

SYSTEMATIC REVIEW

Traditional Chinese medicine for bone metastasis of breast cancer: a systematic review and meta-analysis

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Abstract

Breast cancer incidence is increasing, and bone metastases in terminal breast cancer cause considerable patient suffering. Many researchers have reported that traditional Chinese medicine (TCM) benefits breast cancer patients with bone metastasis. However, no conclusive evidence can be proved for its effects. This paper assesses the effects of TCM on bone metastasis of breast cancer. Databases were searched independently for randomized controlled trials about TCM for bone metastasis of breast cancer by two reviewers. The effective rate was assessed as the primary outcome. Patient's condition and adverse events were assessed as secondary outcomes. Thirteen articles were included in our meta-analysis. The results showed that TCM is effective for treating bone metastasis of breast cancer (RR (Risk ratio) = 1.10, 95% CI (Confidence interval) (1.04, 1.16), $p < 0.05$). TCM can improve metastasis to the bone in breast cancer (RR = 1.52, 95% CI (1.33, 1.74), $p < 0.05$). TCM also relieved pain in patients with bone metastasis of breast cancer (RR = 1.41, 95% CI (1.22, 1.63), $p < 0.05$). Six studies reported adverse events (RR = 0.41, 95% CI (0.28, 0.62), $p < 0.05$). This shows that adjuvant treatment with TCM can reduce the incidence of adverse reactions. TCM treatment is an effective and safe adjuvant therapy for bone metastasis in breast cancer patients.

Keywords

Traditional Chinese medicine; Bone metastasis; Breast cancer; Meta-analysis; Systematic review

1. Introduction

The incidence of breast cancer is increasing. It ranks first in the type of cancer threatening women's lives and health. Bone is the most common distant metastasis site of breast cancer. At present, the most recognized explanation for bone metastasis is the "seed soil" theory proposed by Stephen Paget in 1889. However, its mechanism is not clear [1]. After secreting a series of growth factors, the cells in the primary focus of breast cancer have enhanced chemotaxis, invasion, proliferation, adhesion and colonization [2]. Therefore, they spread into bone and destroy the bone microenvironment. Finally, they disrupt the homeostasis of bone and cause bone metastasis of breast cancer [3].

The incidence of bone metastases in breast cancer is very high, accounting for approximately 60% of terminal cancers [4]. The related symptoms of bone metastases occur in nearly 30% of patients [5]. Bone metastasis of breast cancer usually manifests as multiple osteolytic lesions, which can cause a series of complications, such as pathological bone pain, fracture, spinal cord compression, and hypercalcaemia. The complications of bone metastasis of breast cancer seriously affect the quality of life of patients and their families [6]. Existing treatment methods include chemotherapy, radiother-

apy, endocrine therapy, molecular targeted therapy, surgery, bisphosphonate therapy and other symptomatic support therapies [7]. They are mainly used to control disease progression and prevent bone-related events. However, they cannot reverse the disease [8].

In the treatment of malignant tumours, TCM has unique advantages and is widely used [9]. Although there has been a summary of treating bone metastasis of breast cancer with TCM, there is still a lack of conclusive evidence. Therefore, this study conducted a meta-analysis on the efficacy and adverse reactions of TCM for bone metastasis of breast cancer to explore the efficacy and value of TCM in the treatment of bone metastasis of breast cancer and provide more conclusive evidence [10].

2. Methods

2.1 Search strategy

Databases (Cochrane Library, Web of Science, PubMed, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database, Chinese Biomedical Literature Database, Wan Fang Database, WHO (World Health Organization) Trials, and Chinese Clinical Trial Registry, ClinicalTrials) were

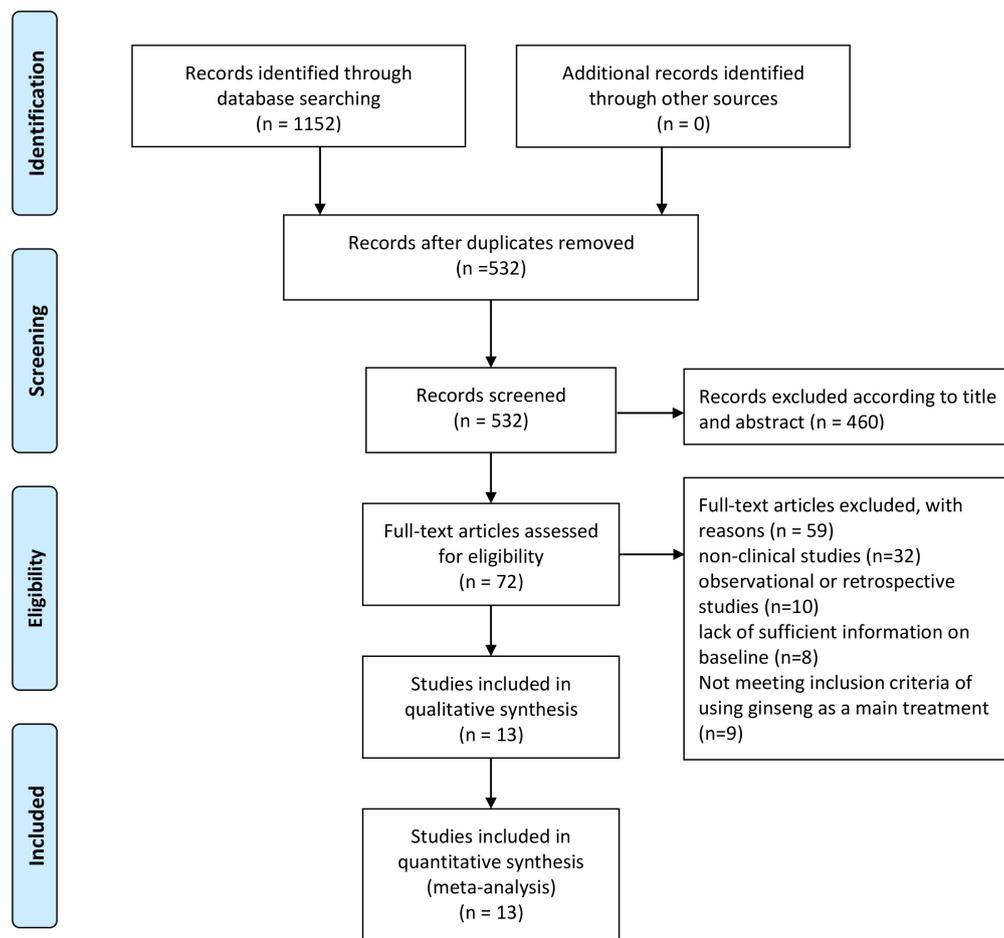


FIGURE 1. Flowchart of study selection.

independently searched for randomized controlled trials about TCM for bone metastasis of breast cancer by two reviewers. The retrieval date is from the database establishment to the current day. The database (PubMed) search strategy was as follows:

#1. Search “Breast Cancer” (Mesh)

#2. Search (((((((((((((((((((((((Breast Neoplasm) OR (Neoplasm, Breast)) OR (Breast Tumors)) OR (Breast Tumor)) OR (Tumor, Breast)) OR (Tumors, Breast)) OR (Neoplasms, Breast)) OR (Breast Cancer)) OR (Cancer, Breast)) OR (Mammary Cancer)) OR (Cancer, Mammary)) OR (Cancers, Mammary)) OR (Mammary Cancers)) OR (Malignant Neoplasm of Breast)) OR (Breast Malignant Neoplasm)) OR (Breast Malignant Neoplasms)) OR (Malignant Tumor of Breast)) OR (Breast Malignant Tumor)) OR (Breast Malignant Tumors)) OR (Cancer of Breast)) OR (Cancer of the Breast)) OR (Mammary Carcinoma, Human)) OR (Carcinoma, Human Mammary)) OR (Carcinomas, Human Mammary)

#3. Search #1 OR #2

#4. Search “Bone Metastasis” (Mesh)

#5. Search “Traditional Chinese medicine” (Mesh)

#6. Search (((((((Traditional Chinese Medicine) OR (Traditional Medicine, Chinese)) OR (Zhong Yi Xue)) OR (Chinese Traditional Medicine)) OR (Chinese Medicine, Traditional)) OR (Tongue Diagnoses, Traditional)) OR (Tongue Diagnosis,

Traditional)) OR (Traditional Tongue Assessment)

#7. Search #5 OR #6

#8. Search #3 AND #4 AND #7

2.2 Study selection

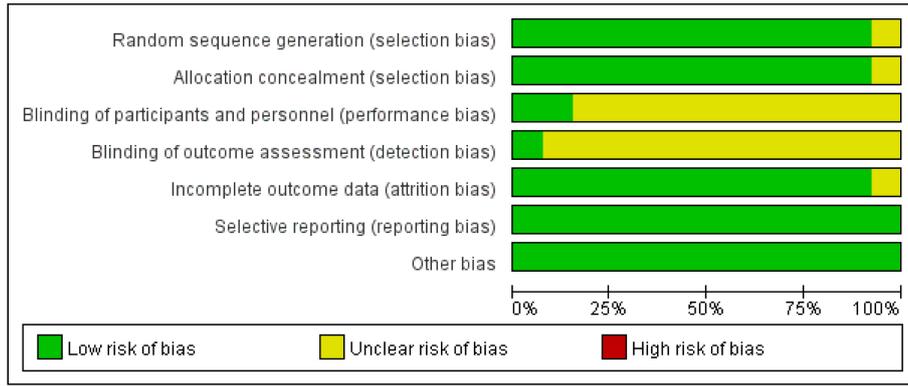
Randomized controlled trials (RCTs) were included for further assessment. The inclusion criteria were (a) Participants need to be diagnosed with bone metastasis of breast cancer. (b) The intervention method used TCM as the main component.

The exclusion criteria were (a) Literature published with duplicate data. (b) Study with fewer than 15 patients in the experimental group or control group. The primary outcomes was the curative effect of bone metastasis of breast cancer. Additional outcomes of the patient’s condition were (a) Improvement of metastatic focus. (b) Pain relief. (c) Adverse events.

2.3 Data collection

The statistical analysis was conducted by RevMan 5.4 (Cochrane Collaboration Review Manager, London, UK). The sensitivity analysis was conducted by Stata. According to the criteria, two different authors (QC and BH) independently scanned the articles and investigated the full text of the potentially eligible articles [11]. Any disagreement was

A



B

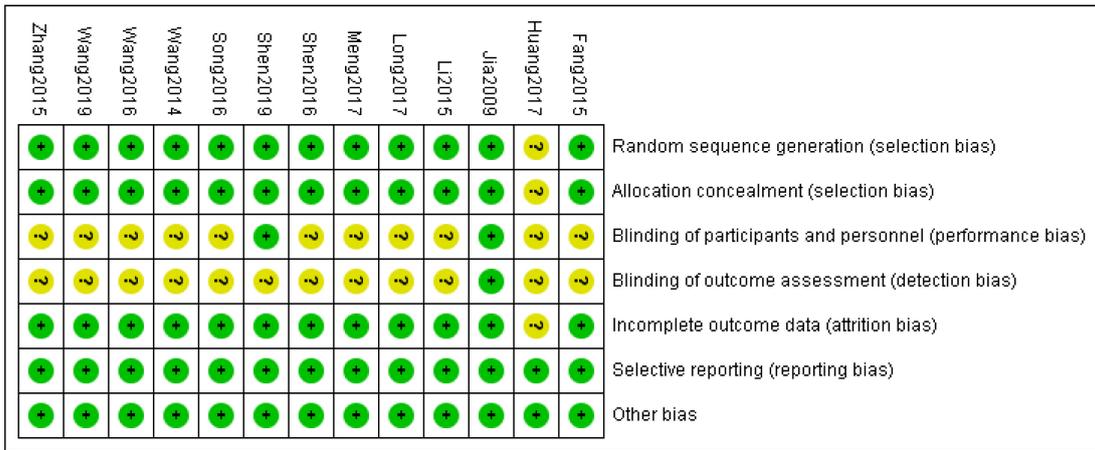
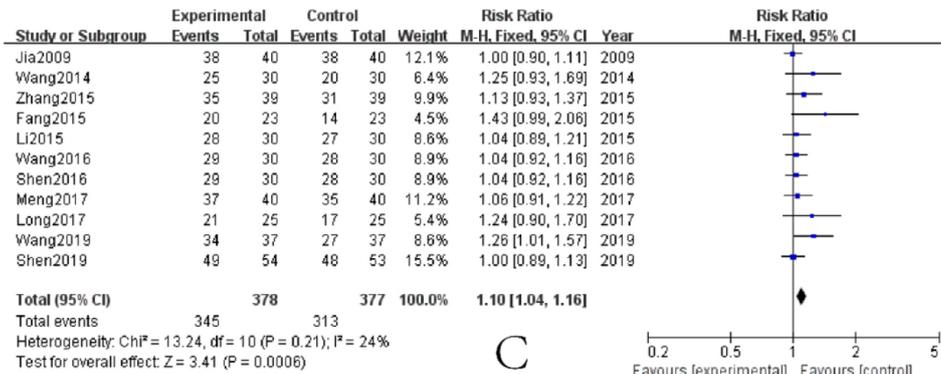
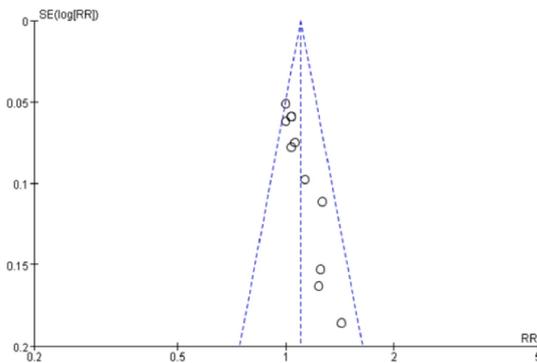


FIGURE 2. Quality assessment of the included studies. (A) Risk of bias summary. (B) Risk of bias graph.

A



B



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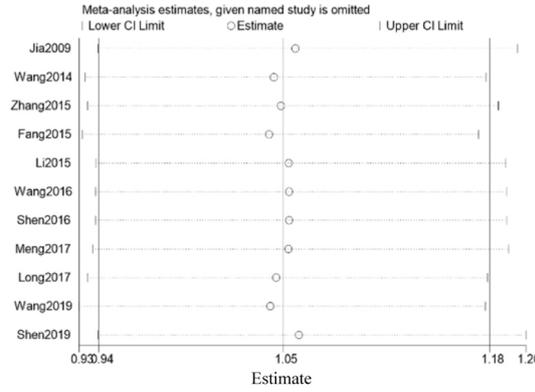
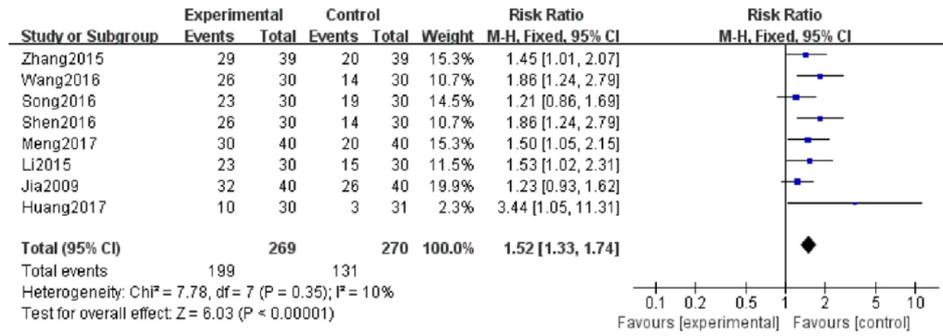
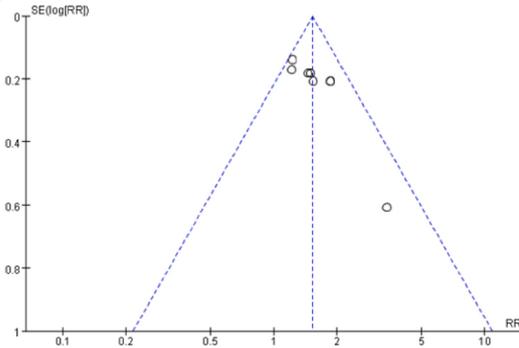


FIGURE 3. Curative effect of bone metastasis of breast cancer. (A) Forest plot of curative effect. (B) funnel plot of curative effect. (C) Sensitivity analysis of curative effect.

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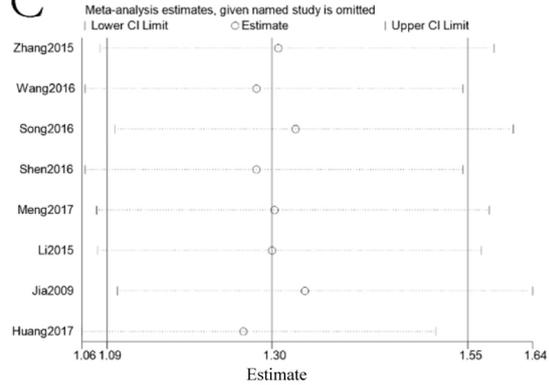
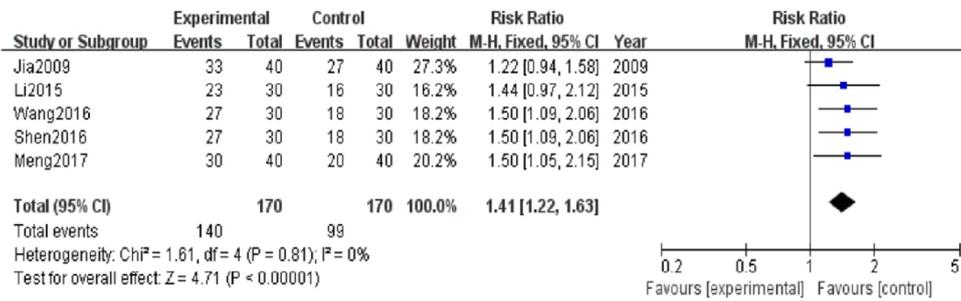
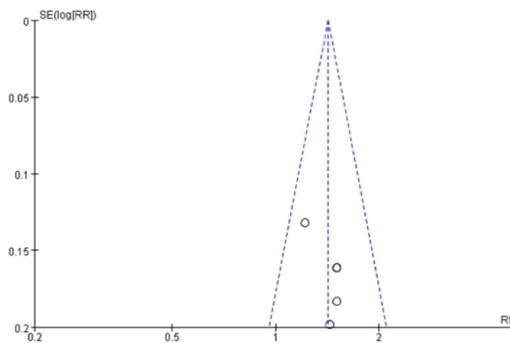


FIGURE 4. Improvement of metastatic focus. (A) Forest plot of improvement of metastatic focus. (B) Funnel plot of improvement of metastatic focus. (C) Sensitivity analysis of improvement of metastatic focus.

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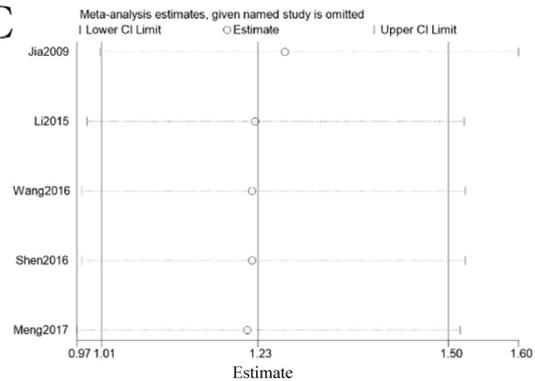


FIGURE 5. Pain relief. (A) Forest plot of improvement of pain relief. (B) Funnel plot of improvement of pain relief. (C) Sensitivity analysis of improvement of pain relief.

TABLE 1. Characteristics of the studies.

Study	Exp. Average age	Exp. Group Number	Con. Average age	Con. Group Number	Exp. Group method	Con. Group method	Research designs
Jia 2009 [16]	56.20	40	50.60	40	TCM + regular treatment	regular treatment	RCT
Wang 2014 [17]	54.00	30	53.00	30	TCM + regular treatment	regular treatment	RCT
Zhang 2015 [18]	33.00	39	32.00	39	TCM + regular treatment	regular treatment	RCT
Fang 2015 [19]	50.80	23	53.10	23	TCM + regular treatment	regular treatment	RCT
Li 2015 [20]	58.53	30	59.33	30	TCM + regular treatment	regular treatment	RCT
Wang 2016 [21]	48.90	30	49.40	30	TCM + regular treatment	regular treatment	RCT
Song 2016 [22]	53.60	30	53.63	30	TCM + regular treatment	regular treatment	RCT
Shen 2016 [23]	48.90	30	49.40	30	TCM + regular treatment	regular treatment	RCT
Meng 2017 [24]	58.20	40	58.60	40	TCM + regular treatment	regular treatment	RCT
Huang 2017 [25]	57.10	31	57.60	30	TCM + regular treatment	regular treatment	RCT
Long 2017 [26]	43.50	25	42.00	25	TCM + regular treatment	regular treatment	RCT
Wang 2019 [27]	44.21	37	43.52	37	TCM + regular treatment	regular treatment	RCT
Shen 2019 [28]	42.16	55	44.58	55	TCM + regular treatment	regular treatment	RCT

TCM: Traditional Chinese Medicine; RCT: randomized controlled trial.

discussed by a third expert (JT). Referring to the Cochrane risk of bias risk guideline [12, 13], two review authors (QC and BH) independently evaluated the quality of the literature. If there were differences in the evaluation results, they were resolved in consultation with the third author. If the included study was a randomized controlled study, the bias risk assessment tool of the Cochrane Collaboration Network was used to evaluate its methodological quality. From the aspects of random sequence generation, concealment of allocation schemes, blinding, completeness of outcome data, and selective reporting to assess the risk of bias, there were three types of evaluation results for each item, namely, low risk, high risk, and unclear [14].

2.4 Statistical analysis

A funnel plot was used to assess the possibility of publication bias. Statistical heterogeneity was evaluated by the I^2 test. When I^2 was 0–50%, we used a fixed-effects model to pool the results; otherwise, we used a random-effects model [15]. The selected indicators are count data and measurement data. We used relative risk (RR) with a 95% confidence interval (CI) for discontinuous variables. Sensitivity analyses were conducted

to assess the effects of the exclusion of studies at high risk of bias influencing the findings.

3. Results

3.1 Literature searches

The initial searches generated 1152 related studies. According to settled criteria, 72 studies were included for full-text consideration. Finally, 13 studies were included in the meta-analysis (Fig. 1).

3.2 Characteristics of the Studies

Nineteen articles were included in this review (Table 1).

3.3 Risk of bias

The results of the risk of bias assessment of the 13 studies are summarized in Fig. 2. Only two articles mentioned blinding of participants and personnel (performance bias), and only one article mentioned blinding of outcome assessment (detection bias) (Fig. 2).

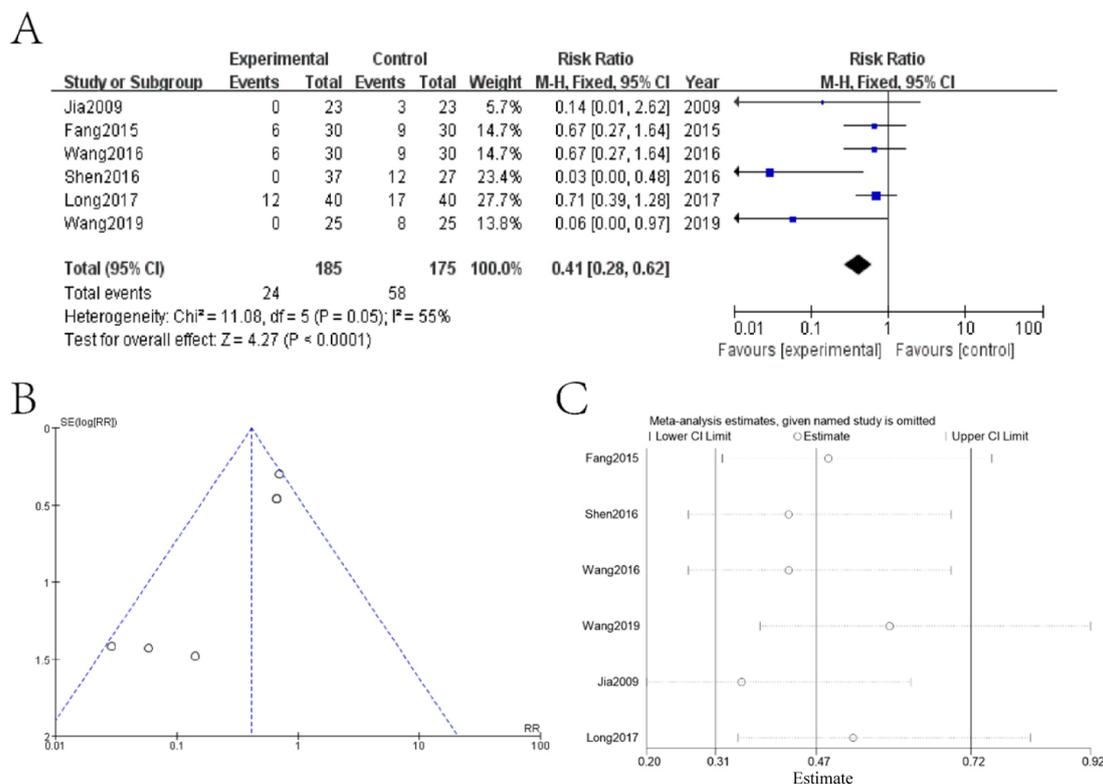


FIGURE 6. Adverse events. (A) Forest plot of improvement of adverse events. (B) Funnel plot of improvement of adverse events. (C) Sensitivity analysis of improvement of adverse events.

3.4 Curative effect of bone metastasis of breast cancer

Eleven studies reported the curative effect of TCM. The results showed that TCM was effective for treating bone metastasis of breast cancer ($\text{RR} = 1.10$, 95% CI (1.04, 1.16), $p = 0.0006$). The effect size is statistically significant. The funnel plot and the sensitivity analysis chart are within the confidence range (Fig. 3).

3.5 Improvement of metastatic focus

Eight studies reported improvement of the metastatic focus. The results showed that TCM could improve bone metastasis of breast cancer ($\text{RR} = 1.52$, 95% CI (1.33, 1.74), $p < 0.00001$). The funnel plot and the sensitivity analysis chart are within the confidence range (Fig. 4).

3.6 Pain relief

Five studies reported pain relief. The results show that TCM can relieve pain for patients with bone metastasis of breast cancer ($\text{RR} = 1.41$, 95% CI (1.22, 1.63), $p < 0.00001$). The effect size is statistically significant. The funnel plot and sensitivity analysis showed that all single studies did not affect the whole analysis results. All of the studies were within the acceptable range (Fig. 5).

3.7 Adverse events

Six studies reported adverse events. The results showed that $\text{RR} = 0.41$, 95% CI (0.28, 0.62), $p < 0.0001$. The effect

size is statistically significant. This shows that adjuvant treatment with TCM can reduce the incidence of adverse reactions (Fig. 6).

4. Discussion

4.1 Summary

Thirteen articles were included in meta-analysis. The results showed that TCM is effective for treating bone metastasis of breast cancer ($\text{RR} = 1.10$, 95% CI (1.04, 1.16), $p < 0.05$). TCM can improve metastasis to the bone in breast cancer ($\text{RR} = 1.52$, 95% CI (1.33, 1.74), $p < 0.05$). TCM also relieved pain in patients with bone metastasis of breast cancer ($\text{RR} = 1.41$, 95% CI (1.22, 1.63), $p < 0.05$). Six studies reported adverse events ($\text{RR} = 0.41$, 95% CI (0.28, 0.62), $p < 0.05$). This shows that adjuvant treatment with TCM can reduce the incidence of adverse reactions.

4.2 Implications for clinical practice and further research

TCM-assisted treatment of bone metastases of breast cancer has better effects than conventional treatment alone in improving bone metastases of breast cancer, relieving pain, improving quality of life and reducing adverse reactions [29]. In clinical practice, we should add TCM to the treatment according to the specific situation of the patients [30] and carry out more rigorous and high-quality trials to further verify the clinical efficacy of TCM [31].

4.3 Strengths and Limitations

Our analysis has some strengths. The data extraction and assessment were conducted independently. Furthermore, our analysis followed the guidelines of the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32]. Limitations mainly originate from the different clinical conditions of breast cancer patients. Clinical heterogeneity may exist. We conducted a sensitivity analysis and found that all of the literature was within the acceptable range. In addition, due to the lack of high-quality and multicentre studies, the level of evidence in this study is limited.

AUTHOR CONTRIBUTIONS

CQ—conceived and designed the analysis. CQ and HB—completed the data retrieval. CQ—analysed the data. CQ—wrote the paper. TJ—revised the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This study was supported by Jiangsu Province “333 high-level talent training project” scientific research support project (BRA2020149).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Cheng Qian, Huwei Bian, Tao Jiang. Traditional Chinese medicine for bone metastasis of breast cancer: a systematic review and meta-analysis. *European Journal of Gynaecological Oncology*. 2022; 43(6): 13-20. doi: 10.22514/ejgo.2022.053.