels (low risk, unclear risk, and high risk), across six specific domains [13]. The six domains include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases, which specifically involve seven items, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other potential sources of biases. In cases of disagreement, a third-party opinion was sought for resolution. Two researchers separately conducted quality assessments of the outcome indicators presented in the studies utilizing GRADEprofiler software (v3.6). Our assessments adhered to the criteria outlined in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [14]. A third researcher was consulted for resolution in case of disagreement.

2.5 Statistical analysis

The data were analyzed utilizing RevMan software (v5.4.1). For continuous data, the mean difference (MD) was applied when measurement units or instruments for assessing the indicator were consistent across studies; otherwise, the standardized mean difference (SMD) was preferred. Dichotomous data were evaluated using the risk ratio (RR). Both continuous and dichotomous data were presented with a 95% confidence interval (CI). Heterogeneity was assessed by the inconsistency index (I^2) statistic. The fixed-effect model was employed when heterogeneity was insignificant ($P \geqslant 0.05$ and $I^2 < 50\%$). Conversely, the random-effects model was adopted when significant heterogeneity was present ($I^2 \geqslant 50\%$ or $P < 0.05$), with sensitivity analyses or subgroup analyses conducted to explore the sources of heterogeneity. Sensitivity analyses were performed using R software (v4.3.1) and subgroup analyses were performed using RevMan software (v5.4.1). $P < 0.05$ was considered statistically significant. Publication bias was analyzed using R software (v4.3.1), with Peter's test for dichotomous variables and Egger's test for continuous variables, and funnel plots were used for visualization. $P > 0.05$ indicated no significant publication bias.

3 Results

3.1 Literature retrieval results

A total of 2 597 papers were collected from ten databases and two registration systems. Next, 735 duplicate articles were eliminated. Subsequently, the titles and abstracts were scrutinized, excluding 1 763 documents that failed to meet the inclusion criteria. Following a thorough examination of the full texts, an additional 56 studies were

discarded. Rigorous screening ultimately led to the inclusion of 43 RCTs in this systematic review [15-57] (Figure 1).

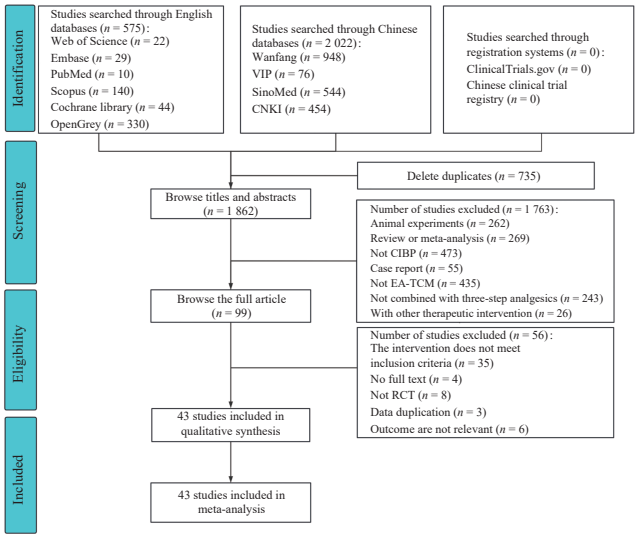

Figure 1 PRISMA flow diagram of the search strategy

3.2 Research characteristics

Our study encompassed 43 studies conducted in China, spanning a period of 15 years, from 2008 to 2023. These studies involved a total of 3 142 participants, with 1 583 assigned to the combination therapy group and 1 559 serving as control group. The sample sizes of these studies ranged from 40 to 159 participants. The duration of the interventions varied widely, ranging from a minimum of 5 d to a maximum of 1 month. The detailed characteristics and specific attributes of these 43 studies are systematically presented in Table 1. We summarized the medications used more than ten times, in descending order of frequency: Bingpian (Borneolum Syntheticum), Ruxiang (Olibanum), Moyao (Myrrha), Xixin (Asari Radix et Rhizoma), Quanxie (Scorpio), Yanhusuo (Corydalis Rhizoma), and Maqianzi (Strychni Semen) (Supplementary Figure S1).

3.3 Risk of bias assessment

Among the 43 studies, 21 studies [16, 19, 20, 23, 25, 26, 28, 30, 31, 33, 36, 37, 41, 43-47, 49, 52, 55] used appropriate randomization methods and were labeled as low risk, and 22 studies [15, 17, 18, 21, 22, 24, 27, 29, 32, 34, 35, 38-40, 42, 48, 50, 51, 53, 54, 56, 57] were classified as unclear risk due to the absence of information regarding their randomization techniques. All studies were categorized as having an unclear risk concerning allocation concealment, as specific methods were not outlined. Seven studies [15, 23, 30, 36, 52, 55, 56] utilized a double-blinded approach for participants and study personnel, and two studies [19, 25] implemented a single-blinded approach for assessors, all of which were classified as low risk. None of the studies had incomplete data and were marked as low risk. Regarding selective reporting, all the studies were assessed as low risk, except one [34], which was evaluated as high risk due to the non-disclosure of a pre-designated primary outcome indicator. The risk of other biases in four trials [15, 32, 38, 47] was classified as unclear, as these studies lacked information on the sex or age of the patients, while the remaining studies with detailed information were classified as low risk. The results of the bias risk assessment for the 43 studies are presented in Figure 2.

3.4 Meta-analysis results

3.4.1 Comparison of pain relief rates between combination therapy and control groups Thirty-four studies [17, 19, 21, 22, 24-33, 35-47, 49-51, 53-55, 57] revealed significant heterogeneity in pain relief rate (P = 0.02, I^2 = 36%). Consequently, a random-effects model was employed to assess pain relief rates across these studies. The findings indicated that patients receiving EA-TCM therapy combined with three-step analgesic ladder therapy exhibited a significantly higher pain relief rate compared with those receiving three-step analgesic ladder therapy alone (RR = 1.32, 95% CI: 1.24 to 1.41, P < 0.000 01; Figure 3). Due to the high level of heterogeneity, a sensitivity analysis was conducted on 34 studies using a step-wise exclusion method. No significant changes were observed compared with the results prior to exclusion, indicating low sensitivity and reliable outcomes (Figure 4).

To ascertain the sources of heterogeneity, we conducted a subgroup analysis of 34 studies, with a specific focus on sample size, treatment duration, prescription characteristics, and study subject. The results of the subgroup analyses suggested that the heterogeneity may stem from differences in the prescription characteristics and study population characteristics. Notably, the subgroup analyses revealed heightened internal heterogeneity among studies focusing on a single cancer type and those excluding insect-derived drugs, suggesting that cancer type and prescription characteristics may influence the meta-analysis results. Detailed results from the subgroup analyses of pain relief rates are presented in Table 2 and Supplementary Figure S2.

3.4.2 Comparison of pain intensity between combination therapy and control groups Twenty-six studies [15-21, 25, 26, 28, 30, 32-34, 36, 40-46, 51, 54, 56, 57] reported pain intensity as the primary outcome indicator, predominantly utilizing the visual analogue scale (VAS) and numerical rating scale (NRS) for assessment. The heterogeneity test for pain intensity showed significant heterogeneity (P < 0.000 01, I^2 = 81%). Consequently, a random-effects model was employed for analysis. The results indicated that patients receiving EA-TCM therapy combined with three-step analgesic ladder therapy exhibited a significant reduction in pain intensity compared with those receiving three-step analgesic ladder therapy alone (MD = – 1.00, 95% CI: – 1.19 to – 0.80, P < 0.000 01; Figure 5).

Table 1 Characteristics of the 43 studies in this meta-analysis

Study	Participant *n* [total (T/C)]	Treatment group	Control group	Average age (T/C, year)	Duration of treatments	Outcome indicator
CHEN H [15], 2018	77 (38/39)	EA-TCM + opioids	External application of placebo + opioids	—	1 week	B, C, E, F, G, H, I
CHEN M [16], 2014	68 (34/34)	EA-TCM + QMD	QMD	51.47 ± 13.59/ 53.62 ± 10.18	1 month	B, H
CHEN XW [17], 2020	70 (35/35)	EA-TCM + QMD	QMD	59.12 ± 3.06/ 59.51 ± 2.24	1 month	A, B
CHEN XZ [18], 2020	98 (49/49)	EA-TCM + oxycontin	Oxycontin	57.64 ± 13.62/ 59.16 ± 12.69	10 days	B, C
CHEN YY [19], 2019	60 (30/30)	EA-TCM + QMD	QMD	64.27 ± 10.38/ 65.44 ± 9.37	2 weeks	A, B, E
CONG Y [20], 2018	40 (20/20)	EA-TCM + oxycontin	Oxycontin	49.35 ± 3.77/ 49.11 ± 3.82	1 month	B, F, G, H, I
GAO HF [21], 2008	41 (21/20)	EA-TCM + MS contin	MS contin	64.43 ± 12.39/ 62.58 ± 12.15	1 month	A, B, E
GAO Y [22], 2011	41 (21/20)	EA-TCM + oxycontin	Oxycontin	64.43 ± 12.39/ 62.58 ± 12.15	2 weeks	A
HAN KL [23], 2013	48 (24/24)	EA-TCM + opioids	External application of placebo + opioids	61.96 ± 10.47/ 62.08 ± 12.16	1 week	C
HE H [24], 2019	54 (27/27)	EA-TCM + morphine	Morphine	59.36 ± 4.46/ 59.81 ± 4.56	1 week	A
HE JJ [25], 2020	60 (30/30)	EA-TCM + oxycontin	Oxycontin	62.37 ± 8.356/ 61.67 ± 9.74	1 week	A, B, C, E, F, G, H, I
HOU ZL [26], 2018	60 (30/30)	EA-TCM + oxycontin	Oxycontin	62.63 ± 12.38/ 61.08 ± 11.96	10 days	A, B, C, E
HUANG CJ [27], 2016	120 (60/60)	EA-TCM + three-ladder analgesic	Three-ladder analgesic	71.80 ± 3.40/ 72.20 ± 4.20	2 weeks	A, F, G, H, I
JIANG L [28], 2021	60 (30/30)	EA-TCM + oxycontin	Oxycontin	51.11 ± 10.33/ 50.17 ± 10.66	5 days	A, B, F, G, H, I
JING NC [29], 2014	60 (30/30)	EA-TCM + oxycontin	Oxycontin	51.07 ± 9.13/ 48.87 ± 10.52	30 days	A, D, F, G, H, I
LAN P [30], 2022	49 (26/23)	EA-TCM + opioids	External application of placebo + opioids	62.96 ± 8.28/ 61.04 ± 7.83	10 days	A, B, C, E, F, G, H, I
LI MN [31], 2022	80 (40/40)	EA-TCM + oxycontin	Oxycontin	63.00/61.00	1 week	A, F, G, H, I
LIU PZ [32], 2015	60 (30/30)	EA-TCM + oxycontin + zoledronic acid injection	Oxycontin + zoledronic acid injection	—	1 month	A, B
LIU SS [33], 2022	78 (39/39)	EA-TCM + oxycontin	Oxycontin	55.34 ± 6.34/ 55.64 ± 6.29	10 days	A, B, C, D, E, H, I
LIU YR [34], 2013	68 (40/28)	EA-TCM + MS contin	MS contin	44.80 ± 11.30/ 43.50 ± 10.80	1 month	B
MA LY [35], 2014	60 (30/30)	EA-TCM + paracetamol and tramadol hydrochloride tablets	Paracetamol and tramadol hydrochloride tablets	58.87/58.27	1 month	A, D, E
RAO AH [36], 2014	64 (32/32)	EA-TCM + hyperthermia + MS contin	External application of placebo + hyperthermia + MS contin	57.20 ± 6.21/ 56.80 ± 5.86	1 week	A, B, C, E, F, I
SHENG YJ [37], 2019	96 (48/48)	EA-TCM + oxycontin	Oxycontin	57.83 ± 11.43/ 58.69 ± 11.83	1 week	A
SHI Y [38], 2019	106 (53/53)	EA-TCM + pregabalin + MS contin	Pregabalin + MS contin	—	2 weeks	A
SUN S [39], 2019	135 (65/70)	EA-TCM + oxycontin	Oxycontin	57.96 ± 10.88/ 61.00 ± 11.34	2 weeks	A, D
SUN ZB [40], 2021	50 (25/25)	EA-TCM + morphine	Morphine	69.20/68.16	1 week	A, B, F
TANG X [41], 2018	80 (40/40)	EA-TCM + oxycontin	Oxycontin	61.92 ± 9.19/ 61.47 ± 8.89	5 days	A, B, C, E, F, G, H, I
TANG Y [42], 2017	72 (36/36)	EA-TCM + oxycontin	Oxycontin	54.90 ± 8.40/ 56.30 ± 5.30	20 days	A, B, F

Table 1 Continued

Study	Participant *n* [total (T/C)]	Treatment group	Control group	Average age (T/C, year)	Duration of treatments	Outcome indicator
WANG F [43], 2023	84 (42/42)	EA-TCM + oxycontin	External application of placebo + oxycontin	58.42 ± 10.63/ 57.07 ± 10.57	3 weeks	A, B, C, E, F, G, H
WANG L [44], 2021	60 (30/30)	EA-TCM + oxycontin	Oxycontin	61.60 ± 7.72/ 63.97 ± 8.04	10 days	A, B, E
WANG X [45], 2023	64 (32/32)	EA-TCM + sodium ibandronate injection + MFK	Sodium ibandronate injection + MFK	64.7 ± 10.2/ 63.1 ± 11.6	12 days	A, B, E, F
WANG Y [46], 2023	60 (30/30)	EA-TCM + oxycontin + five elements music therapy	Oxycontin + five elements music therapy	54.37 ± 7.37/ 53.35 ± 7.62	20 days	A, B, E
XU DK [47], 2020	126 (63/63)	EA-TCM + three-ladder analgesic	Three-ladder analgesic	—	1 week	A, F
XU JX [48], 2014	50 (25/25)	EA-TCM + MS contin + thermotherapy	MS Contin + thermotherapy	63.00/65.00	2 weeks	C, E
YNAG T [49], 2019	60 (30/30)	EA-TCM + aminophenoxycodone tablets	Aminophenoxy-codone tablets	59.61 ± 8.68/ 58.28 ± 8.29	2 weeks	A
YANG ZM [50], 2016	159 (84/75)	EA-TCM + MFK	MFK	51.60 ± 9.60/ 52.81 ± 8.22	10 days	A, E, F, G, H, I
YUAN H [51], 2015	64 (32/32)	EA-TCM + QMD	QMD	56.60 ± 3.70/ 57.89 ± 4.18	1 month	A, B
YU M [52], 2015	132 (66/66)	EA-TCM + morphine	Morphine	62.20 ± 14.10/ 59.60 ±10.40	1 week	C
YU XF [53], 2015	93 (48/45)	EA-TCM + futalin enteric solution tablets	Futalin enteric solution tablets	65.20/64.80	12 days	A
ZHANG J [54], 2021	45 (23/22)	EA-TCM + MFK	MFK	65.00 ± 4.70/ 63.00 ± 5.10	3 weeks	A, B, E
ZHANG LW [55], 2018	60 (30/30)	EA-TCM + oxycontin	Oxycontin	62.10 ± 9.09/ 60.37 ± 8.29	1 week	A, F, G, H
ZHANG LW [56], 2019	70 (35/35)	EA-TCM + oxycontin	External application of placebo +oxycontin	61.37 ± 8.91/ 59.89 ± 7.90	1 month	B, C, E
ZHOU TT [57], 2023	60 (30/30)	EA-TCM + oxycontin	Oxycontin	66.23 ± 9.72/ 66.2 ± 9.93	1 week	A, B, E, F, H, I

T/C, treatment/control. MFK, morphine hydrochloride sustained-release tablets. QMD, tramadol hydrochloride sustained-release tablets. —, not mentioned. A, pain relief rate. B, pain intensity. C, breakthrough pain frequency. D, analgesia duration. E, quality of life. F, nausea. G, vomiting. H, constipation. I, drowsiness.

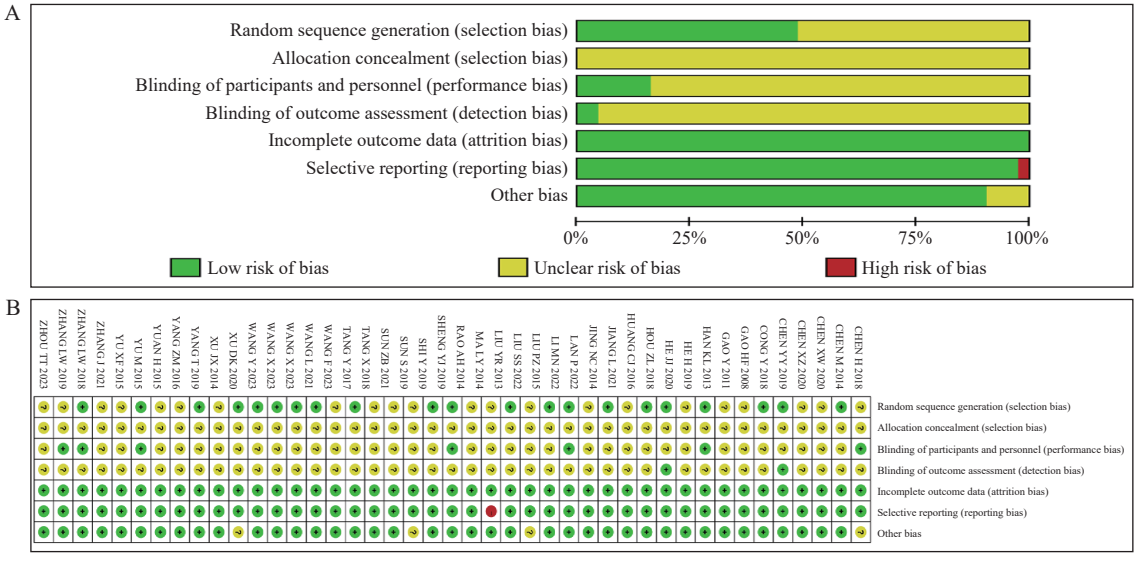

Figure 2 Risk of bias graph for included studies

A, risk of bias percentage graph. B, risk of bias summary graph.

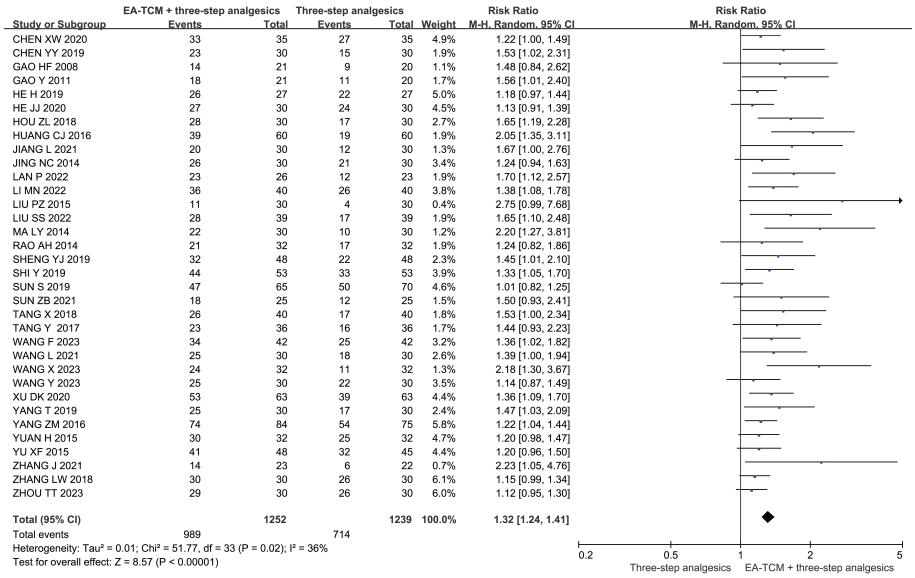

Figure 3 Forest plot of the pain relief rates in combination therapy group and control group

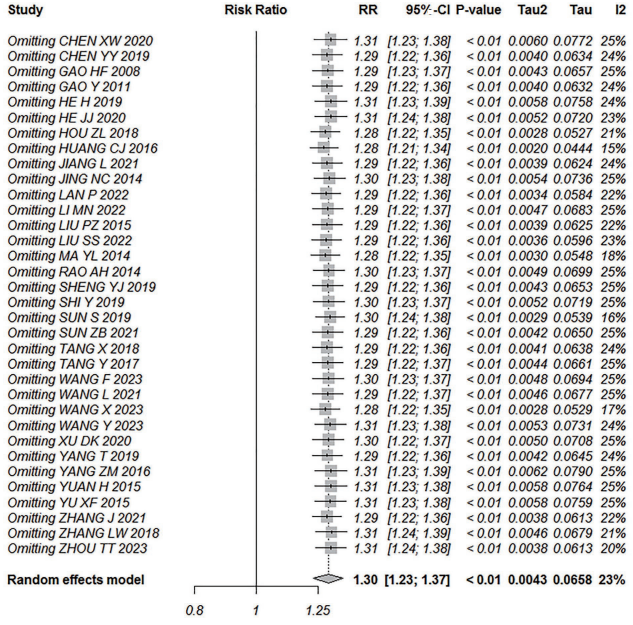

Figure 4 Forest plot of sensitivity analysis for pain relief rate

Sensitivity analysis conducted using the one-by-one exclusion method failed to demonstrate significant differences compared with the results obtained prior to the exclusion, indicating low sensitivity and reliable results (Figure 6).

Considering the significant heterogeneity, we conducted subgroup analyses among 26 studies from five perspectives: sample size, assessment method, treatment duration, prescription characteristics, and study subject. The results of these subgroup analyses indicated that the observed high heterogeneity likely stemmed from variations in treatment duration rather than differences in sample size, assessment methods, prescription characteristics, or study subjects. Based on the subgroup analysis, the internal heterogeneity within the group that received treatment for less than two weeks decreased, suggesting that the treatment duration may influence the results of the meta-analysis. Detailed findings from these subgroup analyses regarding pain intensity are presented in Table 3 and Supplementary Figure S3.

Table 2 Subgroup analyses of pain relief rate

Item	Subgroup	Study (*n*)	Participant (*n*)		RR	95% CI	I^2	*P* value
			EA-TCM + three-step analgesics	Three-step analgesics				
Sample size	< 60	6	113	72	1.45	1.18 to 1.78	32%	0.000 40
	⩾ 60	28	876	642	1.31	1.22 to 1.40	38%	< 0.000 01
Treatment duration	< 2 weeks	18	561	404	1.30	1.20 to 1.41	35%	< 0.000 01
	2 – 4 weeks	10	292	214	1.37	1.19 to 1.58	44%	< 0.000 10
	> 4 weeks	6	136	96	1.34	1.11 to 1.63	47%	0.002 00
Prescription characteristic	Containing-insect drugs	19	608	442	1.29	1.20 to 1.38	25%	< 0.000 01
	No insect drugs	15	382	272	1.39	1.23 to 1.57	50%	< 0.000 01
Study subject	Single cancer	5	141	87	1.63	1.11 to 2.39	85%	0.010 00
	Multiple cancer	29	848	627	1.28	1.21 to 1.35	12%	< 0.000 01

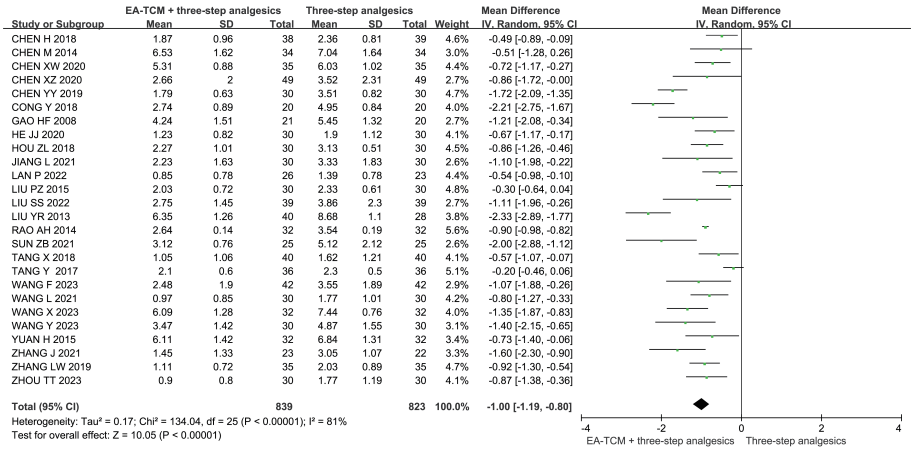

Figure 5 Forest plot of pain intensity in combination therapy group and control group

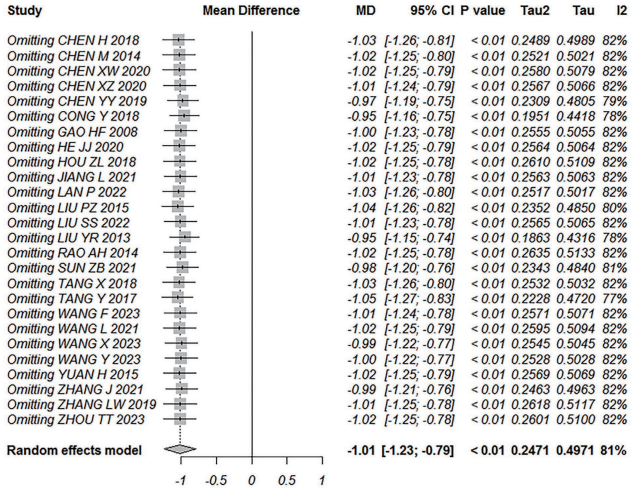

Figure 6 Forest plot of sensitivity analysis for pain intensity

3.4.3 Comparison of breakthrough pain frequency between combination therapy and control groups Twelve studies [18, 23, 25, 26, 30, 33, 36, 41, 43, 48, 52, 56] reported on breakthrough pain frequency, demonstrating no significant heterogeneity (P = 0.13, I^2 = 33%). The results indicatedthat,comparedwiththeadministrationoforalthree-step analgesic ladder therapy alone, the adjunctive use of EA-TCM significantly reduced the breakthrough pain frequency (MD = – 0.43, 95% CI: – 0.51 to – 0.36, P < 0.000 01; Figure 7).

3.4.4 Comparison of analgesic duration between combination therapy and control groups Four studies [29, 33, 35, 39] showed that patients with CIBP treated with the combined therapy of EA-TCM and three-step analgesic ladder exhibited a longer analgesic duration compared with those who received three-step analgesics ladder alone (MD = 1.33, 95% CI: 0.97 to 1.69, P < 0.000 01), without obvious heterogeneity (P = 0.70, I^2 = 0%; Figure 8).

3.4.5 Comparison of quality of life between the combination therapy and control groups Nineteen studies [15, 19, 21, 25, 26, 30, 33, 35, 36, 41, 43-46, 48, 50, 54, 56, 57] reported on quality of life and subsequently conducted a heterogeneity assessment

Table 3 Subgroup analyses of pain intensity

Item	Subgroup	Study (n)	Participant (n)		MD	95% CI	I^2	P value
			EA-TCM + three-step analgesics	Three-step analgesics				
Sample size	< 60	5	115	110	– 1.34	– 1.62 to –1.07	84%	< 0.000 01
	⩾ 60	21	724	713	– 0.86	– 0.92 to – 0.80	79%	< 0.000 01
Assessment method	NRS	21	671	667	– 0.87	– 0.92 to – 0.82	76%	< 0.000 01
	VAS	5	161	149	– 1.36	– 1.61 to – 1.10	89%	< 0.000 01
Treatment duration	< 2 weeks	13	431	429	– 0.85	– 1.00 to – 0.69	35%	< 0.000 01
	2 – 4 weeks	9	292	291	– 0.89	– 1.34 to – 0.45	87%	< 0.000 10
	> 4 weeks	4	116	103	– 1.67	– 2.46 to – 0.89	88%	< 0.000 10
Prescription characteristic	Containing-insect drugs	13	402	402	– 0.97	– 1.24 to – 0.70	86%	< 0.000 01
	No insect drugs	13	437	421	– 1.05	– 1.38 to – 0.72	76%	< 0.000 01
Study subject	Single cancer	3	87	87	– 1.48	– 2.22 to – 0.73	86%	0.000 10
	Multiple cancer	13	752	736	– 0.93	– 1.13 to – 0.73	79%	< 0.000 01

on the reported data. The results of the assessment showed no significant heterogeneity (P = 0.33, I^2 = 11%), indicating homogeneity in the data. Consequently, a fixed-effect model was used for subsequent analyses. The study indicated that participants receiving the combined therapy of EA-TCM and oral three-step analgesic ladder therapy exhibited significantly improved quality of life compared to those receiving oral three-step analgesics alone (MD = 5.66, 95% CI: 4.88 to 6.44, P < 0.000 01; Figure 9).

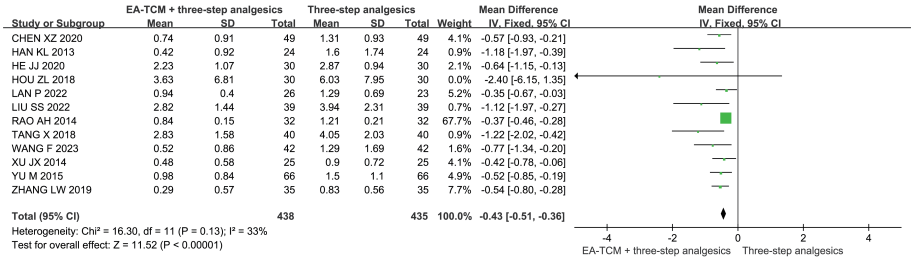

Figure 7 Forest plot of breakthrough pain frequency in combination therapy group and control group

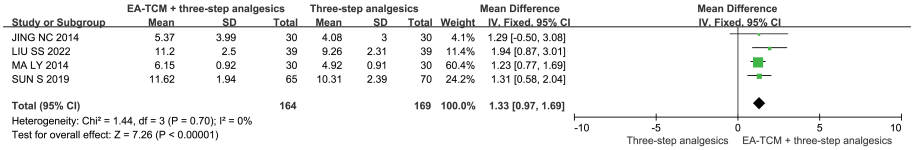

Figure 8 Forest plot of analgesic duration in combination therapy group and control group

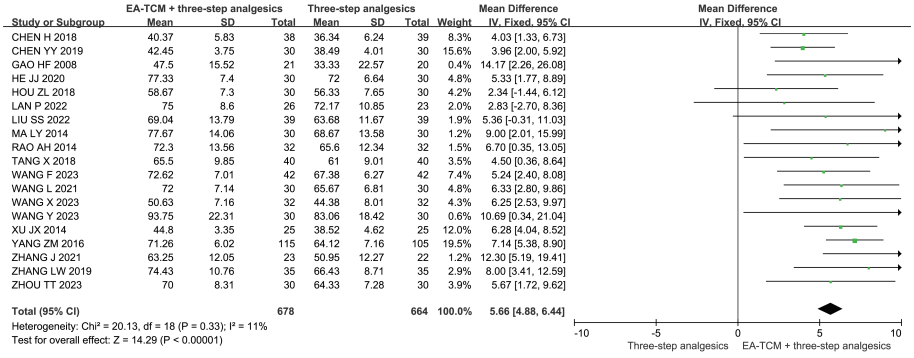

Figure 9 Forest plot of quality of life in combination therapy group and control group

3.4.6 Comparison of adverse effects between combination therapy and control groups This study primarily focused on the common adverse reactions associated with three-step analgesic ladder therapy, including nausea, vomiting, constipation, and drowsiness. Eighteen studies [15, 20, 25, 27-31, 36, 40-43, 45, 47, 50, 55, 57] reported nausea; 12 studies [15, 20, 25, 27-31, 41, 43, 50, 55] revealed vomiting; 15 studies [15, 16, 20, 25, 27-31, 33, 41, 43, 50, 55, 57] mentioned constipation; 13 studies [15, 20, 25, 27-31, 33, 36, 41, 50, 57] noted drowsiness. Heterogeneity tests indicated no significant heterogeneity in these adverse effects between the groups (P = 0.99, I^2 = 0%; P = 0.98, I^2 = 0%; P = 0.14, I^2 = 29%; P = 0.88, I^2 = 0%, respectively). The overall results suggested that patients treated with the combined therapy of EA-TCM and oral three-step analgesic ladder therapy exhibited a significantly lower incidence of adverse effects, compared with those receiving oral three-step analgesic ladder therapy alone (RR = 0.60, 95% CI: 0.53 to 0.68, P < 0.000 01; Figure 10).

3.5 Publication bias analysis

R software (v4.3.1) was utilized to create funnel plots for pain relief rate, pain intensity, analgesia duration, breakthrough pain frequency, quality of life, and adverse effects (including nausea, vomiting, constipation, and drowsiness) to assess the publication bias of their combined results (Figure 11). These plots revealed incomplete symmetry, indicating potential publication bias. Peter's test was conducted to assess pain relief rate, nausea, vomiting, and constipation, with P values of 0.084 2, 0.762 1, 0.792 9, and 0.302 0, respectively, showing no significant publication bias. However, for drowsiness, the P value of 0.001 8 confirmed the presence of publication bias. Egger's test for pain intensity, analgesia duration, and quality of life revealed no significant publication bias, with P values of 0.347 5, 0.439 7, and 0.212 5, respectively. However, Egger's test for breakthrough pain

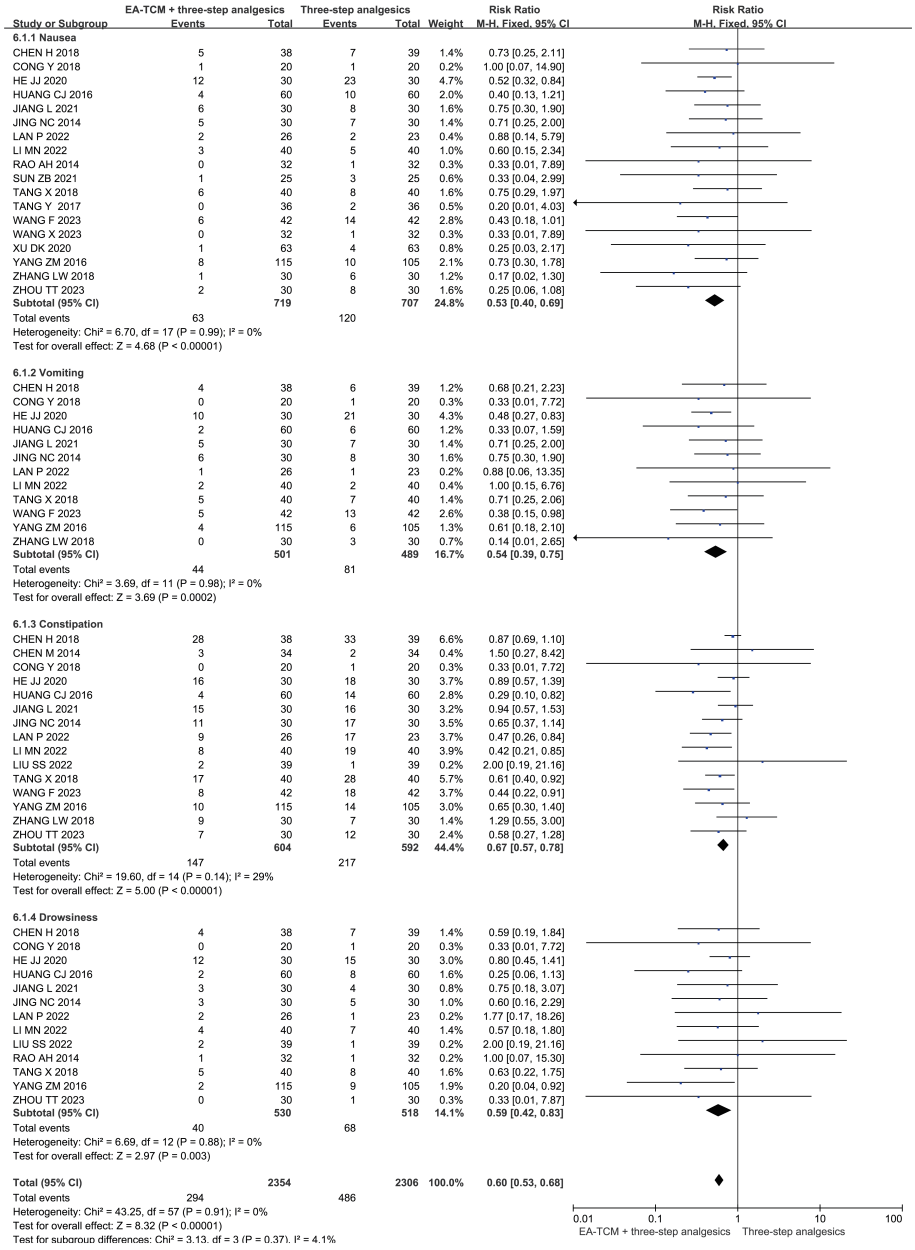

Figure 10 Forest plot of the incidence of adverse events in combination therapy group and control group

frequency showed significant publication bias, with a *P* value of 0.000 1. The significant publication bias in the adverse reaction of drowsiness was adjusted using trim-and-fill method. The results showed that, after incorporating four hypothetical studies, the incidence of drowsiness in patients was lower compared with receiving three-step analgesic ladder therapy alone (RR = 0.72, 95% CI: 0.52 to 0.99, *P* = 0.042 6). The difference was not statistically significant compared with the original value (RR = 0.59, 95% CI: 0.42 to 0.83, *P* = 0.003), indicating that despite the presence of publication bias, the original results remain stable (Supplementary Figure S4). The significant publication bias in the frequency of breakthrough pain was adjusted using the trim-and-fill method. The results showed that after incorporating six hypothetical studies, the frequency of breakthrough pain in patients was lower compared with those with only three-step analgesic ladder therapy alone (MD = – 0.414 2, 95% CI: – 0.501 8 to – 0.326 5, *P* < 0.000 1). The difference was not statistically significant compared with the original value (MD = – 0.43, 95% CI: – 0.51 to – 0.36, *P* < 0.000 01), indicating that despite the presence of publication bias, the original results remain stable (Supplementary Figure S5).

3.6 Quality of evidence

Table 4 presents the quality ratings from 43 studies. Based on the GRADE criteria, the combination therapy group showed moderate-quality evidence in pain relief

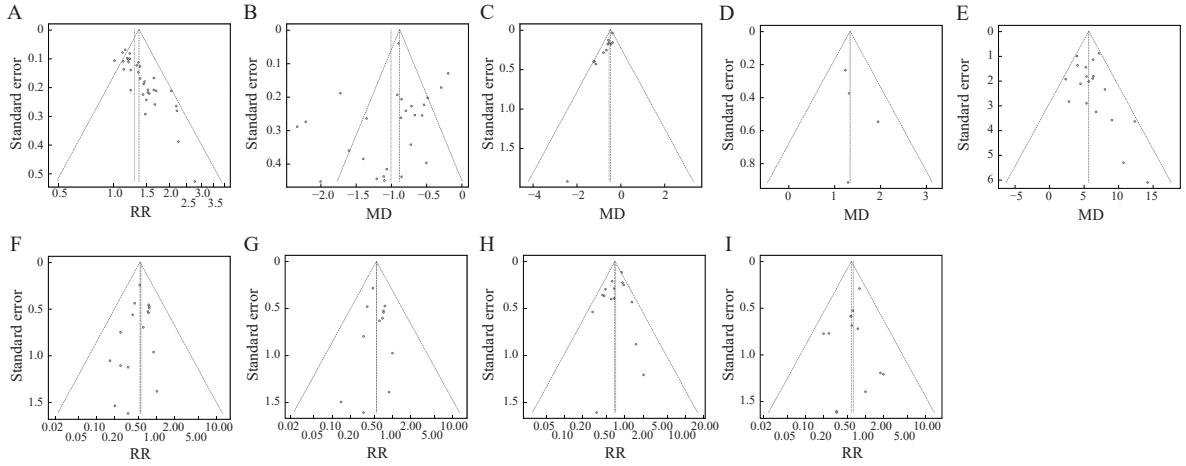

Figure 11 Funnel plots of outcome indicators for EA-TCM combined with three-step analgesic ladder therapy in treating CIBP

A, pain relief rate. B, pain intensity. C, frequency of breakthrough pain. D, analgesic duration. E, quality of life. F, nausea. G, vomiting. H, constipation. I, drowsiness.

Table 4 Quality assessment of the EA-TCM +three-step analgesic ladder therapy and three-step analgesic ladder therapy alone by GRADE

Outcome	Study (*n*)	Quality assessment				
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration
Pain relief rate	34	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None
Pain intensity	26	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None
Breakthrough pain frequency	12	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[4]
Analgesia duration	4	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None
Quality of life	19	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None
Nausea	18	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None
Vomiting	12	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None
Constipation	15	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None
Drowsiness	13	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[4]

Outcome	Participant		Effect (95% CI)		Quality
	EA-TCM + three-step analgesic ladder	Three-step analgesic ladder	Relative effect	Absolute effect	
Pain relief rate	989/1 252 (79%)	714/1 239 (57.6%)	RR 1.37 (1.30 to 1.40)	213/1 000 more (173 to 254)[5]	Moderate
Pain intensity	839	823	None	MD 1.00 lower (0.80 to 1.19)[5]	Low
Breakthrough pain frequency	438	435	None	MD 0.43 lower (0.36 to 0.51)[5]	Low
Analgesia duration	164	169	None	MD 1.33 higher (0.97 to 1.69)[5]	Low
Quality of life	678	664	None	MD 5.66 higher (4.88 to 6.44)[5]	Moderate
Nausea	63/719 (8.8%)	120/707 (17%)	RR 0.53 (0.40 to 0.69)	80/1 000 fewer (53 to 102)[5]	Moderate
Vomiting	44/501 (8.8%)	81/489 (16.6%)	RR 0.54 (0.39 to 0.75)	76/1 000 fewer (41 to 101)[5]	Moderate
Constipation	147/604 (24.3%)	217/592 (36.7%)	RR 0.67 (0.57 to 0.78)	12/1 000 fewer (81 to 158)[5]	Moderate
Drowsiness	40/530 (7.5%)	68/518 (13.1%)	RR 0.59 (0.42 to 0.83)	54/1 000 fewer (22 to 76)[5]	Low

[1] Significant biases in randomization, allocation concealment, and blindness. [2] $I^2 > 50\%$. [3] Sample size too small. [4] High publication bias. [5] Comparison of EA-TCM combined with three-step analgesic group with three-step analgesic ladder group.

rate, quality of life, nausea, vomiting, and constipation. The moderate quality assessment was due to the significant biases in randomization, allocation concealment, or blinding. The assessment of pain intensity received a low-quality rating, primarily due to considerable bias in randomization, allocation concealment, or blinding, compounded by high heterogeneity among study results. The quality ratings for breakthrough pain frequency and drowsiness were low, primarily due to substantial biases in randomization, allocation concealment, blinding, and significant publication biases. Additionally, the quality of evidence for analgesia duration was deemed low, which was attributed to inadequate randomization, allocation concealment, blinding, as well as insufficient sample sizes.

4 Discussion

4.1 Mechanisms of EA-TCM in treating CIBP

As a unique medical system originating from China, TCM complements and exists alongside western medicine. TCM alleviates various forms of pain, including CIBP, by replenishing Qi, enhancing resistance, reducing inflammation, promoting blood circulation, and eliminating blood stasis. Numerous studies have elucidated the multifactorial pathological mechanisms underlying EA-TCM in the treatment of CIBP: (i) inhibiting the release of inflammatory mediators [58, 59]; (ii) inhibiting osteoclast activation [60, 61]; (iii) suppressing glial cell activation [62, 63].

4.2 Efficacy of EA-TCM combined with three-step analgesic ladder therapy in treating CIBP

Our systematic review analyzed data from 43 RCTs involving 3 142 patients with CIBP. The findings revealed that the combined therapy of EA-TCM and oral three-step analgesic ladder therapy for treating CIBP led to several favorable outcomes: a higher rate of pain relief, lower pain intensity, a reduced incidence of breakthrough pain, a longer analgesic duration, higher quality of life scores, and fewer adverse effects, including constipation, nausea and vomiting, and drowsiness. The GRADE evidence quality assessment results indicate that the credibility of these outcome indicators needs to be further strengthened, and the results should be treated with caution.

During the analysis, we found high heterogeneity in pain relief rate and pain intensity. Subgroup and sensitivity analyses were conducted to identify the source of the heterogeneity. The sensitivity analysis did not identify the source of the heterogeneity. In the subgroup analysis of pain relief rate, the primary sources of heterogeneity were the prescription characteristics (whether or not containing insect-derived drugs) and the target intervention subjects (single cancer type versus multiple cancer types). The subgroup not containing insect-derived drugs increased heterogeneity, which was attributed to the diversity of research methods. The subgroup with a single cancer type increased heterogeneity, possibly related to the small number of included studies. In the subgroup analysis of pain intensity, the treatment duration was the primary source of heterogeneity. The subgroup with a treatment duration of less than two weeks reduced heterogeneity, which might be related to the smaller sample sizes of the other two subgroups. Considering the limitations of this systematic review and the included studies, the results still need to be validated through multicenter, large-sample RCTs to provide higher-level evidence.

4.3 Common drugs of EA-TCM in treating CIBP

We conducted a statistical analysis of the topical application of TCM in 43 studies. The herbs most frequently utilized, each appearing in over 10 applications, included Bingpian (Borneolum), Ruxiang (Olibanum), Moyao (Myrrha), Xixin (Asari Radix et Rhizoma), Quanxie (Scorpio), Maqianzi (Strychni Semen), and Yanhusuo (Corydalis Rhizoma). Among these, Bingpian (Borneolum) was the most frequently used, followed by Ruxiang (Olibanum) and Moyao (Myrrha). Xixin (Asari Radix et Rhizoma) and Quanxie (Scorpio) ranked third, while Maqianzi (Strychni Semen) and Yanhusuo (Corydalis Rhizoma) ranked fourth. Bingpian (Borneolum), a bicyclic organic compound derived from terpenes, has been found in modern research to specifically activate transient receptor potential cation channel subfamily M member 8 (TRPM8) channels, thereby achieving analgesic effects [64]. Clinically, Ruxiang (Olibanum) and Moyao (Myrrha) are often combined to create a synergistic effect for pain relief. A study found that the combination of Ruxiang (Olibanum) and Moyao (Myrrha) alleviates pain by modulating transient receptor potential vanilloid 1 (TRPV1) channels [65]. NIE et al. [66] employed a water decoction of Xixin (Asari Radix et Rhizoma) to treat an inflammatory mouse model and found that it had significant anti-inflammatory and analgesic effects. It was found that Quanxie (Scorpio) can alleviate pain symptoms in a rat model of bone cancer pain by inhibiting bone destruction and activation of spinal cord astrocytes [67]. Maqianzi (Strychni Semen) has been found to reduce the thermal pain threshold in mice with bone cancer pain, potentially through inhibiting osteoclast activity [68]. Yanhusuo (Corydalis Rhizoma), widely used to treat cancer pain, joint pain, and visceral pain, is renowned as the “premier analgesic in traditional Chinese medicine”. A study found that Yanhusuo (Corydalis Rhizoma) extract exhibits significant dopamine receptor antagonistic properties, which may mediate pain through dopamine D2 receptor antagonism [69]. This paper presents a concise review of seven herbs frequently used in EA-TCM

that have demonstrated robust analgesic effects in various experimental studies. It indirectly supports the efficacy reported in clinical cases and offers valuable guidance for oncologists utilizing topical TCM to treat CIBP.

4.4 Strengths and limitations

This study represents the first systematic review to assess the efficacy of the combined therapy of EA-TCM and oral three-step analgesic ladder therapy in treating CIBP. Additionally, this study assesses the quality of evidence according to the GRADE criteria to provide a reference for clinical decision-making. However, several limitations should be acknowledged. First, publication biases in the reporting of breakthrough pain frequency and drowsiness may lead to inaccurate results, instability in conclusions, and potentially mislead clinical decision-making. Second, EA-TCM, being a unique traditional Chinese medicine intervention, lacks standardized protocols for the timing and dosage of administration, which may potentially impact the study results. Third, significant heterogeneity in pain intensity may affect the reliability or interpretation of the results. Fourth, the subjects of this study are all from the Chinese population, which may affect the general applicability of the research results and could also limit the promotion of EA-TCM. Fifth, some included studies failed to adequately detail the specific implementation of the blinding method, resulting in a lower quality of evidence.

4.5 Directions for future research

There is still limited evidence supporting the use of EA-TCM combined with three-step analgesic ladder therapy for treating CIBP. Future research should conduct multicenter, large-scale clinical trials with standardized treatment protocols to furnish a more impartial and robust evidence base for medical decision-making. Specifically, all studies should be registered on a public registry platform prior to initiation, enabling the tracking of all conducted research, including those that remain unpublished. Journals should be encouraged to publish all research outcomes, including negative results and those without statistical significance. Enhancing transparency in research, including data sharing and detailed methodological reporting, thereby enabling other researchers to replicate the study or conduct secondary analyses. When conducting systematic reviews and meta-analyses, effort should be made to identify and include unpublished studies, utilize grey literature searches, as well as reach out to study authors to obtain unpublished data. Clearly define sample size calculations for superiority or non-inferiority trials and provide more detailed descriptions of randomization methods, allocation concealment, and blinding implementation in the reports to improve the accuracy and completeness of clinical research results and reduce clinical heterogeneity in systematic reviews. Provide detailed specifications for the definition or measurement methods of outcome indicators. Establish an international research collaboration network and cooperate with scientific research institutions in other countries and regions to conduct multicenter studies. Provide more detailed information when including patients, such as average age and pain severity levels, to facilitate the analysis of heterogeneity sources. Register the study in clinical trial registries to ensure all results can be obtained.

5 Conclusion

The combined therapy of EA-TCM and the three-step analgesic ladder therapy can significantly enhance the pain relief in patients with CIBP and improve their overall quality of life. This integrative approach not only reduces pain but also minimizes the side effects associated with high-dose opioid use. Our study presents a novel and promising therapeutic strategy for CIBP, potentially reshaping clinical guidelines for palliative care in oncology.

Fundings

Provincial Key Research and Development Project of Hunan (2018SK2127), and Hunan Province Traditional Chinese Medicine Research and Development Project (201946).

Competing interests

The authors declare no conflict of interest.

References

[1] ZHOU YQ, GAO HY, GUAN XH, et al. Chemokines and their receptors: potential therapeutic targets for bone cancer pain. Current Pharmaceutical Design, 2015, 21(34): 5029–5033.

[2] DIAZ-DELCASTILLO M, HANSEN RB, APPEL CK, et al. Modulation of rat cancer-induced bone pain is independent of spinal microglia activity. Cancers, 2020, 12(10): 2740.

[3] TRIPP DA, MIHAJLOVIC V, FRETZ K, et al. Quality of life, depression, and psychosocial mechanisms of suicide risk in prostate cancer. Canadian Urological Association Journal, 2020, 14(10): E487–E492.

[4] DAI JJ, DING ZF, ZHANG J, et al. Minocycline relieves depressive-like behaviors in rats with bone cancer pain by inhibiting microglia activation in hippocampus. Anesthesia and Analgesia, 2019, 129(6): 1733–1741.

[5] LIU MZ, MA J, LI JD, et al. A comparison of the clinical effectiveness between low-dose strong opioids and non-steroidal anti-inflammatory drugs in the treatment of mild cancer pain: a randomized trial. Journal of Pain Research, 2021, 14: 3411–3419.

[6] JING DD, ZHAO Q, ZHAO YB, et al. Management of pain in patients with bone metastases. Frontiers in Oncology, 2023, 13: 1156618.

[7] LUCCHESI M, LANZETTA G, ANTONUZZO A, et al. Developing drugs in cancer-related bone pain. Critical Reviews in Oncology/Hematology, 2017, 119: 66–74.

[8] NAFZIGER AN, BARKIN RL. Opioid therapy in acute and chronic pain. Journal of Clinical Pharmacology, 2018, 58(9): 1111–1122.

[9] WANG KY, DONNELLY CR, JIANG CY, et al. STING suppresses bone cancer pain via immune and neuronal modulation. Nature Communications, 2021, 12(1): 4558.

[10] ZHU JL, ZHANG S, JIA YJ. Research progress of external therapy of traditional Chinese medicine in the treatment of cancerous pain. Journal of Tianjin University of Traditional Chinese Medicine, 2019, 38(5): 518–520.

[11] ZHU WF, WANG YQ, WU WT, et al. Modern research progress in external application of traditional Chinese medicine to acupoints. China Journal of Chinese Materia Medica, 2023, 48(3): 579–587.

[12] MOHER D, LIBERATI A, TETZLAFF J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine, 2009, 6(7): e1000097.

[13] BALSHEM H, HELFAND M, SCHÜNEMANN HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology, 2011, 64(4): 401–406.

[14] GUYATT GH, OXMAN AD, VIST GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008, 336(7650): 924–926.

[15] CHEN H, ZHANG SS, YANG K, et al. Clinical study on the treatment of bone metastasis cancer pain syndrome with Dingxiang Gutong recipe and opioids. Journal of Basic Chinese Medicine, 2018, 24(1): 108–110.

[16] CHEN M, MENG QM, ZHOU XT. Clinical observation on the combination of Chinese and western medicine in the treatment of painful bone metastases of malignant tumours. Journal of Practical Traditional Chinese Medicine, 2014, 30(1): 29–30.

[17] CHEN XW. Study on the effect of tramadol hydrochloride sustained-release tablets combined with Dingxiang Powder external application in the treatment of bone metastatic pain in malignant tumor. Contemporary Medical Symposium, 2020, 18: 194–195.

[18] CHEN XZ, CHEN XK, TIAN HQ, et al. Clinical observation of external application of Ailitong Plaster in controlling cancer-induced bone pain. Acta Chinese Medicine and Pharmacology, 2020, 48(11): 49–52.

[19] CHEN YY, REN L, XIE NL, et al. Clinical study on the treatment of Yin syndrome of bone metastasis cancer pain by external application of clove analgesia. Hebei Journal of Traditional Chinese Medicine, 2019, 41(2): 205–209.

[20] CONG Y, LI JX, LI HM, et al. Efficacy observation of external application of Shentong Zhuyu Paste combined with strong opioids in the treatment of moderate and severe pain of bone metastasis from lung cancer. World Latest Medicine Information, 2018, 18(35): 92–93.

[21] GAO HF, HOU AJ, ZHANG HW, et al. Clinical efficacy of external medical herbs combining morphine sulfate on metastatic bone tumor pains. Shanghai Journal of Traditional Chinese Medicine, 2008, 42(10): 27–29.

[22] GAO Y, FENG L. Clinical observation on metastatic bone pain treated with application therapy with pseudobulbus cremastrae seu pleiones. World Journal of Integrated Traditional and Western Medicine, 2011, 6(7): 574–576.

[23] HAN KL, WANG WP, YU M, et al. 24 cases of bone metastasis cancer pain treated with topical Chinese medicine analgesic patch. Global Traditional Chinese Medicine, 2013, 6(4): 279–281.

[24] HE H. Study on the clinical effect of external application of traditional Chinese medicine combined with morphine in the treatment of bone metastatic cancer pain. Medical Diet and Health, 2019: 125–126.

[25] HE JJ. Clinical study of Huayu Zhitong Powder external application based on the theory of pathogenesis of stasis and toxin in the treatment of moderate and severe bone metastasis and cancer pain. Jinan: Shandong University of Traditional Chinese Medicine, 2020.

[26] HOU ZL. An exploratory clinical study on the external application of gutting patch for the treatment of bone metastasis cancerous pain with cold-Yin stagnation type. Beijing: Beijing University of Chinese Medicine, 2018.

[27] HUANG CJ, LIU JB, LIAO TH. Clinical observation of analgesic balms combined with "three-step analgesic ladder" therapy on the treatment of elderly bone metastasis from lung tumor. Heibei Journal of Traditional Chinese Medicine, 2016, 38: 530–533.

[28] JIANG L, ZHAO CJ, JIAO J, et al. Clinical study on the combination of Zhitong Sanjie Paste and oxycontin for the treatment of bone metastases with moderate to severe pain. Journal of Shaanxi University of Traditional Chinese Medicine, 2021, 44: 102–105.

[29] JING NC, GUO HY, WANG J, et al. Efficacy of Shentong Zhuyu Paste combined with strong opioids in the treatment of bone

metastases from lung cancer with moderate and severe pain. Chinese Journal of Gerontology, 2014, 34: 5428–5430.

[30] LAN P. Clinical study on external application of Dingxiong Xiaotong Prescription in the treatment of pain with bone metastases from malignant tumors. Chengdu: Southwest Medical University, 2022.

[31] LI MN, WANG GC, ZHANG ZM. Clinical study on external application of Cancer Gutong Ointment on the control of bone metastatic cancer pain. Clinical Journal of Chinese Medicine, 2022, 14: 102–105.

[32] LIU PZ. Clinical study on the treatment of bone metastasis pain by external application of bursa cream combined with disodium pamiphosphate. Practical Clinical Journal of Intergrated Traditional Chinese and Western Medicine, 2015, 15: 31–32.

[33] LIU SS, LAO ZY, HUANG SS, et al. Clinical efficacy and safety of Ailitong Ointment combined with strong opioid analgesics for cancerous bone pain. Chinese Journal of Clinical Oncology and Rehabilitation, 2022, 29: 717–720.

[34] LIU YR. Effect of Chinese medicine acupoint application and morphine sulphate extended-release tablets in the treatment of bone metastatic cancer pain. Chinese Community Doctors, 2013, 15: 218–219.

[35] MA LY. Clinical research of ta stains of Chinese medicine combined with paracetamol and tramadol hydrochloride tablets in the treatment of lung cancer with bone metastasis. Changchun: Changchun University of Chinese Medicine, 2014.

[36] RAO AH, WANG YS, XU JX. Clinical studies of topical treatment of breakthrough pain of acute bone metastases with pain elimination combined with hyperthermia. Journal of Emergency in Traditional Chinese Medicine, 2014, 23(12): 2192–2193.

[37] SHENG YJ, SUN Y, LIU J. Clinical observation on collapsing impregnation with traditional Chinese medicine in the treatment of cancer pain of bone metastases. Zhejiang Journal of Traditional Chinese Medicine, 2019, 54(2): 125.

[38] SHI Y, ZHANG SP, YANG XH, et al. Analysis of 106 cases of metastatic bone cancer pain treated by external application of traditional Chinese medicine combined with pregabalin and morphine sulphate sustained-release tablets. Journal of Medical Aesthetics and Cosmetology, 2019, 28: 51.

[39] SUN S, YU CQ, ZHANG DY, et al. Clinical study of rhubarb and mirabilite external treatment on improving metastatic cancer-induced bone pain. Journal of Liaoning University of Traditional Chinese Medicine, 2019, 21(2): 82–85.

[40] SUN ZB. Clinical study of Chinese medicine external treatment combined with morphine in the treatment of bone metastasis cancer pain. Health Management, 2021: 33–34.

[41] TANG X. Clinical observation of analgesic paste combined with oxycontin in the treatment of moderate and severe bone cancer pain. Xianyang: Shaanxi University of Chinese Medicine, 2018.

[42] TANG Y, ZHANG H. Clinical observation on cancer-induced bone pain by traditional Chinese medicine packet and compound sophora injection. Guiding Journal of Traditional Chinese Medicine and Pharmacy, 2017, 23: 64–66.

[43] WANG F, LAI GH, NIE DR, et al. Clinical observation on the treatment of 42 cases of moderate to severe bone metastatic cancer pain by combining local external application of Xiaozhong Zhitong Powder and oral administration of oxycontin. Shandong Medical Journal, 2023, 63: 71–74.

[44] WANG L. Clinical observation on the treatment of bone metastatic cancer pain of malignant tumors by combining Zhentong Sanjie Cream through traditional Chinese medicine directional drug transmission with oxycodone hydrochloride prolonged-release tablets. Xianyang: Shaanxi University of Chinese Medicine, 2021.

[45] WANG X, XU JH, CHEN L, et al. Clinical study on medium frequency electrotherapy combined with Chinese materia medica iontophoresis in treatment of pain caused by vertebrae metastasis of non-small cell lung cancer. Shandong Journal of Traditional Chinese, 2023, 42: 969–974.

[46] WANG Y, YANG F, HUANG R. The application of five elements music therapy combined with external application of Chinese medicine in pain of malignant spinal bone metastases. Chinese Medicine Modern Distance Education of China, 2023, 21: 102–105.

[47] XU DK. Clinical efficacy of self-proposed analgesic formula for the treatment of carcinogenic pain caused by bone metastases. China Health Care & Nutrition, 2020, 30: 86.

[48] XU JX, RAO AH, WANG YS, et al. The efficacy of external application of Aitongxiao combined with thermotherapy in the treatment of bone metastatic cancer pain in 25 cases. Journal of New Chinese Medicine, 2014, 46: 151–154.

[49] YANG T, TANG JQ. 30 cases of compound Xiaotong Paste combined with aminophenoxycodone tablets for the treatment of moderate pain in bone metastases. Traditional Chinese Medicinal Research, 2019, 32(1): 12–14.

[50] YANG ZM, XIE G, LIAO DZ, et al. Clinical observation of pain control in malignant tumor with bone metastases by Aitong Powder. Chongqing Medical Journal, 2016, 45: 3893–3895, 3899.

[51] YU M, WANG HW, WANG WP, et al. Multicenter study on traditional Chinese medicine analgesic plaster combined with morphine in treatment of moderate and severe cancer pain. Chinese Journal of New Drugs and Clinical Remedies, 2015, 34: 617–621.

[52] YU XF. 48 cases of cancer analgesic powder combined with Futalin enteric solution tablets in the treatment of bone metastatic pain from malignant tumors. Zhejiang Journal of Chinese

Medicine, 2015, 50: 274.

[53] YUAN H, QIAO BL. Clinical effect analysis of Dingxiang Powder combined with tramadol extended-release tablets in the treatment of painful bone metastases from malignant tumors. Research of Integrated Traditional Chinese and Western Medicine, 2015, 7(2): 83–84.

[54] ZHANG J, YANG XY, REN JW. Effect of external application of self-made Aitong Powder on pain relief and treatment compliance for patients with bone metastases. Journal of Sichuan of Traditional Chinese Medicine, 2021, 39(1): 205–208.

[55] ZHANG LW, LI LN, HE CX, et al. Clinical observation of Wenjing Zhitong Recipe in treating cancer pain in lung cancer with bone metastases. Chongqing Medical Journal, 2019, 48: 1327–1329.

[56] ZHANG LW, LI LN, HE CX, et al. Observation on the effect of traditional Chinese medicine warm compresses on back meridians combined with oxycodone hydrochloride extended-release tablets in the treatment of moderate-to-severe cancer pain in bone metastases of lung cancer. Shandong Medical Journal, 2018, 58: 55–57.

[57] ZHOU TT, GAO JD. Clinical effect of external application of Bushen Tongluo Zhitong Prescription combined with opioids in treatment of bone metastatic cancer pain: an analysis of 30 cases. Hunan Journal of Traditional Chinese Medicine, 2023, 39(9): 9–12.

[58] LIU R, LI Z, BAI H, et al. Study on the effect of Zhentong Plaster in external use on the alleviation of cancer pain and its mechanism. Acta Chinese Medicine, 2010, 25(4): 611–615.

[59] HOU GJ, BAI ZP, ZENG PH, et al. Effects of Chanlong Zhentong Paste on pain threshold and serum levels of PGE2, TNF-α, IL-6 and β-EP in bone metastatic cancer pain model rats. Traditional Chinese Drug Research and Clinical Pharmacology, 2019, 30(10): 1222–1227.

[60] CUI WJ. Mechanism of external application of Tongluo Sanjie Gel in regulating bone cell and CaN/NFATc1 signaling pathway in treating cancer induced bone pain. Shanghai: Shanghai University of Tradtional Chinese Medicine, 2023.

[61] BAO YJ, WANG GM, GAO YB, et al. Topical treatment with Xiaozheng Zhitong Paste alleviates bone cancer pain by inhibiting proteinase-activated receptor 2 signaling pathway. Oncology Reports, 2015, 34(3): 1449–1459.

[62] HE PS, FENG XZ, JIANG M, et al. Effect of xiangxin prescription on inflammatory medium and MCP-1 in mice with bone metastatic cancer pain. Chinese Journal of Surgery of Integrated Traditional and Western Medicine, 2019, 25(3): 262–266.

[63] JIANG Y, WANG L, CAO Y, et al. The experimental study of mechanism in external treatment of cancer pain. Lishizhen Medicine and Materia Medica Research, 2013, 24(7): 1780–1783.

[64] WANG S, ZHANG D, HU JS, et al. A clinical and mechanistic study of topical borneol-induced analgesia. EMBO Molecular Medicine, 2017, 9(6): 802–815.

[65] HU DY, WANG CM, LI FX, et al. A combined water extract of frankincense and myrrh alleviates neuropathic pain in mice via modulation of TRPV1. Neural Plasticity, 2017, 2017: 3710821.

[66] NIE AZ, RU QG, FU ZH. Anti-inflammatory and analgesic effects of asarum decoction. Information on Traditional Chinese Medicine, 38(7): 40–42.

[67] YU JC, LUO YY, JIN HD, et al. Scorpion alleviates bone cancer pain through inhibition of bone destruction and Glia activation. Molecular Pain, 2020, 16: 1744806920909993.

[68] QIAO CX, ZHANG XF, CHENG XF, et al. Effect of strychnos nux-vomica decoction on pain in mice with bone metastasis and osteoclasts in bone metastatic lesions. Chinese Traditional Patent Medicine, 2020, 42(7): 1907–1910.

[69] WANG LE, ZHANG Y, WANG ZW, et al. The antinociceptive properties of the *Corydalis yanhusuo* extract. PLoS One, 2016, 11(9): e0162875.

中药外敷联合三阶梯镇痛药物治疗癌性骨痛：一项系统评价和 meta 分析

王菲[a], 赖桂花[b], 周芳[a], 聂多锐[a], 程雄涛[a], 王岳[a], 曹建雄[c*]

a. 湖南中医药大学研究生院, 湖南 长沙 410208, 中国
b. 南华大学第一附属医院康复科, 湖南 衡阳 421001, 中国
c. 湖南中医药大学第一附属医院肿瘤科, 湖南 长沙 410007, 中国

【摘要】目的 对中药外敷联合口服三阶梯镇痛药物对癌性骨痛患者的总体疗效进行系统评价。**方法** 我们在 10 个数据库和 2 个注册系统中检索了关于中药外敷联合三阶梯镇痛疗法治疗癌性骨痛的随机对照试验，其中包括 4 个中文数据库：中国生物医学文献数据库（SinoMed）、中国知网（CNKI）、万方数据库、维普数据库（VIP），6 个英文数据库（Scopus、Embase、Web of Science、PubMed、Cochrane Library 和 OpenGrey）和 2 个注册系统（中国临床试验注册中心和 ClinicalTrials.gov）。文献检索的时间范围从各数据库建立之日至 2023 年 12 月 31 日。使用 RevMan（v5.4.1）进行 meta 分析，并使用 GRADEprofiler（v3.6）对结局指标（疼痛缓解率、镇痛持续时间、生活质量、疼痛强度、爆发痛次数及不良反应）进行证据质量分级。**结果** 根据既定的纳入和排除标准，共 43 项研究符合条件，包括 3142 名癌性骨痛患者。meta 分析结果表明，中药外敷联合三阶梯镇痛药物与单独口服三阶梯镇痛药物相比，疼痛缓解率 [风险比（RR）= 1.32，95% 置信区间（CI）：1.24 ~ 1.41, $P < 0.000\ 01$]、镇痛持续时间 [平均差（MD）= 1.33，95% CI：0.97 ~ 1.69, $P < 0.000\ 01$] 和生活质量（MD = 5.66，95% CI：4.88 ~ 6.44, $P < 0.000\ 01$）均有显著改善。中药外敷联合口服三阶梯镇痛药物还可显著降低癌性骨痛患者的疼痛强度（MD = – 1.00，95% CI：– 1.19 ~ – 0.80, $P < 0.000\ 01$）、爆发痛发生频率（MD = – 0.43，95% CI：– 0.51 ~ – 0.36, $P < 0.000\ 01$）和不良反应（RR = 0.60，95% CI：0.53 ~ 0.68, $P < 0.000\ 01$）。根据 GRADE 评估，证据等级从低到中不等。**结论** 中药外敷联合三阶梯镇痛药物可有效缓解癌性骨痛患者的疼痛症状，提高其生活质量。此外，中药外敷还能有效降低三阶梯镇痛药物的不良反应发生率。

【关键词】中药外敷；三阶梯镇痛药物；癌性骨痛；系统评价；meta 分析