



Review

Efficacy of traditional Chinese medicine external therapy on sleep quality in patients with cancer: A systematic review and network meta-analysis

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ABSTRACT

Objective: This network meta-analysis aims to assess and compare the effectiveness of various external therapies from traditional Chinese medicine (TCM) in enhancing sleep quality among patients with cancer.

Methods: We systematically searched nine electronic databases, encompassing five English and four Chinese databases, for randomized controlled trials (RCTs) from their inception up to August 10, 2023. The random effects model was utilized for effect size analysis, and the standardized mean difference (SMD) along with its corresponding 95% confidence interval (CI) were computed. Network meta-analysis and comparative effects ranking were executed utilizing STATA 14.0.

Results: We included thirty-four RCTs involving seven distinct external TCM therapies. Among these, Chinese medicine pillow (SMD = -3.27; 95% CI: -6.03 to -0.51), auricular acupressure (SMD = -2.33; 95% CI: -3.36 to -1.29), moxibustion (SMD = -2.28; 95% CI: -3.63 to -0.94), acupressure (SMD = -1.67; 95% CI: -2.64 to -0.70), and acupuncture (SMD = -1.43; 95% CI: -2.65 to -0.21) demonstrated significant effects in improving sleep quality when compared to usual care or waitlist. The cumulative ranking curve values revealed that the Chinese medicine pillow exhibited the highest potential for effectively enhancing sleep quality in patients with cancer, followed by auricular acupressure, moxibustion, acupressure, acupuncture, Tuina, and electroacupuncture.

Conclusions: Our study highlights the Chinese medicine pillow as an optimal external TCM therapy for ameliorating sleep quality in cancer patients, but more RCTs are needed to validate this conclusion. These findings serve as valuable support for future clinical trials and research endeavors.

Systematic review registration: CRD42022381370.

Introduction

Sleep disturbance is one of the most prominent and distressing problems in patients with cancer, which is also a persistent symptom.^{1,2} A study found that the overall incidence of sleep disturbance in patients with cancer is 60.7%, but the prevalence of sleep disturbance varied across treatment periods and cancer types.³ Wang et al investigated 330 patients with cancer in the radiotherapy department, and the prevalence of sleep disturbance was 38.3%, with lung cancer patients (45.2%) being more likely to suffer from sleep disturbance.⁴ Sanford et al found that 60.5% of patients with breast cancer had sleep disturbances during chemotherapy.⁵ Mercadante et al assessed the quality of sleep in 219 patients with advanced cancer and found that all patients had consistent

sleep disturbances.⁶ Although symptoms improve over time, a proportion of survivors still have severe sleep disturbance 9 years after cancer diagnosis.²

Sleep disturbance is defined as dysregulation of sleep homeostasis, insufficient sleep, or impairment of sleep quality or quantity, specifically including prolonged sleep onset, difficulty initiating and maintaining sleep, poor sleep efficiency, and excessive daytime sleepiness.⁷ The term “sleep disturbances” is used in relation to sleep by clinicians, researchers, and the public, designating insufficient or excessive sleep duration or poor self-reported sleep quality regardless of whether they fulfill the criteria for specific diagnoses.⁸ Sleep disturbance has been reported to be associated with decreased health-related activities (eg, exercise, healthy eating, and social interaction),⁹ cognitive impairment,¹⁰ and reduced

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quality of life in patients. In addition, sleep disturbance can affect an individual's immunity, resulting in poor healing and a higher risk of infection and mortality in these patients.^{11–13}

Pharmacological therapy is often applied to sleep management, such as benzodiazepines, but these agents have side effects such as drug dependence, impaired cognitive attention, and suicidal tendencies.¹⁴ Long-term use of medications can cause adverse effects such as tolerance and drug dependence (particularly, psychologic dependence) in patients.¹⁵ Paltiel et al found that patients with cancer who reported taking tranquilizers or sleeping medications had substantially poorer quality of life in terms of functional and symptom scales than those who did not take them.¹⁶ However, few studies have reported side effects of hypnotic drugs for the treatment of sleep problems in cancer patients.¹⁷ In recent years, a growing body of literature is exploring the emerging role of alternative therapies, such as external therapy of traditional Chinese medicine (TCM), which has played a significant role in improving cancer patients' sleep quality. External therapy of TCM generally refers to the method of applying herbs, techniques, or instruments to the skin (mucosa) on the body surface or applying treatment from outside the body under the guidance of TCM theory, including acupuncture, acupressure, and moxibustion.¹⁸

Valid evidences have confirmed the positive efficacy of multiple external therapies of TCM, such as acupuncture,¹⁹ and acupressure,²⁰ on the improvement of sleep quality in patients with cancer. The limitations of traditional pairwise meta-analyses and the lack of randomized controlled trials (RCTs) directly comparing interventions have resulted in the inability to compare the effectiveness of all available interventions. Network meta-analysis (NMA) methods can be performed in which direct evidence and indirect evidence are combined, and interventions are ranked according to their effect sizes.²¹ Therefore, the primary objective of this study was to compare the effects of different external therapies of TCM on subjective sleep quality in patients with cancer. Furthermore, we aimed to identify the most effective therapy of TCM for improving sleep health in order to provide an evidence-based clinical decision-making process.

Methods

This systematic review and NMA included intervention studies that involved participants aged at least 18 years, with any type of cancer, who underwent external therapy of TCM to improve sleep quality. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for NMA guidelines.²² The protocol of this review was registered on the PROSPERO website (Registration No. CRD42022381370).

Search strategy

We searched for relevant studies in five English databases (PubMed, Embase, Cochrane Library, CINAHL, Web of Science) and four Chinese databases (Chinese Biomedical Literature Database, WANFANG Database, China National Knowledge Internet, and VIP Database) from the inception of these databases to October 10, 2022 in the initial search. On August 10, 2023, the first reviewer (NL) updated the search to include any RCTs published since October 10, 2022. The search was performed in English language and Chinese. No publication date or language restriction was applied. The terms used in all searches were as follows: (“cancer” OR “neoplasms”) AND “sleep” AND (“external therapy of TCM” OR “acupuncture” OR “auricular” OR “moxibustion” OR “acupressure” OR “Tuina” OR “Chinese medicine pillow” OR “cupping therapy”) AND “RCT.” Searches were conducted using a combination of MeSH terms and free-text words, with appropriate search formulas developed according to the characteristics of the database. The electronic database search was supplemented by a manual search of the reference lists of included studies or published reviews. The full search strategy for each database is described in Supplementary File 1.

Inclusion and exclusion criteria

Eligible studies were RCTs that met the following criteria: (1) involving adult participants (aged ≥ 18 years) who were diagnosed with cancer; (2) using external therapy of TCM as the intervention arm; (3) using either external therapy of TCM, usual care, waitlist, sham control, health education (psychoeducation, sleep hygiene education), or western medicine (diazepam, estazolam, fluoxetine, gabapentin) as the control arm; (4) reporting sleep quality as the outcome, assessed using reliable and valid scales, such as Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Athens Insomnia Scale (AIS), the sleep/insomnia subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and MD Anderson Symptom Inventory (MDASI). Studies that lacked sufficiently important details of the intervention (eg, total length and frequency of interventions, duration of each intervention), combined two or more external therapy of TCM or involved a combination of external therapy of TCM and other interventions were excluded.

Literature selection and data extraction

Endnote X9 software (Clarivate Analytics, PA, USA) was adopted to manage the literature and exclude duplicates. Two authors (LB and WG) independently screened the titles and abstracts during preliminary screening according to the inclusion and exclusion criteria. Subsequently, the full texts of the remaining studies were retrieved and assessed by both authors. Full texts were sought from corresponding authors if necessary. Any disagreement was resolved by discussion until consensus was reached or by consulting a third author (JH).

Two authors (LB and WG) independently extracted data from the included studies using a pre-designed table, including the first author, year of publication, country, study design, participants' characteristics (sample sizes, cancer type, stage of cancer, mean age), details of the interventions (intervention time point, intensity, and acupoints), control conditions, outcome measure tools, adverse events, and outcomes at post-intervention (mean/mean changes between pre and post, standard deviation [SD]). For studies with missing outcome results, we contacted corresponding authors to supplement the missing results via emails; alternatively, we calculated the SD using the 95% confidence interval (CI) or the standard error (SE).

Quality appraisal (risk of bias)

The same two authors (LB and WG) independently assessed the risk of bias using the revised Cochrane risk of bias tool (RoB 2.0), which assesses the following 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. There are several signal questions in each domain, and the two authors can answer “yes,” “probably yes,” “probably no,” “no,” and “no information” to the signal questions. The answers led to judgments of “low risk of bias,” “some concerns,” or “high risk of bias” for each domain. The results within each domain led to an overall risk-of-bias judgment for the assessed studies.²³ Any discrepancies between the two authors were resolved by the corresponding author of this study (JH).

Data analysis

This meta-analysis was conducted using STATA version 14.0. The statistical analysis was carried out using a frequentist framework. The included studies used different outcome measurement tools, such as PSQI, ISI, AIS, EORTC-QLQ-C30, and MDASI; consequently, we calculated the effect size for the comparison of sleep quality using standardized mean differences (SMDs). In addition, the mean changes between post-intervention assessment and baseline were calculated.

We used STATA version 14.0 to draw a network diagram to present the connections between all interventions. The global inconsistency and node-splitting method was used to estimate heterogeneity between the direct and indirect comparisons, and if the difference was not statistically significant ($P > 0.05$), a consistency model was used to analyze and rank the results. Moreover, a random effects model was used to analyze the effect size considering the heterogeneity within the study (eg, different cancer types, and intervention duration), and SMD and 95% CI were calculated. The likelihood of each intervention being the best intervention was presented by the surface under the cumulative ranking area (SUCRA), ranging from 0 to 100. Larger values of SUCRA indicate that the intervention has a greater likelihood of being the best intervention. We also plotted a funnel plot to assess the presence of publication bias in this study.

Certainty of evidence assessment

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation methodology by two authors (LB and WG). All included comparisons were defaulted to high-quality evidence and then downgraded based on criteria, including study limitations, inconsistency, indirectness, imprecision, reporting bias, and other considerations. The severity of the above six aspects can be divided into no concern, some concern, and major concern. Finally, the evidence was graded as “high”, “moderate”, “low”, or “very low”.²⁴

Results

Study selection

As shown in Fig. 1, a total of 2753 potentially relevant studies were obtained. After removing duplicates and irrelevant studies, 53 studies remained for full-text screening. Among these remaining studies, 20

were excluded for the following reasons: outcomes do not match ($n = 5$), no available data for analysis ($n = 9$), not a RCT ($n = 3$), secondary analysis ($n = 1$), and lack details of the intervention ($n = 2$). An updated search identified 1 new article published from 72 records being deemed eligible for inclusion. In the end, 34 primary studies were included in this NMA.

Characteristics of included studies

The characteristics of the included studies for systematic review are presented in Table 1. The 34 studies involving 2534 participants were included in this study, published between 2011 and 2023. The studies were mostly conducted in Asia ($n = 26$), followed by North America ($n = 7$) and Europe ($n = 1$). Twenty-five were two-arm studies, eight were three-arm studies, and one was a four-arm study. The number of participants ranged from 21²⁵ to 288.²⁶ Fourteen, nine and three studies included patients with cancer at any stage,^{20,25,27-38} the early stage,^{19,26,39-45} and the advanced stage,⁴⁶⁻⁴⁸ respectively. The remaining eight studies did not report the cancer stage.⁴⁹⁻⁵⁶ The type of cancer involved breast cancer, which was the most frequent cancer type. Moreover, lung, ovarian, thyroid cancer, primary hepatocellular carcinoma, colon, and pancreatic cancer were also represented. Eight studies included mixed cancer types.

External therapies of TCM among the included studies were shown as follows: acupuncture, acupressure, auricular acupressure, moxibustion, electroacupuncture, Chinese medicine pillow, and Tuina. Eight studies reported acupuncture,^{19,25,32,37,41,47,54,55} with intervention durations ranging from 1 to 8 weeks, and the interventions specifically included auricular acupuncture, press-needle, wrist-ankle acupuncture, and scalp acupuncture. Eight studies reported acupressure,^{20,26,27,39,44-46,56} with intervention durations ranging from 7 days to 5 months, and commonly used acupoints included Sanyinjiao (SP6), Zusanli (ST36), Hegu (LI4), Yintang (DU29), Neiguan (PC6), and Baihui (GV20). Eight studies reported auricular acupressure,^{30,33,36,38,40,48,50,52} with intervention durations

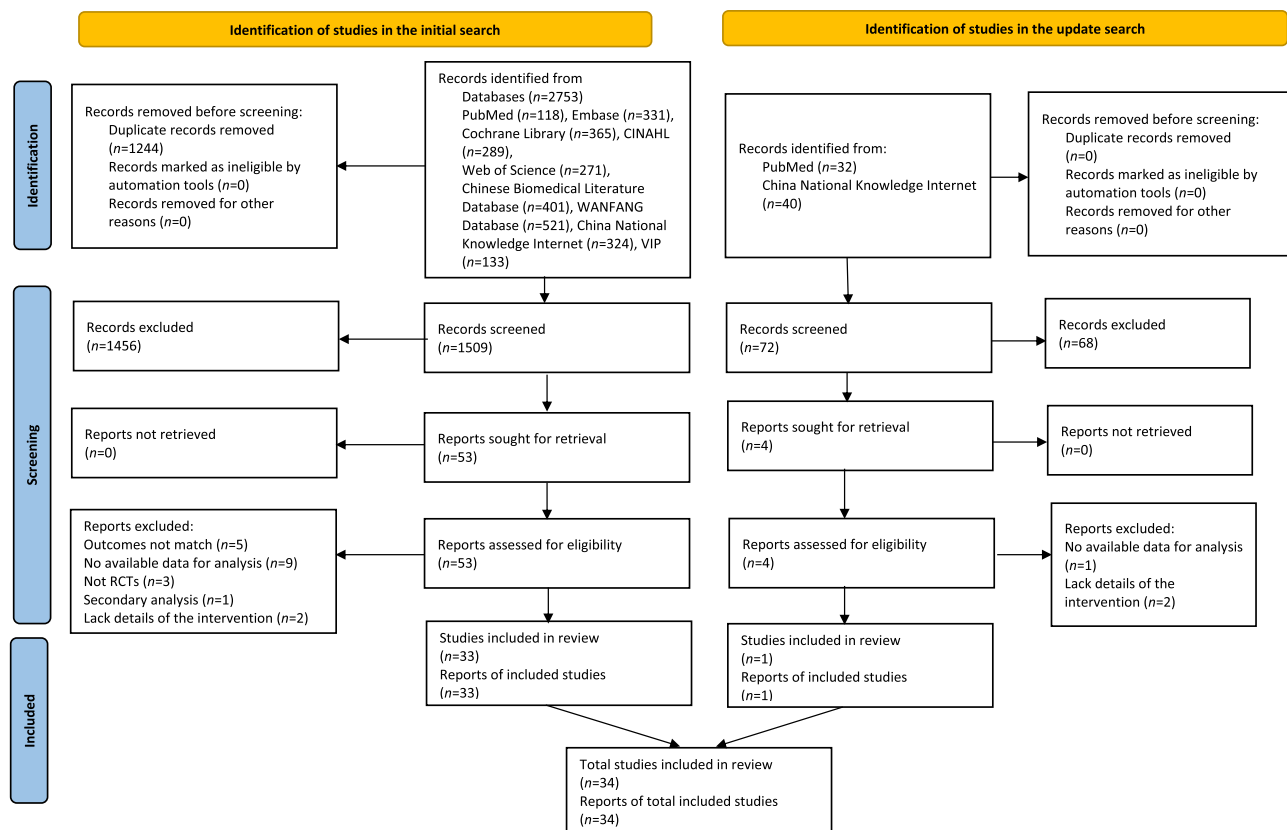


Fig. 1. Study flow diagram.

Table 1
Basic characteristics of the 34 studies.

| Author, year | Country | Study design | Sample size (N); population | Mean age (year) | Intervention, N | Control, N | Outcome measure tools | Adverse events | Outcomes at post-intervention: mean \pm SD |
|--------------------------------------|----------------|-------------------------------|---|--|---|--|-----------------------|---|--|
| Nourizadeh et al, ³⁹ 2022 | Iran | Parallel RCT; three-arm | 66, breast cancer (stage II-III) | NR | Self-acupressure, 33 Intervention time point: finished the last chemotherapy or radiotherapy period 8 weeks before; Intensity: 8 weeks, 3 times per day, stimulate each point for 10 min; Acupoints: HE7, LI4, SP6 | Usual care, 33 | PSQI | No adverse effects | Self-acupressure: 8.90 \pm 2.00 Usual care: 12.90 \pm 2.40 |
| Yoon et al, ⁴⁰ 2019 | Korea | Parallel RCT | 41, breast cancer (stage I-III) | Intervention: 45.05 Control: 44.57 | AA, 20 Intervention time point: undergoing chemotherapy; Intensity: 6 weeks, 6 times a week, press the seed-applied areas for 1 min before going to bed; Acupoints: Shenmen, Heart, Anterior lobe, Occiput | Placebo AA, 21 Receiving placebo AA on points not associated with improving sleep quality. | PSQI | No adverse effects | AA: 7.70 \pm 2.77 Placebo AA: 10.57 \pm 3.23 |
| Tang et al, ²⁷ 2014 | China (Taiwan) | Parallel pilot RCT; three-arm | 40, lung cancer (stage I-IV) | Intervention: 54.80 Control: 66.10 | Acupressure, 24 Intervention time point: undergoing chemotherapy; Intensity: 5 months, stimulate each acupoint for 1 min; Acupoints: Hegu (LI4), Zusanli (ST36), Sanyinjiao (SP6) | Sham acupressure, 16 Sham acupressure was applied on the first metacarpal head, patella, and inner ankle. | PSQI | NR | Acupressure: 7.47 \pm 4.88 Sham acupressure: 10.09 \pm 4.76 |
| Höxtermann et al, ⁴¹ 2021 | Germany | Parallel RCT | 52, breast cancer survivors (stage I-III) | Intervention: 56.58 Control: 54.80 | Auricular acupuncture, 26 Intervention time point: patients who were undergoing or planned chemotherapy, radiation, follow-up treatment, or reconstructive plastic surgery during the study period were excluded; Intensity: 5 weeks, twice weekly, needles remained for at least 20 min per time; Acupoints: postantitragal belt, helix channel, Shenmen | Psychoeducation, 26 Receiving a single 90-min psychoeducation group session. | PSQI | Participants reported non-serious adverse events, such as pain, hot flushes, insatiable hunger, etc. | Auricular acupuncture: 7.80 \pm 3.40 Psychoeducation: 9.30 \pm 3.50 |
| Lee et al, ²⁸ 2022 | Korea | Parallel pilot RCT; three-arm | 22, mixed cancer (stage 0-IV) | EA: 57.63 Sham EA: 62.33 Usual care: 61.38 | EA, 8 Intervention time point: cessation of cancer-related treatments at least 12 weeks prior to enrolment (ongoing hormone therapy was allowed if it was initiated from at least 3 weeks before the trial); Intensity: 4 weeks, 2-3 times a week, 30 min per time, a total of 10 sessions; Acupoints: Baihui (GV20), Yintang (EX-HN3), Shenmen (HT7), Neiguan (PC6), Jinmen (BL63), Dazhong (KI4) | Sham-EA, 6 A placebo Streitberger acupuncture needle was inserted at 10 non-acupoints. Usual care, 8 | PSQI | All adverse effects were considered to be unrelated to the study. | EA: 9.25 \pm 3.49 Sham EA: 10.56 \pm 2.25 Usual care: 11.63 \pm 3.30 |
| Bao et al, ²⁹ 2021 | USA | Parallel RCT; three-arm | 75, mixed cancer (stage I-IV) | EA: 63.05 Sham EA: 63.09 Usual care: 54.73 | EA, 27 Intervention time point: completed chemotherapy at least 3 months; Intensity: 8 weeks, biweekly treatments for the first 2 weeks and weekly treatments thereafter, needles remained for 30 min per time; Acupoints: ear : ShenMen (TF4); body: Hegu (LI4), Neiguan (PC6), Houxi (SI3), Taichong (LR3), Xiashi (GB43), Fenglong (ST-40), Bafeng 2, Bafeng 3 | Sham-EA, 24 Acupuncturist tapped empty needle guiding tubes adjacent to each of the eight acupoints in the arm and leg (LI4, SJ-5, LI-11, ST-40). Usual care, 24 | ISI | Six patients in the EA group reported grade 1 adverse events such as pain, bruising, and feeling claustrophobic with the eye mask on. | EA: 9.78 \pm 5.27 Sham EA: 9.73 \pm 5.01 Usual care: 10.38 \pm 5.15 |

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Table 1 (continued)

| Author, year | Country | Study design | Sample size (N); population | Mean age (year) | Intervention, N | Control, N | Outcome measure tools | Adverse events | Outcomes at post-intervention: mean \pm SD |
|----------------------------------|----------------|-------------------------------|--|--|--|--|-----------------------|--|---|
| Zick et al, ²⁶ 2016 | USA | Parallel RCT; three-arm | 288, breast cancer survivors (stage 0-III) | Intervention: 60.24 Control: 61.00 | Acupressure, 192 Intervention time point: completed cancer treatments (except hormone therapy) at least 12 months previously; Intensity: 6 weeks, once per day, stimulate each point for 3 min; Acupoints: anmian, heart 7, spleen 6, liver 3, yin tang, or large intestine 4, stomach 36, spleen 6, and kidney 3, du 20, conception vessel 6 | Usual care, 96 | PSQI | All were non-serious cases of mild bruising at acupressure sites. | Acupressure: 6.74 \pm 3.03 Usual care: 7.60 \pm 3.33 |
| Bao et al, ¹⁹ 2014 | USA | Parallel RCT | 47, breast cancer (stage 0-III) | Intervention: 62.62 Control: 61.68 | Acupuncture, 23 Intervention time point: receiving AI therapy for \geq 1 month; Intensity: 8 weeks, 1 time per day, remained in the body for 20 min per time; Acupoints: CV4, CV6, CV12, LI4, MH6, GB34, ST36, KI3, BL65 | Sham acupuncture, 24 Sham needles (non-penetrating retractable needles) were placed in 14 sham acupoints located at the midpoint of the line connecting two real acupuncture points. Sleep hygiene practices, 20 Giving sleep hygiene advice. | PSQI | NR | Acupuncture: 8.40 \pm 7.11 Sham acupuncture: 9.50 \pm 7.88 |
| Kuo et al, ³⁰ 2018 | China (Taiwan) | Parallel pilot RCT | 40, ovarian cancer (stage I-IV) | Intervention: 51.56 Control: 54.73 | AA, 20 Intervention time point: undergoing chemotherapy; Intensity: 6 weeks, 3 times per day, 3 min per time; Acupoints: Shenmen (TF4), Xin (Heart; CO15), Pizhixia (Subcortex; AT4), Neifenmi (Endocrine; CO18) | Sham acupuncture, 20 Giving sleep hygiene advice. | PSQI | Worrisome skin problems (ie, a mild allergic reaction). | AA: 4.21 \pm 1.36 Sleep hygiene practices: 12.75 \pm 4.36 |
| Hoang et al, ²⁰ 2022 | Vietnam | Parallel pilot RCT; three-arm | 114, mixed cancer (stage I-IV) | Acupressure: 54.60 Sham acupressure: 53.50 Enhanced standard care group: 56.60 | Acupressure, 38 Intervention time point: undergoing chemotherapy; Intensity: 4 weeks, 1 time per day, 28 min per time; Acupoints: Baihui (GV20), Yintang (DU29), Fengchi (GB20), Neiguan (PC6), Shenmen (HT7), Taichong (LR3) | Sham acupressure, 38 Using 6 sham acupoints. Enhanced standard care group, 38 Providing a 30-min training session on ten recommendations to manage the targeted symptoms. | ISI | Participants reported mild severity adverse events, such as pain, tired. | Acupressure: 15.08 \pm 7.45 Sham acupressure: 15.13 \pm 5.93 Enhanced standard care group: 20.26 \pm 5.63 |
| Cheung et al, ⁴⁶ 2022 | China | Parallel pilot RCT | 30, advanced cancer (stage IIIB-IV) | Intervention: 61.80 Control: 58.93 | Acupressure, 15 Intervention time point:none; Intensity: 3 weeks, 2 times per day, 15 min per time; Acupoints: Baihui (GV20), Neiguan (PC6), Zusanli (ST36), Sanyinjiao (SP6) | Healthy education, 15 Received the usual care, and it was contacted in the third week to attend a health talk unrelated to symptom management | PSQI | NR | Acupressure: 7.65 \pm 3.21 Healthy education: 4.99 \pm 2.63 |
| Ming, ⁴⁹ 2018 | China | Parallel RCT | 57, breast cancer | Intervention: 55.79 Control: 56.10 | CMP, 28 Intervention time point: NR Intensity: 4 weeks, giving CMP at 21:00 respectively, and 7:00 the next day replace with normal pillow; Acupoints: none | Placebo CMP, 29 | PSQI | NR | CMP: 7.71 \pm 2.34 Placebo CMP: 13.07 \pm 2.07 |
| Yang et al, ³¹ 2021 | China | Parallel RCT | 75, lung cancer (stage I-IV) | Intervention: 47.96 Control: 47.65 | Moxibustion, 37 Intervention time point: undergoing chemotherapy; Intensity: 15 days, 1 time per day, 20–30 min per time; Acupoints: Zhongwan (RN12), Guanyuan (RN4), Qihai (RN6), Shenque (RN8), Zusanli (ST36), Feishu (BL13), Pishu (BL20) | Usual care, 38 | PSQI | No serious side effects. | Moxibustion: 6.30 \pm 1.35 Usual care: 13.16 \pm 1.83 |

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Table 1 (continued)

| Author, year | Country | Study design | Sample size (N); population | Mean age (year) | Intervention, N | Control, N | Outcome measure tools | Adverse events | Outcomes at post-intervention: mean ± SD |
|--------------------------------|---------|------------------------|---|---------------------------------------|---|---|-----------------------|---|--|
| Yang, ⁵⁰ 2020 | China | Parallel RCT | 60, Primary hepatocellular carcinoma | Intervention: 55.97 Control: 56.67 | AA, 30 Intervention time point: after surgery; Intensity: 4 days, 3 times per day, stimulate each point for 1–2 min; Acupoints: Shenmen (TF4), Sympathetic (CO18), Liver (CO12), Kidney (CO10) | Usual care, 30 | PSQI | No side effects. | AA: 9.73 ± 1.11 Usual care: 11.00 ± 1.23 |
| Xia et al, ⁵¹ 2019 | China | Parallel RCT | 74, thyroid cancer | Intervention: 47.60 Control: 46.20 | Moxibustion, 37 Intervention time point: after radical thyroidectomy; Intensity: 7 days, 1 time per day; 20 min per time; Acupoints: Baihui (GV20) | Usual care, 37 | PSQI | NR | Moxibustion: 7.95 ± 1.28 Usual care: 13.22 ± 2.75 |
| Wang et al, ³² 2019 | China | Parallel RCT | 80, breast cancer (stage I-IV) | Intervention: 52.47 Control: 50.16 | Thumb-tack needle for subcutaneous embedding therapy, 40 Intervention time point: undergoing chemotherapy; Intensity: 4 weeks, 5 days per week, press each point 3 times a day for 1 min each time; Acupoints: Shenmen (HT7), Anmian, Sanyinjiao (SP6), Zusanli (ST36), Taibai (SP3) | Sham intervention, 40 Using a sham snap-needle (no needle body on the inner surface) which had no needle stimulation effect. | PSQI | Patient has slight pain. | Intervention: 8.91 ± 2.73 Control: 10.86 ± 4.53 |
| Shang, ⁴⁷ 2021 | China | Parallel RCT | 74, lung cancer (stage III-IV) | Intervention: 65.92 Control: 65.11 | Wrist-ankle acupuncture, 37 Intervention time point: undergoing chemotherapy; Intensity: 10 days, 1 time per day, 20 min per time; Acupoints: no specific acupoints | Usual care, 37 | AIS | Only two patients had slight subcutaneous cyanosis. | Acupuncture: 8.43 ± 2.08 Usual care: 9.70 ± 1.79 |
| Lei, ³³ 2020 | China | Parallel RCT | 95, Primary hepatocellular carcinoma (stage I-IV) | Intervention: 51.49 Control: 52.49 | AA, 47 Intervention time point: NR; Intensity: 4 weeks, 3 times per day, press each point for 30 s each time; Acupoints: Shenmen (TF4), Subcortex (AT4), Heart (CO15), Sympathetic (AH6), Endocrine (CO18), Liver (CO12), Spleen (CO13) | Wait list, 49 | PSQI | No side effects. | AA: 9.17 ± 2.18 Wait list: 13.20 ± 2.90 |
| Zhang, ³⁴ 2017 | China | Parallel RCT | 69, mixed cancer (stage I-IV) | Intervention: 64.06 Control: 64.46 | Moxibustion, 35 Intervention time point: NR; Intensity: 7 days, 1 time per day, 20 min per time; Acupoints: Shenque (RN8), Shenmen (HT7), Sanyinjiao (SP6), Xinshu (2BL15), Pishu (BL20) | Usual care, 34 | PSQI | NR | Moxibustion: 7.71 ± 3.06 Usual care: 11.56 ± 2.44 |
| Wei et al, ⁵² 2019 | China | Parallel RCT | 148, mixed cancer | Intervention: 59.28 Control: 59.14 | AA, 74 Intervention time point: NR; Intensity: 2 weeks, 5 times per day, 1–2 min per time; Acupoints: none | Usual care, 74 | PSQI | NR | AA: 4.02 ± 0.32 Usual care: 6.18 ± 0.36 |
| Li et al, ³⁵ 2020 | China | Parallel RCT; four-arm | 98, breast cancer (stage I-IV) | Intervention: 40.40 Control: 42.40 | Tuina, 50 Intervention time point: undergoing chemotherapy; Intensity: 6 weeks, 1 time per day; 24–30 min per time; Acupoints: none | Usual care, 48 | PSQI | NR | Tuina: 10.50 ± 3.30 Usual care: 15.10 ± 3.10 |

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Table 1 (continued)

| Author, year | Country | Study design | Sample size (N); population | Mean age (year) | Intervention, N | Control, N | Outcome measure tools | Adverse events | Outcomes at post-intervention: mean \pm SD |
|-----------------------------------|---------|--------------|---------------------------------|---------------------------------------|--|--|-----------------------|---|--|
| Wang et al, ⁵³ 2021 | China | Parallel RCT | 84, breast cancer | Intervention: 42.99 Control: 42.96 | Moxibustion, 42 Intervention time point: postoperative; Intensity: 14 days, 1 time per day, 20–30 min per time; Acupoints: Xinshu (BL15), Pishu (BL20), Baihui (GV20), Yongquan (KI1), Shenmen (HT7), Taixi (KI3) | Diazepam, 42 Participants took one pill (2.5 mg) at bedtime. | PSQI | No side effects. | Moxibustion: 5.33 \pm 2.56 Diazepam: 6.98 \pm 3.08 |
| Shi, ⁵⁴ 2020 | China | Parallel RCT | 80, mixed cancer | Intervention: 48.70 Control: 44.90 | Scalp acupuncture, 40 Intervention time point: after chemotherapy; Intensity: 3 weeks, 1 time per day, 40 min per time; Acupoints: Baihui (GV20), Xinhui (DU22), Shenting (DU24), Yintang (DU29) | Diazepam, 40 5 mg/d for 3 weeks. | PSQI | NR | Scalp acupuncture: 5.14 \pm 1.83 Diazepam: 7.66 \pm 2.46 |
| Fan et al, ⁵⁵ 2020 | China | Parallel RCT | 97, lung cancer | NR | Press-needle, 49 Intervention time point: undergoing chemotherapy; Intensity: 1 week, 3 times per day, press each acupoint for 2–3 min; Acupoints: body: Baihui (GV20), Shenmen (HT7), Zusanli (ST36), Sanyinjiao (SP6); ear: Shenmen (TF4), Xin (CO15), Pizhixia (AT4), Chuiqian (L04) | Estazolam, 48 Participants took one pill (1 mg) half an hour before bedtime for 7 days, 1 time per day. | PSQI | Participants reported slight pain when pressing. | Press-needle: 6.59 \pm 3.65 Estazolam: 5.27 \pm 3.64 |
| Lu et al, ²⁵ 2012 | USA | Parallel RCT | 21, ovarian cancer (any stage) | Intervention: 50.80 Control: 50.00 | Acupuncture, 11 Intervention time point: undergoing chemotherapy; Intensity: 4 weeks, 2–3 times per week, 30 min per time, 10 sessions of acupuncture treatment; Acupoints: GV20, SP10, ST36, SP6, K3, LR3, LI11, PC6, LI4 | Sham acupuncture, 10 Using 5 nonacupuncture points (9 needling sites) | EORTC QLQ-C30 | No significant adverse events were observed. | Acupuncture: 14.3 \pm 17.8 Sham acupuncture: 38.1 \pm 23.0 |
| Yeh et al, ⁴⁸ 2016 | USA | Parallel RCT | 31, breast cancer (stage II-IV) | NR | AA, 16 Intervention time point: no limit; Intensity: 4 weeks, once a week, 3 times per day, 3 min per time; Acupoints: Shenmen (TF4), Sympathetic (AH6), Occiput (AT3), Subcortex (AT4) | Sham AA, 15 Using acupoints unrelated to the symptom cluster of interest. | MDASI | Participants in both groups reported mild outer ear pain, discomfort, itchiness, and tenderness after seed placement. | AA: -2.08 \pm 2.02 Sham AA: -0.23 \pm 2.77 (mean change \pm SD) |
| Zhang et al, ⁵⁶ 2017 | China | Parallel RCT | 48, breast cancer | Intervention: 51.8 Control: 52.4 | Acupressure, 24 Intervention time point: surgically treated with lumpectomy or mastectomy, receiving chemotherapy; Intensity: 12 weeks, 3 days weekly, 30 min per day, 10 min each point; Acupoints: Hegu (LI4), Zusanli (ST36), Snayinjiao (SP6) | Sham acupressure, 24 Massage on non-acupoints. | PSQI | None | Acupressure: -3.5 \pm 1.54 Sham acupressure: -1.9 \pm 1.30 (mean change \pm SD) |
| Garland et al, ⁴² 2017 | USA | Parallel RCT | 58, breast cancer (stage 0-III) | Intervention: 52.9 Control: 50.4 | EA, 30 Intervention time point: finish cancer treatment; Intensity: 8 weeks, twice a week for 2 weeks and once for 6 weeks, 30 min per session; Acupoints: NR | Gabapentin, 28 900 mg per day. | PSQI | Participants reported intolerance of Gabapentin. | EA: -2.6 \pm 3.2 Gabapentin: -0.8 \pm 3.0 (mean change \pm SD) |

(continued on next page)

Table 1 (continued)

| Author, year | Country | Study design | Sample size (N); population | Mean age (year) | Intervention, N | Control, N | Outcome measure tools | Adverse events | Outcomes at post-intervention: mean \pm SD |
|----------------------------------|----------------|-------------------------|---|--|---|---|-----------------------|---|--|
| Mao et al, ⁴³ 2014 | USA | Parallel RCT; three-arm | 67, breast cancer (I-III) | EA: 57.5 Sham EA: 60.9 Wait list: 60.6 | EA, 22 Intervention time point: receiving aromatase inhibitor therapy; Intensity: 8 weeks, total 10 sessions, twice a week for 2 weeks and once for six weeks, 30 min per session; Acupoints: acupoints around different joints | Sham EA, 22 A Streitberger non-penetrating needles was inserted at nonacupuncture, nontrigger points and connect to TENS without electricity. Wait list, 23 | PSQI | NR | EA: -1.4 ± 3.50 Sham EA: -0.8 ± 2.59 Wait list: 0.1 ± 2.89 (mean change \pm SD) |
| Lin et al, ³⁶ 2021 | China | Parallel RCT; three-arm | 100, lung cancer (I-IV) | Intervention: 60.82 Control: 61.85 | AA, 66 Intervention time point: undergoing chemotherapy; Intensity: 9 weeks, press each acupoint for 20–30 s, 4–6 times per session, 5 sessions per day; Acupoints: Lung (CO14), Shenmen (TF4), Subcortex (AT4), Liver (CO12), Spleen (CO13) | Usual care, 34 | PSQI | None | AA: -0.87 ± 2.25 Usual care: 0.32 ± 1.45 (mean change \pm SD) |
| Feng et al, ³⁷ 2011 | China | Parallel RCT | 80, mixed cancer (any stage) | Intervention: 63.80 Control: 63.60 | Acupuncture, 40 Intervention time point: NR; Intensity: 30 days, 1 time per day, 20–30 min per time; Acupoints: Fenglong (ST40), Yinlingquan (SP 9), Xuehai (SP10), Sanyinjiao (SP 6), Yintang (EX-HN3), Baihui (DU20), Sishencong (EX-HN1), Neiguan (PC 6), Shenmen (TF4) | Fluoxetine, 40 20 mg/d. | PSQI | NR | Acupuncture: 7.92 ± 1.22 Fluoxetine: 11.44 ± 1.89 |
| Liu et al, ⁴⁴ 2016 | China | Parallel RCT | 80, breast cancer (not advance stage) | Intervention: 47.40 Control: 46.65 | Acupressure, 40 Intervention time point: perioperative period; Intensity: 7 days (2 days prior to surgery until 5 days post-surgery), 2 times per day, 15–20 min per time; Acupoints: Taiyang (EX-HN5), Yintang (DU29), Baihui (DU20), Sishencong (EX-HN1), Neiguan (PC6), Hegu (LI4), Shenmen (HT7), Sanyinjiao (SP6), Zusanli (ST36), Taichong (LR3) | Usual care, 40 | AIS | NR | Acupressure: 3.63 ± 1.21 Usual care: 8.30 ± 2.09 |
| Chun-I et al, ³⁸ 2015 | China (Taiwan) | Parallel RCT | 89, mixed cancer (any stage) | Intervention: 60.00 Control: 63.20 | AA, 33 Intervention time point: no limit; Intensity: 4 weeks, 3 times per day, press each point for 20–30 times; Acupoints: Shenmen (TF4), Subcortex (AT4), Heart (CO15), Occiput (AT3) | Education, 56 Receive nursing guidance and counseling to improve sleep. | AIS | Participants reported discomfort from the seed. | AA: 5.62 ± 3.34 Education: 10.39 ± 4.65 |
| Gülcan et al, ⁴⁵ 2023 | Turkey | Parallel RCT | 60, colon and pancreatic cancer (stage I-III) | Intervention: 58.06 Control: 59.56 | Acupressure, 30 Intervention time point: undergoing chemotherapy; Intensity: 4 weeks, total 16 acupressure sessions, 2 days a week, 2 times per day (morning and afternoon), 18 min per time, massage each point for 2 min; Acupoints: Shenmen (HT7), Zusanli (ST36), Hegu (LI4), Sanyinjiao (SP6) | Wait list, 30 | PSQI | NR | Acupressure: 5.40 ± 1.84 Wait list: 12.63 ± 1.09 |

AA, auricular acupressure; AIS, Athens Insomnia Scale; CMP, Chinese medicine pillow; EA, electroacupuncture; EORTC-QLQ-C-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ISI, Insomnia Severity Index; MDASI, MD Anderson Symptom Inventory; NR, not report; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; SD, standard deviation; USA, United States of America.

ranging from 4 days to 9 weeks, and commonly used auricular acupoints included Shenmen (TF4), Heart (CO15), Endocrine (CO18), and Subcortex (AT4). Four studies reported electroacupuncture,^{28,29,42,43} with intervention durations ranging from 4 to 8 weeks, and each study contained 6 or 8 different acupoints. Four studies reported moxibustion,^{31,34,51,53} with intervention durations ranging from 7 to 15 days, and commonly used acupoints included Pishu (BL20), Xinshu (BL15), Shenque (RN8), Baihui (GV20), and Shenmen (HT7). Chinese medicine pillow⁴⁹ and Tuina³⁵ were reported in only one study, with intervention durations of 4 weeks and 6

weeks, respectively.

Among all the included studies, thirteen, four, eight, and five studies used usual care or waitlist,^{26,31,33-36,39,44,45,47,50-52} health education,^{30,38,41,46} sham external therapy of TCM,^{19,25,27,32,40,48,49,56} and western medicine^{37,42,53-55} as the control group intervention, respectively. Furthermore, four studies included a usual care group and a sham control group.^{20,28,29,43} Different outcome scales were used to evaluate sleep disturbance. The PSQI was the most frequently used scale, which was applied in 27 studies.^{19,26-28,30-37,39-43,45,46,49-56} Moreover, ISI,^{20,29}

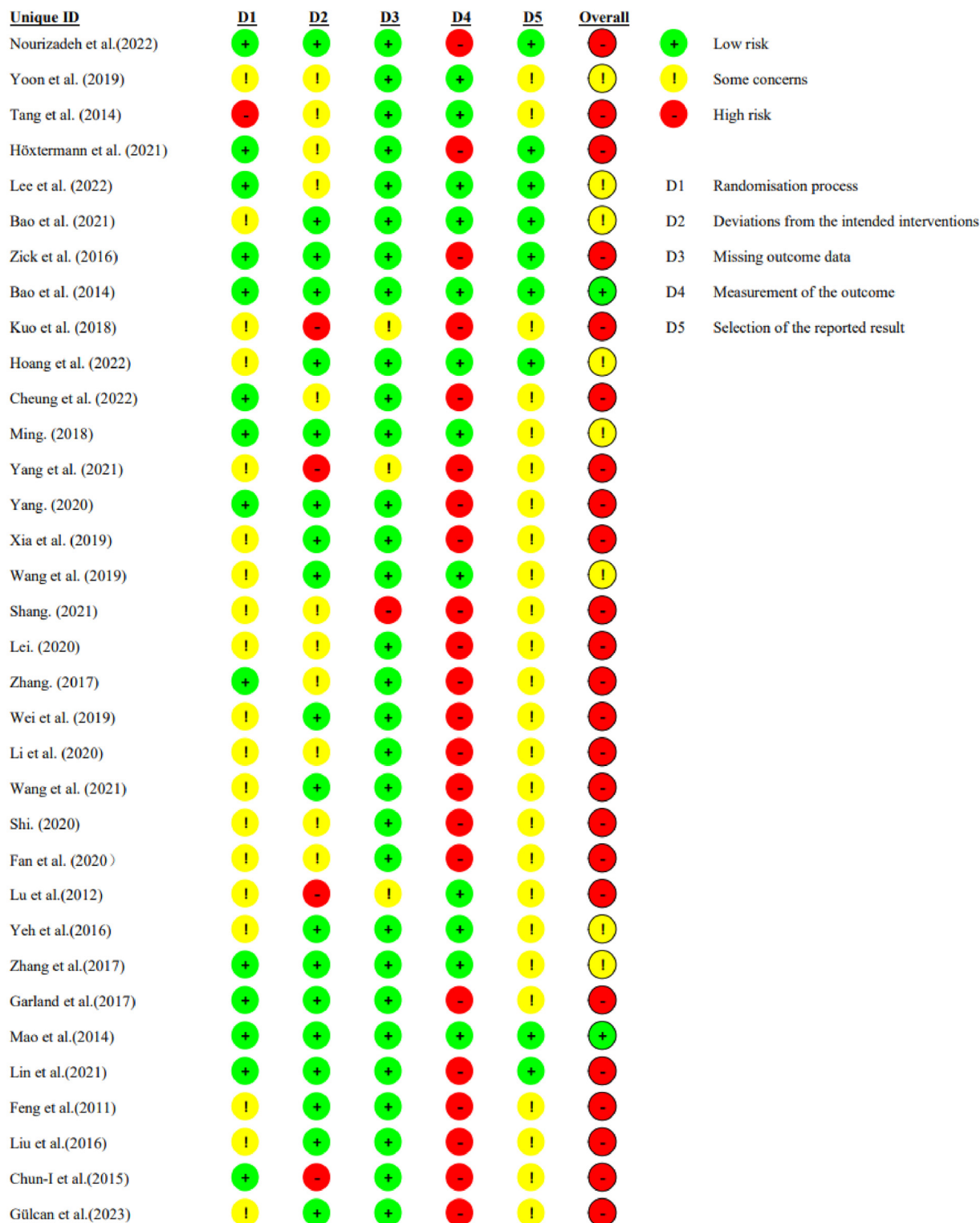


Fig. 2. Risk of bias.

AIS,^{38,44,47} EORTC-QLQ-C30²⁵, and MDASI⁴⁸ were used in two, two, one, and one studies, respectively. Adverse events were mentioned in 21 studies, and the remaining thirteen studies did not.

Risk of bias assessment

The results of risk of bias in the 34 included studies are presented in Fig. 2. For the randomization process domain, 14 and 19 RCTs had a low risk of bias and some concern, respectively, and 1 had a high risk of bias. Regarding the domain of deviations from the intended interventions, 19 RCTs had a low risk of bias, 11 had some concern, and 4 had a high risk of bias. Regarding the missing data domain, 30 RCTs had a low risk of bias, 3 had some concern, and 1 had a high risk of bias. Regarding the outcome measurement domain, 12 RCTs had a low risk of bias and 22 RCTs had a high risk of bias because the outcome assessors were the patients, who were aware of the interventions they were receiving. Concerning the domain of selection of the reported result, 9 RCTs had a low risk of bias and 25 had some concern due to the lack of a previously published protocol or registration to assess potential selective outcome reporting. Among the 34 included studies, 2 studies had a low risk of bias,^{19,43} 8 had some concern,^{20,28,29,32,40,48,49,56}, and 24 had a high risk of bias.^{25-27,30,31,33-39,41,42,44-47,50-55}

Network meta-analysis

Network plot

The network plot of sleep quality (Fig. 3) presents an adequate connection between the results. There were 11 nodes in the network plot, which, respectively, represent seven external therapies of TCM (acupuncture, acupressure, auricular acupressure, moxibustion, electroacupuncture, Chinese medicine pillow, and Tuina) and four comparison interventions (usual care/waitlist, sham control, health education, and medicine).

All seven external therapies of TCM were directly compared with one of the comparison interventions. Acupuncture, acupressure, and auricular acupressure were the most common intervention arm, and usual care/waitlist was the most common comparison arm, followed by sham control.

Efficacy outcomes

The efficacy of different external therapies of TCM on sleep quality is presented in Table 2. Chinese medicine pillow (SMD = -3.27; 95% CI: -6.03 to -0.51), auricular acupressure (SMD = -2.33; 95% CI: -3.36 to -1.29), moxibustion (SMD = -2.28; 95% CI: -3.63 to -0.94), acupressure (SMD = -1.67; 95% CI: -2.64 to -0.70), and acupuncture (SMD = -1.43; 95% CI: -2.65 to -0.21) had significant effects on sleep quality improvement compared with usual care or waitlist. Furthermore, auricular acupressure (SMD = -1.45; 95% CI: -2.60 to -0.30) significantly improved sleep quality compared with sham control. No statistically significant differences were observed between the remaining interventions.

Rank probabilities

With respect to ranking probabilities, the Chinese medicine pillow showed the highest cumulative probability (SUCRA: 88.3%), and thus became the best intervention to improve sleep quality in patients with cancer, followed by auricular acupressure (SUCRA: 81.4%), moxibustion (SUCRA: 78.3%), acupressure (SUCRA: 61.3%), acupuncture (SUCRA: 53.5%), and Tuina (SUCRA: 51.3%) (Fig. 4 and Table 3).

Publication bias

To detect a possible publication bias in the included studies, we generated the funnel plots for 34 studies. The studies showed low risks of

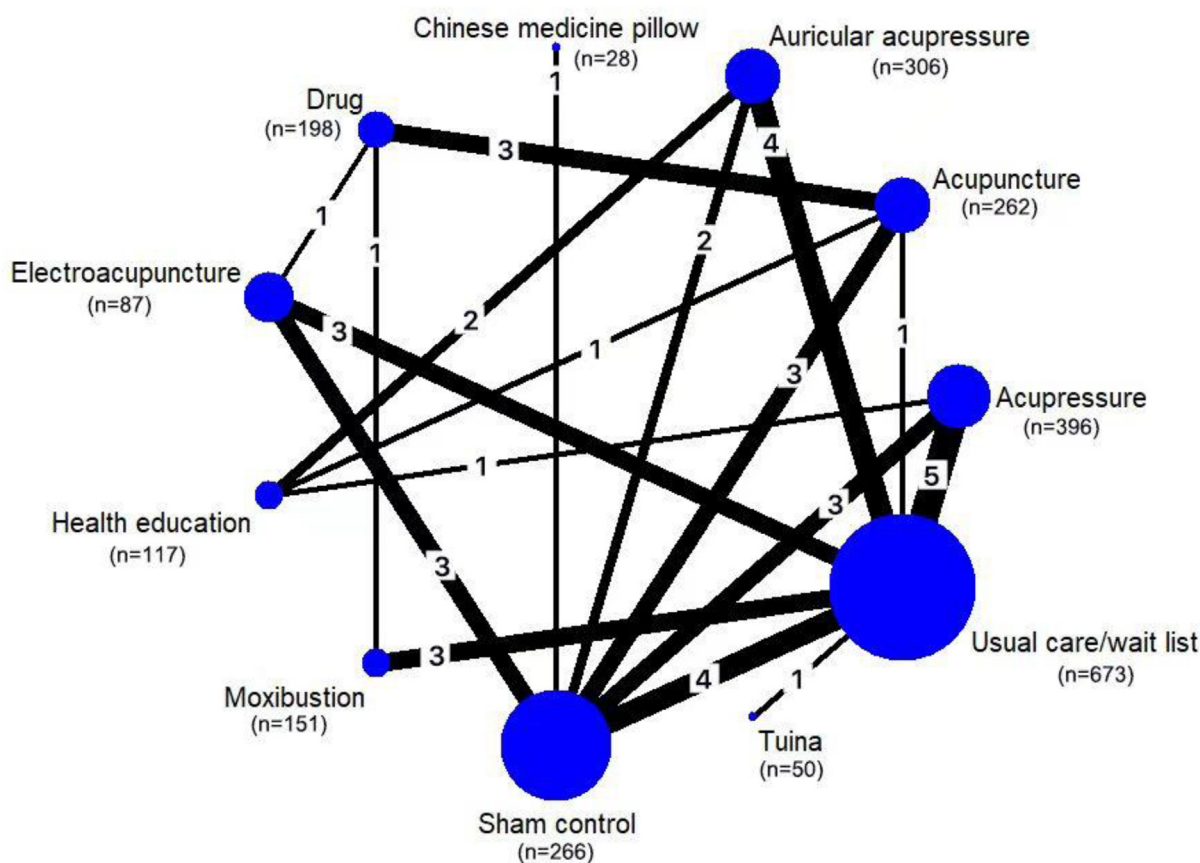


Fig. 3. Network graph for subjective sleep quality of included studies. Nodes represent different intervention; The size of each node represents the size of the population involved in each intervention; The connect line of nodes indicate the direct comparison of 2 interventions; The width of the line is proportional to the number of studies for direct comparison.

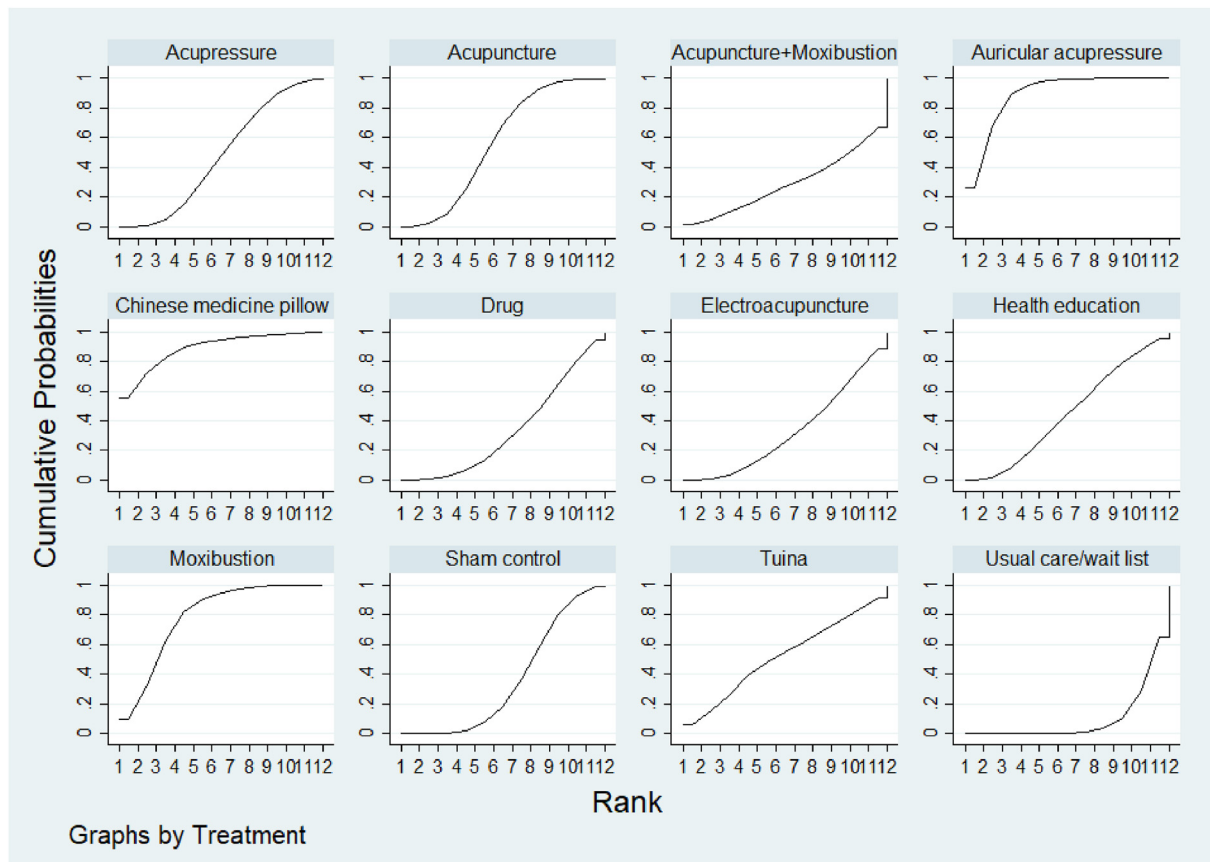


Fig. 4. Cumulative ranking probabilities of all interventions.

Moxibustion uses the heat and medicinal power of ignited moxa to stimulate acupoints on the surface of the body and promote the self-regulation of the body. It has the effect of warming the meridians and harmonizing Yin and Yang, which can significantly improve the quality and efficiency of sleep.⁵⁹

Acupressure and acupuncture are based on the same TCM theories of improving sleep disturbance by unblocking meridians and balancing Yin and Yang. Acupressure refers to applying pressure to acupoints of the body for treatment purposes. Acupuncture is an invasive intervention that involves the stimulation of acupoints in the body through manual manipulation, electrical impulses, or heat therapy after stainless steel needles are inserted into these points.⁶⁰ Basic science research reveals the effects of acupuncture are mediated via modulation of nervous system activities.⁶¹

In the included studies, the external therapies of TCM emphasized the stimulation of specific acupoints, including auricular acupressure,

moxibustion, acupuncture, acupressure, and electroacupuncture. The main acupoints commonly used for treating sleep problems in cancer patients are somatic acupoints such as Baihui (GV20), Sanyinjiao (SP6), Zusanli (ST36), Shenmen (HT7), and the ear acupoints such as Shenmen (TF4), Heart (CO15), Pizhixia (AT4), Neifenmi (CO18). According to the principle of syndrome differentiation and treatment of TCM, the clinical stimulation of acupoint is mostly done by using the main acupoint plus the matching acupoint, which is the main acupoint for treating insomnia, while the matching point is added or subtracted according to the symptoms of patients.

As an important complementary therapy to comprehensive cancer treatment, external therapy of TCM has unique advantages such as fewer adverse reactions, higher acceptance, and faster onset of action.⁶² Therapies such as acupressure and auricular acupressure are safe, convenient, and inexpensive and can be used by researchers, healthcare workers, family members, and patients themselves with a little training. In the included studies, participants only reported non-serious or mild side effects, such as subcutaneous cyanosis, pain, bruising, and allergic skin reactions.

Table 3

Ranking probability of all interventions.

| Intervention | SUCRA | PrBest | MeanRank |
|-------------------------|-------|--------|----------|
| Chinese medicine pillow | 88.3 | 61.9 | 2.2 |
| Auricular acupressure | 81.4 | 11.6 | 2.9 |
| Moxibustion | 78.3 | 14.5 | 3.2 |
| Acupressure | 61.3 | 1.2 | 4.9 |
| Acupuncture | 53.5 | 0.5 | 5.6 |
| Tuina | 51.3 | 9.7 | 5.9 |
| Health education | 41.2 | 0.5 | 6.9 |
| Electroacupuncture | 32.2 | 0.1 | 7.8 |
| Sham control | 31.4 | 0.0 | 7.9 |
| Drug | 25.6 | 0.1 | 8.4 |
| Usual care/wait list | 5.5 | 0.0 | 10.4 |

SUCRA, surface under the cumulative ranking area.

Limitations

There are some limitations in this study. First, our search was limited to English or Chinese publications and did not include RCT registries. Second, the diversity in intervention procedures and cancer types was extremely high, although separate-group and random-effects models were used in the NMA. Third, the quality of the included literature determines the credibility of the study results. In this study, some studies did not explicitly report information on randomization, allocation concealment, and the reasons for missing data, which might reduce the credibility of this conclusion. Fourth, the present NMA only used subjective sleep quality as outcome due to few relevant studies reporting

objective sleep quality. Fifth, the inclusion of studies with different follow-up time points and small data volumes did not allow for NMA of the follow-up data. Sixth, the inclusion of studies with different intervention durations increases the heterogeneity of the study. Subgroup analyses based on different intervention durations could be conducted in future effect evaluations. Finally, the number of studies included in the analysis of some external therapies of TCM, such as Chinese medicine pillow and Tuina, is small; thus, the efficacy of the interventions may be overestimated.

Implication for practice and research

External therapy of TCM has a positive impact on sleep quality and high safety in patients with cancer. The dependence of patients on external therapy of TCM is lower than dependence on pharmaceutical agents; thus, it could be an option for the improvement of sleep quality in patients with cancer. It is also convenient, low-cost, and well-accepted; furthermore, some external therapies of TCM (eg, Chinese medicine pillow, auricular acupressure, and acupressure) can be easily learned and practiced by patients and are widely available to hospitalized patients and community-dwelling individuals. Moreover, external therapy of TCM acts on the surface of the body, and thus, patient local skin condition assessment is required before intervention. In addition, further studies are needed to confirm our study findings regarding the outcomes of external therapy of TCM in improving sleep quality.

Conclusions

The findings of our NMA provide evidence for the efficacy and safety of external therapy of TCM in improving subjective sleep quality, and Chinese medicine pillow may be the most effective choice for enhancing sleep quality in patients with cancer, but the quality of the evidence is rated as low. Therefore, the results must be interpreted with caution. The certainty of the effectiveness of auricular acupressure, moxibustion, acupressure, and acupuncture on sleep improvement in patients with cancer was moderate. Therefore, our results can enhance clinical decision-making by nurses, with potential therapeutic benefits in addressing problems associated with the use of pharmaceutical agents.

CRedit author statement

Liuna Bi: Methodology, Formal analysis, Writing – original draft. **Wenjuan Gao:** Methodology, Formal analysis, Data curation. **Xian Zhang:** Visualization. **Na Li:** Conceptualization. **Jing Han:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Ming Shi:** Conceptualization, Writing – review & editing. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

All authors have none to declare.

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Ethics statement

Not required.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Disclosure

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Declaration of generative AI in scientific writing

No AI tools/services were used during the preparation of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.apjon.2023.100308>.

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