

## Effects of somatic acupoint stimulation on anxiety and depression in cancer patients: An updated systematic review of randomized controlled trials

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### ABSTRACT

**Objectives:** To explore the effectiveness of somatic acupoint stimulation (SAS) for cancer patients with anxiety and depression.

**Methods:** Thirteen electronic databases were searched systematically until August 2022. Randomized controlled trials (RCTs) investigating SAS for anxiety and/or depression in cancer patients were retrieved. Methodological quality of the included studies was assessed by utilizing the Cochrane Back Review Group Risk of Bias Assessment Criteria. Evidence level was assessed by using the approach of Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Both meta-analysis and descriptive analysis were conducted for outcome assessment.

**Results:** Twenty-eight records were finally included including 22 journal articles and six ongoing registered clinical trials. The overall methodological quality and level of evidence of the included studies were suboptimal, with no high-quality evidence identified. Moderate evidence showed that SAS could significantly decrease the anxiety of cancer patients (Acupuncture: [random effect model, SMD = -0.52, 95% CI = -0.79 to -0.24,  $p = 0.0002$ ] and Acupressure: [random effect model, SMD = -0.89, 95% CI = -1.25 to -0.52,  $p < 0.00001$ ]. While for depression, although the data analysis indicated that SAS can decrease depression significantly (Acupuncture: [random effect model, SMD = -1.26, 95% CI = -2.08 to -0.44,  $p = 0.003$ ] and Acupressure: [random effect model, SMD = -1.42, 95% CI = -2.41 to -0.42,  $p = 0.005$ ]), relevant evidence was rated as low. No statistically significant difference was identified between true and sham acupoints stimulation for both anxiety and depression.

**Conclusions:** This systematic review provides the latest research evidence to support SAS as a promising intervention for alleviating anxiety and depression in cancer patients. However, the research evidence should be interpreted prudently as methodological concerns were identified in some included studies, and some sub-group analyses were performed with a relatively small sample size. More rigorously designed large-scale RCTs with placebo-controlled comparisons are warranted to generate high-quality evidence.

**Registration:** The systematic review protocol has been registered with PROSPERO (CRD42019133070).

### 1. Introduction

Cancer has become the second leading cause of death globally, and the deaths of cancer has increased from 8.2 million in 2012 [1] to 9.6 million in 2018 [2]. According to the World Health Organization (WHO)

statistic [3], the morbidity and mortality of cancer would increase continuously, and over 15 million people would be diagnosed with cancer and 10 million will die of cancer per year by 2020. With the advances in anti-cancer therapies and care, the cancer trajectory and prognosis have shifted, and patients diagnosed with cancer, even those

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at an advanced stage, can live a relatively long life [4,5]. According to the National Cancer Institute, around two-thirds of patients could survive with cancer for at least five years after the diagnosis [6]. Although the survival rate of cancer patients has been rising throughout the past years, lengthy cancer experience and relevant side events of anticancer treatments make patients suffer from a wide range of distress, both physically and psychologically [7,8]. Apart from physical problems such as pain, fatigue and sleep problems, emotional distress especially anxiety and depression are also the common long-term resultant of cancer [9]. The prevalence of anxiety and depression in cancer survivors ranges from 15% to 48% [10,11] and from 12% to 24% [10,12,13], respectively. For cancer patients at the palliative care stage, the prevalence of depression was higher than that of the cancer survivors, with the percentage up to 70% [14]. The emotional distress can bring significantly detrimental health impacts including deterioration of quality of life, low tolerance to cancer treatment, and poor prognosis and survival [8,12,15].

Pharmacological treatment for cancer-related anxiety and depression can lead to considerable chemical burden and additional adverse events [16]. As a result, the use of complementary therapies in addition to standard cancer therapies to improve survivors' emotional well-being has been recommended [17]. Among which, somatic acupoints stimulation (SAS), including manual acupuncture and manual acupressure, is a commonly used method for cancer symptom management. This technique is supported by traditional meridian theory and is frequently utilised in practice for the prophylaxis and treatment of various health problems [18]. Many clinical trials and systematic reviews have been conducted to assess the effects of SAS for managing mental distress in non-cancer patients, including anxiety and depression [19]. While cancer patients usually experience a higher risk of anxiety and depression (nearly twice) than the general population [20]. A number of randomized control trials (RCTs) have been performed to explore the effectiveness of SAS for managing anxiety and depression in cancer. In 2015, a systematic review conducted by our group provided preliminary but inconclusive evidence on the promising role of SAS in reducing anxiety and depression in cancer patients [21]. Since the publication of the systematic review in 2016, a few RCTs have been conducted afterwards to further explore the effects of SAS on anxiety and depression among cancer patients. It is therefore important to include the recent clinical trials in an updated systematic review to identify the latest evidence of using SAS for anxiety and depression management in patients with cancer. The current systematic review was conducted to update the evidence from our previous work and provide updated implications for future research and practice.

## 2. Methods

The systematic review protocol has been registered with PROSPERO (CRD42019133070).

### 2.1. Search strategies

Thirteen electronic databases were systematically searched for potential records from the inception of each database to August 2022, which included PubMed, EMBase, Web of Science, Cochrane library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, OVID, Medline, Science Direct, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), and Wan Fang Data. Mesh terms, key word, and free words such as "acupuncture", "acupuncture therapy", "acupressure", "anxiety", "anxiety disorders", "depression", "depressive disorder", "neoplasms", and "randomized controlled trial" were used in the search strategies. Restriction regarding language was not set for the electronic database search. In addition to the database search, manual search was also performed by retrieving the literature in the review authors' university libraries such as printed conference proceedings and

unpublished thesis. The reference lists of all the finally included publications were also searched for more potentially eligible records. Representative search strategies for one database (PubMed) are presented in Table 1. Ongoing registered clinical trials were searched on trial registries including ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR), and Chinese Clinical Trial Registry (ChiCTR).

### 2.2. Selection criteria and outcome measures

Studies meeting the following criteria were included: (1) patients with the diagnosis of cancer regardless of the type and stage of cancer; (2) adult patients ( $\geq 18$  years) with anxiety and/or depression; (3) RCTs comparing SAS (manual acupuncture or manual acupressure) to one or more of the following: sham SAS, waiting-list, or standard methods of treatment and/or care (usual care or standard medication). No restrictions were set in terms of the study settings and the person who delivered the intervention. All types of auricular therapy and electro-acupoint stimulation were excluded from this review.

The primary outcomes for this review were anxiety and/or depression as measured by any patient-reported measures such as Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAMD), Self-rating Anxiety Scale, Self-rating Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), Beck Depression Questionnaire, 0–10 Numerical Rating Scale (NRS) or Center for Epidemiologic Studies Depression Scale (CESD). The secondary outcomes were patients' quality of life (QoL) and adverse events associated with SAS.

### 2.3. Study identification and data extraction

A reference management software (EndNote) was used to identify and eliminate any duplicated records. Two review authors (WT and YLQ) screened the titles and abstracts of the remaining records independently. Then, full-text of all potentially eligible studies were obtained for further screening. Data of the finally included studies were extracted by the same two authors independently using a data extraction form after pre-testing. The following data were extracted: the basic information of the study (first author, publication year, country/region),

**Table 1**  
Selected search strategies.

#1	Search (((("acupuncture"[MeSH Terms]) OR "acupuncture therapy"[MeSH Terms]) OR "acupressure"[MeSH Terms]) OR "acupuncture points"[MeSH Terms])
#2	Search (((((((acupoint*[Title/Abstract]) OR acupunctur*[Title/Abstract]) OR acupressur*[Title/Abstract]) OR acupotom*[Title/Abstract]) OR needle*[Title/Abstract]) OR Shiatsu[Title/Abstract]) OR Zhi Ya[Title/Abstract]) OR Chih Ya[Title/Abstract]) OR Shiatsu[Title/Abstract]
#3	#1 OR #2
#4	Search (((((("anxiety"[MeSH Terms]) OR "anxiety disorders"[MeSH Terms]) OR "depression"[MeSH Terms]) OR "depressive disorder"[MeSH Terms]) OR "mood disorders"[MeSH Terms]) OR "affective disorders, psychotic"[MeSH Terms]) OR "stress, psychological"[MeSH Terms])
#5	Search (((((("anxiety*[Title/Abstract]) OR anxious*[Title/Abstract]) OR nervousness[Title/Abstract]) OR hypervigilance*[Title/Abstract]) OR depression*[Title/Abstract]) OR emotion*[Title/Abstract]) OR psychology*[Title/Abstract]) OR affective*[Title/Abstract]
#6	#4 OR #5
#7	Search ("neoplasms"[MeSH Terms]) OR "leukemia"[MeSH Terms])
#8	Search (((((("cancer*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR tumo*[Title/Abstract]) OR tumour*[Title/Abstract]) OR oncology*[Title/Abstract]) OR malignant*[Title/Abstract]) OR leukaemia*[Title/Abstract])
#9	#7 OR #8
#10	Search (((((("randomized controlled trial"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR random*[Title/Abstract]) OR control*[Title/Abstract]) OR intervention[Title/Abstract]) OR trial[Title/Abstract]) OR placebo[Title/Abstract]) OR sham[Title/Abstract]) OR groups[Title/Abstract]
#11	#3 AND #6 AND #9 AND #10

characteristics of participants (diagnosis, sample size, and age), SAS intervention protocol details (practitioner acupoints formula, intervention duration, and frequency), details of control group, and study findings (primary and secondary outcomes). Any discrepancies in the process of study identification and data extraction were resolved by involving another review author (TJY).

#### 2.4. Quality appraisal of the included studies

Methodological quality of the included RCTs were assessed by using the assessment tool developed by the Cochrane Back Review Group [22]. Thirteen criteria were included in the tool: (1) "Was the method of randomization adequate?"; (2) "Was the treatment allocation concealed?"; (3) "Was the patient blinded to the intervention?"; (4) "Was the care provider blinded to the intervention?"; (5) "Was the outcome assessor blinded to the intervention?"; (6) "Was the drop-out rate described and acceptable?"; (7) "Were all randomized participants analysed in the group to which they were allocated?"; (8) "Are reports of the study free of suggestion of selective outcome reporting?"; (9) "Were the groups similar at baseline regarding the most important prognostic indicators?"; (10) "Were co-interventions avoided or similar?"; (11) "Was the compliance acceptable in all groups?"; (12) "Was the timing of the outcome assessment similar in all groups?"; (13) "Are other sources of potential bias unlikely?" (e.g. the validity of the outcome measures, conflicts of interests) (p. 1665) [22]. These items were adapted from Cochrane Handbook for Systematic Review for Intervention and were suggested for studies involving non-pharmacological intervention [22]. Risk of bias for each item can be rated as "low", "unclear", or "high" [22]. The risk of bias of the included RCTs were assessed by two review authors independently (WT and YLQ). For any disagreement, discussion was performed to achieve consistency. If consensus was not achieved via discussion, a third review author was involved (TJY).

#### 2.5. Data analysis

Statistical synthesis and descriptive analysis were conducted. Review Manager 5.3 was used to perform the data synthesis. All outcome variables analysed in this review were continuous variables with the estimation of mean difference (MD) [for studies using a same measurement] or standardized mean difference (SMD) [for studies using different measurements] and 95% confidence interval (CI). Clinical heterogeneity (e.g., differences in intervention protocol and control comparisons), methodological heterogeneity (e.g., differences in risk of bias of the study) and statistical heterogeneity were assessed and considered to determine the heterogeneity of each comparison. Statistical heterogeneity was analysed by calculating the  $I^2$ . If  $I^2 < 50\%$  and no significant clinical heterogeneity and methodological heterogeneity were identified, a fixed effects model was employed. Otherwise, a random effect model was selected. Both the overall and subgroup assessment were performed. The overall effects of the SAS versus sham comparisons or standard methods of treatment/care were examined first. For the comparisons with significant heterogeneity, subgroup synthesis was conducted afterwards based on the SAS types (acupuncture and acupressure), and the intervention duration ( $\leq 4$  weeks [short-term], 4–8 weeks [mid-term], and  $\geq 8$  weeks [long-term]) to minimize the clinical heterogeneity. Although other clinical heterogeneities such as the types of measurement scales existed between included studies as well, subgroup analysis was not conducted due to the insufficient number of studies. In addition, a sensitivity analysis was performed to examine the stability of the synthesized results, and to preliminarily detect the potential sources of statistical heterogeneity. Descriptive analysis was adopted for studies that cannot be included in the meta-analysis and the ongoing registered clinical trials. Publication bias of the included studies was not analysed in this review due to the inadequate number of studies for each subgroup meta-analysis.

### 3. Results

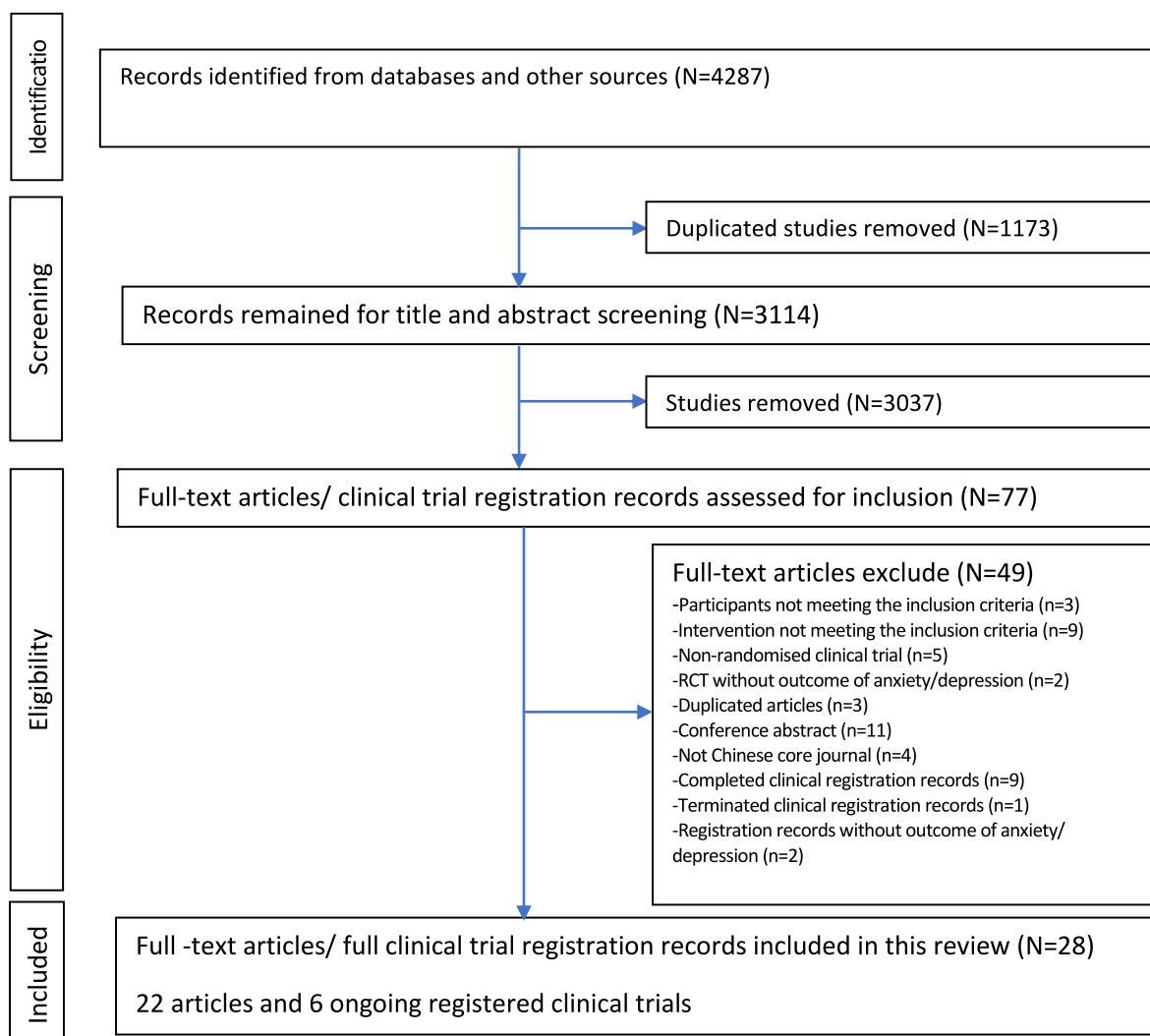
#### 3.1. Characteristics of the included studies

In total, 4287 records were located from the electronic databases and manual search. Among which, 1173 were excluded due to duplication; 3037 records were further excluded after browsing the title and abstract. A total of 77 full-text articles/clinical trial registration records, which were published in English and Chinese, were accessed for final eligibility evaluation. Of which, 49 records were further removed, and 28 records [23–25,27–51] were finally included in this review including 22 journal articles [23–25,27–45] and six [46–51] ongoing registered clinical trials (Fig. 1). The 22 journal articles [23–25,27–45] were published from 2011 to 2022, and the six [46–51] ongoing clinical trials were registered between the year of 2015 and 2020. Study sample of each journal article ranged from 30 to 500, and the average sample size was 107. In total, 2354 patients (randomized patients) with different types of cancer were involved. Of the 22 included articles, 16 [25,28,31–33,35–45] were published in English and six [23,24,27,29,30,34] were in Chinese. Nine studies [25,29,31,33,34,36,40,43,45] focused on breast cancer, ten studies [23,24,28,32,35,38,39,41,42,44] involved two or more types of cancer, two studies [30,37] on lung cancer and one study [27] on rectal cancer. Thirteen studies [23,24,27,29–31,33,34,36,39–42] were two-arm design and the other nine [25,28,32,35,37,38,43–45] were three-arm studies. For the types of SAS, twelve studies [23,24,29,31–33,36,39–41,43,45] used body acupuncture and the rest [25,27,28,30,34,35,37,38,42,44] utilised body acupressure. Among studies using the acupressure, five studies [25,27,37,42,44] applied self-administrated acupressure at home. Fourteen studies [25,27,29,30,32,34,36–40,42–44] assessed both anxiety and depression, while the other eight studies assessed anxiety (n = 3) [28,33,35] or depression (n = 5) [23,24,31,41,45] only. Ten studies [23,25,27,32,36,38–40,42,44] assessed patients' QoL. The adverse events of SAS were assessed and reported in eleven studies [23–25,28,29,32,36,39,40,43,44] (section 3.5.5). Table 2 summarises the characteristics of the included journal articles.

For the six ongoing registered clinical trials [46–51], five [46–48,50,51] adopted acupuncture and one [49] used self-acupressure. The acupressure trial was registered in 2019 [49], which was about self-acupressure on cancer patients with three arms (true acupressure + enhanced standard care, sham acupressure + enhanced standard care, and enhanced standard care only); 114 patients with cancer were estimated and intervention duration was 4 weeks using the following acupoint formula: Baihui (DU20), Yintang (EX-HN3), Fengchi (GB20), Neiguan (PC6), Shenmen (HT7), and Taichong (LR3); HADS was proposed to measure anxiety and depression. Regarding the five acupuncture trials [46–48,50,51], three employed a three-arm design with the sample size of 74 [48], 120 [51], and of 50 [47], respectively. Of which, one study [48] set the depression as the primary outcome measured by the HAMD; one [47] measured anxiety and depression as the secondary outcomes without reporting the instruments for outcome measures; the other one [51] used HADS to measure anxiety and depression as secondary outcomes. For the two acupuncture trials [46,50] with a two-arm design, acupuncture was proposed to compare with either sham acupuncture [46] or usual care [50], with an estimated sample size of 20 and 40, respectively. Both studies assessed anxiety and depression using HADS. Only one acupuncture trial [51] reported the acupoint formula: Guanyuan (CV4), Xuanzhong (GB39), Sanyinjiao (SP6), Yinlingquan (SP9), Yintang (EX-HN3), Zusani (ST36), Baihui (DU20), and Qihai (CV6).

#### 3.2. Instruments used for measuring anxiety, depression and quality of life in the included journal articles

Anxiety was assessed in 17 studies. The most commonly used instrument was the anxiety subscale of HADS (HADS-A), which was utilised in twelve studies (n = 12/17) [25,29,30,32,36–40,42–44]. Other



**Fig. 1.** Flowchart of study selection.

used instruments were the SAS ( $n = 2$ ) [27,34], STIA ( $n = 2$ ) [28,35] and 0–10 Numerical Rating Scale (NRS) ( $n = 1$ ) [33]. Depression was assessed in 19 studies, of which, 11 studies ( $n = 11/19$ ) employed the subscale of HADS for depression (HADS-D) [25,29,30,32,37–40,42–44], two studies applied SDS [27,34], one study used HAMD [23], one study employed both the HAMD and SDS [41], and another one [24] used HAMD combined with another scale for depression (9-item Patient Health Questionnaire). For the two studies using combined instruments, only data from one instrument (SDS for [41] and HAMD for [24]) was used for data analysis considering the homogeneity of outcome measures among studies. The Beck Depression Questionnaire [31,45] and CESD [36] were used in the other three studies, respectively. All the used instruments for anxiety and depression were validated scales with acceptable psychometric properties. QoL was assessed in ten studies [23, 25,27,32,36,38–40,42,44]. Of which, two [23,32] used the EORTC Quality of Life questionnaire (EORTC-QOL-C30), four [38,39,42,44] applied the Functional Assessment of Cancer Therapy-General (FACT-G), one study [40] employed the FACT-G and the breast cancer module of the FACT-G (FACT-B), while the other three studies used the Long-term Quality of Life Instrument (LTOL) [26], WHO Quality of Life-100 (WHOQOL-100) [27] and EuroQol survey [36], respectively. All instruments used in the included studies were designed for measuring QoL with well-documented psychometric properties.

### 3.3. Intervention protocol in the included journal articles: somatic acupoint stimulation

Two SAS modalities were used in the 22 included studies: manual acupuncture ( $n = 12$ ) and manual acupressure ( $n = 10$ ). Of the twelve studies [23,24,29,31–33,36,39–41,43,45] using manual acupuncture, three studies [32,43,45] used a three-arm design. Of which, one study [32] designed with the following three groups: acupuncture plus morphine, adopting morphine only, and acupuncture only; and the other two studies [43,45] explored the effects of acupuncture by comparing acupuncture with sham acupuncture and usual care, respectively. For the nine studies [23,24,29,31,33,36,39–41] employing a two-arm design, three [29,36,39] investigated the therapeutic effects of acupuncture by comparing true acupuncture with sham acupuncture; while the remaining six studies [23,24,31,33,40,41] compared true acupuncture with standard methods of treatment and/or care (three [23, 24,41] used standard medication, and the other three adopted attention control-booklet of fatigue management [40], kinesiotherapy [31], and usual care [33]). For the ten studies [25,27,28,30,34,35,37,38,42,44] using manual acupressure, six [25,28,35,37,38,44] were three-arm design. Of which, four [28,35,38,44] explored the effects of acupressure by comparing true acupressure with other two types of controls—sham acupressure and usual care. One [25] compared two types of true self-acupressure (relaxing acupressure and stimulating acupressure) with usual care. The relaxing acupressure adopted a formula

**Table 2**

Characteristics of included studies.

Study & setting	Type of cancer	Sample size	Intervention	Control	Outcome measures
S1 <sup>a</sup> : Deng & Xu, 2019 [23], China	Cancer patients (mixed sample)	<b>Randomized:</b> 60 <b>Completed:</b> 60 <b>Intervention G<sup>b</sup>:</b> 30/30, age(yr) = 53 ± 9 <b>Control G:</b> 30/30, 49 ± 11	Manual acupuncture + Standard Methods of Treatment/Care (SMT/C)	SMT/C	- <b>Depression:</b> Hamilton Depression Rating Scale (HAMD) - <b>QoL:</b> EORTC Quality of Life questionnaire (EORTC-QOL-C30) - <b>Adverse events</b> - <b>Outcome assessment at baseline, and week 4</b>
S2: Liu et al., 2019 [24], China	Cancer patients (mixed sample)	<b>Randomized:</b> 80 <b>Completed:</b> 80 <b>Intervention G:</b> 40/40, age(yr) = 63 ± 13 <b>Control G:</b> 40/40, age(yr) = 63 ± 12	Manual acupuncture+ SMT/C	SMT/C	- <b>Depression:</b> HAMD and PHQ-9 (9-item Patient Health Questionnaire) - <b>Adverse events</b> - <b>Outcome assessment at baseline and week 12</b>
S3*: Zick et al., 2018 [25], USA	Breast cancer patients	<b>Anxiety</b> <b>Randomized:</b> 142 <b>Completed:</b> 107 <b>Group A:</b> 27/42, age(yr) = 59.0 ± 9.4 <b>Group B:</b> 41/56, age(yr) = 59.9 ± 9.2 <b>Group C:</b> 39/44, age(yr) = 58.6 ± 9.7 <b>Depression</b> <b>Randomized:</b> 92 <b>Completed:</b> 67 <b>Group A:</b> 17/27, age(yr) = 58.0 ± 9.9 <b>Group B:</b> 27/36, age(yr) = 62.2 ± 8.6 <b>Group C:</b> 23/29, age(yr) = 59.8 ± 7.8	Group A (relaxing acupressure): Self-acupressure + SMT/C (as determined by the healthcare professionals) Group B (stimulating acupressure): Self-acupressure + SMT/C (as determined by the healthcare professionals)	SMT/C (as determined by the healthcare professionals)	- <b>Anxiety:</b> Hospital Anxiety and Depression Scale- Anxiety (HADS-A) - <b>Depression:</b> Hospital Anxiety and Depression Scale- Depression (HADS-D) - <b>QoL</b> [26]: Long-term Quality of Life Instrument (LTOL) - <b>Adverse events</b> - <b>Outcome assessment at baseline, week 6 and week 10.</b>
S4: Feng & Sun, 2018. [27], China	Rectal cancer patients	<b>Randomized:</b> 90 <b>Completed:</b> 90 <b>Intervention G:</b> 45, age(yr) = 58.24 ± 6.32 <b>Control G:</b> 45, age(yr) = 56.28 ± 5.85	Manual acupressure + SMT/C	SMT/C	- <b>Anxiety:</b> Self-rating Anxiety Scale - <b>Depression:</b> SDS - <b>QoL:</b> WHO Quality of Life-100 (WHOQOL-100) - <b>Outcome assessment at baseline, and week 12</b>
S5: Sharifi Rizi et al., 2017 [28], Iran	Cancer patients undergoing bone marrow biopsy	<b>Randomized:</b> 90  <b>Completed:</b> 90, age(yr) = 56.67 ± 10.9 <b>Group A:</b> 30/30 <b>Group B:</b> 30/30 <b>Group C:</b> 30/30	<b>Group A:</b> Manual acupressure + SMT/C  <b>Group B (sham acupressure):</b> the points located 1.5 cm away from the true points + SMT/C <b>Group C:</b> SMT/C		- <b>Anxiety:</b> State-Trait Anxiety Inventory (STAI) - <b>Adverse events</b> - <b>Outcome assessment at 10 min before and after the procedure of bone marrow biopsy</b>
S6: Yu et al., 2017 [29], China	Breast cancer patients	<b>Randomized:</b> 72 <b>Completed:</b> 64 <b>Intervention G:</b> 34/36, age(yr) = 50.2 ± 8.0 <b>Control G:</b> 30/36, age(yr) = 51.4 ± 8.4	Manual acupuncture + SMT/C (as determined by the healthcare professionals)	<b>Sham acupuncture:</b> non-acupoints located away from the meridians + SMT/C (as determined by healthcare professionals)	- <b>Anxiety:</b> HADS-A - <b>Depression:</b> HADS-D - <b>Adverse events</b> - <b>Outcome assessment at baseline and week 4</b>
S7: Xu et al., 2017 [30], China	Lung cancer patients	<b>Randomized:</b> 60 <b>Completed:</b> 60 <b>Intervention G:</b> 30/30, age(yr) = 63.2 ± 8.9 <b>Control G:</b> 30/30, age(yr) = 62.7 ± 9.5	Manual acupressure + SMT/C	SMT/C	- <b>Anxiety:</b> HADS-A - <b>Depression:</b> HADS-D - <b>Outcome assessment at baseline and week 8</b>
S8: Giron et al., 2016 [31], Brazil	Breast cancer patients	<b>Randomized:</b> 50 <b>Completed:</b> 48, age(yr) = 53.7 ± 11.1 <b>Intervention G:</b> 24/25 <b>Control G:</b> 24/25	Manual acupuncture + SMT/C (Kinesiotherapy)	SMT/C (Kinesiotherapy)	- <b>Depression:</b> Beck questionnaire - <b>Outcome assessment at baseline, week 5 (session 5) and week 10 (session 10)</b>
S9: Minchom et al., 2016 [32] Out-patient clinics, UK	Lung cancer and mesothelioma patients	<b>Randomized:</b> 173  <b>Completed:</b> 145	<b>Acupuncture G:</b> Manual acupuncture	- <b>Morphine G:</b> Oral morphine - <b>Combination G:</b> Manual acupuncture + oral morphine	- <b>Anxiety:</b> HADS-A - <b>Depression:</b> HADS-D - <b>QoL:</b> EORTC-QOL-C30 - <b>Adverse events</b>

(continued on next page)

**Table 2 (continued)**

Study & setting	Type of cancer	Sample size	Intervention	Control	Outcome measures
S10: Quinlan-Woodward et al., 2016 [33], USA	Breast cancer patients	<p><b>Acupuncture G:</b> 49/57, age(yr) = median 74 (50–88)</p> <p><b>Morphine G:</b> 45/60, age(yr) = median 75 (42–87)</p> <p><b>Combination G:</b> 51/56, age(yr) = median 70 (49–88)</p> <p><b>Randomized:</b> 30</p> <p><b>Completed:</b> 26</p> <p><b>Intervention G:</b> 12'/15, age(yr) = 53.7 ± 9.4</p> <p><b>Control G:</b> 14/15, age(yr) = 62.5 ± 11.5</p>	Manual acupuncture only	SMT/C (post-operative visit)	<ul style="list-style-type: none"> <li>- <b>Outcome assessment at baseline, day 7 (week 1) and day 14 (week 2)</b></li> </ul>
S11: Liu et al., 2016. [34], China	Breast cancer patients	<p><b>Randomized:</b> 80</p> <p><b>Completed:</b> 80</p> <p><b>Intervention G:</b> 40, age(yr) = mean 47.4</p> <p><b>Control G:</b> 40, age(yr) = mean 46.65</p>	Manual acupressure + SMT/C	SMT/C	<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> SAS</li> <li>- <b>Depression:</b> SDS</li> <li>- <b>Outcome assessment at baseline, and day 7</b></li> </ul>
S12: Beikmoradi et al., 2015 [35], Iran	Cancer patients (mixed sample)	<p><b>Randomized:</b> 90</p> <p><b>Completed:</b> 85</p> <p><b>Group A:</b> 27/30, age(yr) = 50 ± 13</p> <p><b>Group B:</b> 28/30, age(yr) = 48 ± 13</p> <p><b>Group C:</b> 30/30, age(yr) = 49 ± 10</p>	<b>Group A:</b> Manual acupressure + SMT/C  <b>Group B (sham):</b> the points located 2 cm away from those used in group A + SMT/C  <b>Group C:</b> SMT/C		<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> STAI</li> <li>- <b>Outcome assessment at baseline, day 5 (session 5) and day 10 (session 10)</b></li> </ul>
S13: Bao et al., 2014 [36], USA	Breast cancer patients	<p><b>Randomized:</b> 51</p> <p><b>Completed:</b> 47</p> <p><b>Intervention G:</b> 23/25, age (yr) = median 61 (45–85)</p> <p><b>Control G:</b> 24/26, age(yr) = median 61 (44–82)</p>	Manual acupuncture	<b>Sham acupuncture:</b> sham acupoints were located between two true acupoints used in the true group, which were stimulated with non-penetrating retractable needles	<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> HADS-A</li> <li>- <b>Depression:</b> Center for Epidemiologic Studies Depression Scale (CESD)</li> <li>- <b>QoL:</b> EuroQol survey</li> <li>- <b>Adverse events</b></li> <li>- <b>Outcome assessment at baseline, week 4, 8 and 12</b></li> </ul>
S14 Tang et al., 2014 [37], Taiwan	Lung cancer patients	<p><b>Randomized:</b> 57</p> <p><b>Completed:</b> 45</p> <p><b>Group A:</b> 15/17, age (yr) = 53.9 ± 9.8</p> <p><b>Group B:</b> 16/24, age (yr) = 54.8 ± 9.5</p> <p><b>Group C:</b> 14/16, age (yr) = 66.1 ± 8.0</p>	<b>Group B:</b> Self-administrated acupressure only  <b>Group A:</b> acupressure with essential oils  <b>Group C (sham acupressure):</b> three sham points located at metacarpal head, patella, and inner ankle		<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> HADS-A</li> <li>- <b>Depression:</b> HADS-D</li> <li>- <b>Outcome assessment at baseline, Day 1 of the third chemotherapy (week 10), and day 1 of the sixth chemotherapy (week 20)</b></li> </ul>
S15: Molassiotis et al., 2014 [38], UK	Cancer patients (mixed sample)	<p><b>Randomized:</b> 500</p> <p><b>Completed:</b> 372 (retained in trial)</p> <p><b>Group A:</b> 132/168, age (yr) = 67.9% &gt; 50yrs</p> <p><b>Group B:</b> 119/166, age(yr) = 66.9% &gt; 50yrs</p> <p><b>Group C:</b> 121/166, age(yr) = 69.3% &gt; 50yrs</p>	<b>Group A:</b> Manual acupressure + SMT/C  <b>Group B (sham acupressure):</b> wear the wristband with bottom away from the Neiguan (PC6), and the button on the exterior of the wristband + SMT/C  <b>Group C:</b> SMT/C		<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> HADS-A</li> <li>- <b>Depression:</b> HADS-D</li> <li>- <b>QoL:</b> Functional Assessment of Cancer Therapy-General (FACT-G)</li> <li>- <b>Outcome assessment at baseline, and day 10 of each cycle (4 cycles)</b></li> </ul>
S16: Deng et al., 2013 [39], USA	Cancer patients (mixed sample)	<p><b>Randomized:</b> 101</p> <p><b>Completed:</b> 74</p> <p><b>Intervention G:</b> 34/49, age(yr) = median 54 (46–58)</p> <p><b>Control G:</b> 40/52, age(yr) = median 53 (45–59)</p>	Manual acupuncture	<b>Sham acupuncture:</b> points located a few millimetres away from the meridians and the real points in acupuncture group	<ul style="list-style-type: none"> <li>- <b>Anxiety:</b> HADS-A</li> <li>- <b>Depression:</b> HADS-D</li> <li>- <b>QoL:</b> FACT-G</li> <li>- <b>Adverse events</b></li> <li>- <b>Outcome assessment at baseline and week 6</b></li> </ul>

(continued on next page)

**Table 2 (continued)**

Study & setting	Type of cancer	Sample size	Intervention	Control	Outcome measures
S17: Molassiotis et al., 2012 [40], UK	Breast cancer patients	<b>Randomized:</b> 302 <b>Completed:</b> 246 (analysed)  <b>Intervention G:</b> 181/227, age(yr) = mean 52(30–75) <b>Control G:</b> 65/75, age(yr) = mean 53 (25–80)	Manual acupuncture + SMT/C	SMT/C (enhanced usual care)	- Anxiety: HADS-A - Depression: HADS-D - QoL: FACT-G and FACT-B (breast cancer) - Adverse events - Outcome assessment at baseline, and week 6
S18 Feng et al., 2011 [41], China	Cancer patients (mixed sample)	<b>Randomized:</b> 80 <b>Completed:</b> 80  <b>Intervention G:</b> 40/ 40, age(yrs) = 63.8 ± 5.47 <b>Control G:</b> 40/40, age(yrs) = 63.6 ± 4.26	Manual acupuncture only	SMT/C (medication treatment)	- Depression: Self-rating Depression Scale (SDS) HAMD  - Outcome assessment at baseline and day 30.
S19 Cheung et al., 2020 [42], Hong Kong	Cancer patients (mixed sample)	<b>Randomized:</b> 30 <b>Completed:</b> 26  <b>Intervention G:</b> 12/ 15, age(yrs) = 61.8 ± 9.92  <b>Control G:</b> 14/15, age(yrs) = 58.93 ± 11.11	Self-administered acupressure + SMT/C	SMT/C	- Anxiety: HADS-A - Depression: HADS-D - QoL: FACT-G - Outcome assessment at baseline, week 4 and 8.
S20 Li et al., 2020 [43], China	Breast cancer patients	<b>Randomized:</b> 40  <b>Completed:</b> 37 <b>Group A:</b> 18/20, age(yr) = mean 47.5 (40–62) <b>Group B:</b> 10/10, age(yr) = mean 42 (32–61) <b>Group C:</b> 9/10, age(yr) = mean 50.5 (33–70)	<b>Group A:</b> Manual acupuncture + SMT/C  <b>Group B (sham acupuncture):</b> 16 non acupoints + SMT/C <b>Group C:</b> SMT/C	  <b>Group B (sham acupuncture):</b> 16 non acupoints + SMT/C <b>Group C:</b> SMT/C	- Anxiety: HADS-A - Depression: HADS-D - Adverse events - Outcome assessment at baseline, week 12, 20 and 24.
S21 Hoang et al., 2021 [44]	Cancer patients (mixed sample)	<b>Randomized:</b> 114  <b>Completed:</b> 74 <b>Group A:</b> 26/38, age(yr) = 54.6 ± 10.9 <b>Group B:</b> 21/38, age(yr) = 53.5 ± 7.1 <b>Group C:</b> 27/38, age(yr) = 56.6 ± 9.0	<b>Group A:</b> Self-administered acupressure + SMT/C	<b>Group B (sham Self-administered acupressure):</b> non acupoints + SMT/C <b>Group C:</b> SMT/C	- Anxiety: HADS-A - Depression: HADS-D - QoL: FACT-G - Adverse events - Outcome assessment at baseline, week 4 and 8.
S22, D'Alessandro et al., 2022 [45]	Breast cancer patients	<b>Randomized:</b> 60  <b>Completed:</b> 58 <b>Group A:</b> 19/20, age(yr) = mean 48.6 <b>Group B:</b> 20/20, age(yr) = mean 51.6 <b>Group C:</b> 19/20, age(yr) = mean 50.8	<b>Group A:</b> Manual acupuncture	<b>Group B (sham acupuncture):</b> same acupoints as that of Group A without invasive stimulation + SMT/C <b>Group C:</b> SMT/C	- Depression: Beck Depression Inventory-II - Outcome assessment at baseline and week 10

Note: S<sup>a</sup> = Study, G<sup>b</sup> = Group; c: in this study, 15 patients were allocated to intervention group, 2 drop-outs, and other 2 didn't drop out but due a technical error, data of the two patients were not analysed. NR: not reported. S3\*: data about anxiety and depression was extracted from article [25] and data about quality of life was from article [26]; articles [25,26] belong to one same clinical trial and article [26] was a secondary data analysis of the study data.

mainly for improving sleep and the stimulating utilised a formula for improving fatigue; the other one [37] was designed with the following three groups: self-acupressure plus essential oils, self-acupressure only, and sham self-acupressure; while the rest four acupressure studies [27, 30,34,42] adopted a two-arm design, and all assessed the therapeutic effects by comparing the acupressure with usual care.

All the 22 included studies described the SAS protocols, including the types of acupoints stimulation, duration and frequency of intervention, and the identification and location of the sham acupoints (for those utilizing a sham comparison). Some studies [23,24,27,28,33,36,39–45]

also reported the practitioner for administering the SAS, and the most commonly reported practitioner was acupuncturists. In terms of the selected acupoints in the true SAS groups, Hegu (LI4), Zusani (ST36), Sanyinjiao (SP6), Neiguan (PC6), Shenmen (HT7), Yintang (EX-HN3) and Baihui (DU20) were the most commonly used acupoints for anxiety and/or depression reported in more than one-third of the included studies. For studies with sham SAS, except for D'Alessandro et al.'s study [45] (same acupoints as that of true acupuncture group without any stimulation), the sham acupoints were all non-acupoints in other studies, which located away from the true acupoints used in the true SAS

**Table 3**

Summary of somatic acupoint stimulation intervention protocols.

Study & setting	Intervention Type	Practitioner	Durations & Frequency	Selected acupoints
S1: Deng & Xu, 2019 [23], China	Manual acupuncture	Acupuncturist	<b>Duration:</b> 4 weeks <b>Frequency:</b> two times per week, lasting 30 min	Zusanli (ST36), Sanyinjiao (SP6), Hegu (LI4), Neiguan (PC6), Taichong (LR3), Shenmen, Yintang (EX-HN3), Baihui (DU20)
S2: Liu et al., 2019 [24], China	Manual acupuncture	Acupuncturist	<b>Duration:</b> 12 weeks (3 months) <b>Frequency:</b> 5 times a week, lasting 30 min	Taichong (LR3), Hegu (LI4), Baihui (DU20), Yintang (EX-HN3)
S3*: Zick et al., 2018 [25], USA	Manual acupressure	Self-administrated	<b>Duration:</b> 6 weeks + 4-week follow-up without acupressure  <b>Frequency:</b> daily and each point for 3 min	<b>Group A</b> (relaxing acupressure): Yintang (EX-HN3), anmian (EX-HN22), Shenmen (HT7), Sanyinjiao (SP6), Taichong (LR3) [bilaterally, except for Yintang (EX-HN3)] <b>Group B</b> (stimulating acupressure): Baihui (DU20), Qihai (CV6), Hegu (LI4), Zusani (St6), Sanyinjiao (SP6), Taixi (KI3). Baihui (DU20), Fengchi (GB20)
S4: Feng & Sun, 2018. [27], China	Manual acupressure	Registered nurses + self-acupressure	<b>Duration:</b> 3 months (12 weeks) <b>Frequency:</b> 2 times per day, lasting 30 min	Hegu (LI4), Shenmen (HT7)
S5: Sharifi Rizi et al., 2017 [28], Iran	Manual acupressure	Acupressure practitioner (the researcher)	<b>Duration &amp; Frequency:</b> after the start and the end of the biopsy, and acupoints were pressed for 2 min	
S6: Yu et al., 2017 [29], China	Manual acupuncture	NR	<b>Duration:</b> 4 weeks + 4 weeks follow-up <b>Frequency:</b> 2 times a week	Baihui (DU20), Neiguan (PC6), Qihai (CV6), Zusani (ST36), Sanyinjiao (SP6)
S7: Xu et al., 2017 [30], China	Manual acupressure	NR	<b>Duration:</b> 8 weeks <b>Frequency:</b> daily, lasting 20 min	Neiguan(PC6), Hegu (LI4), Shenmen (HT7), Ganshu (BL18)
S8: Giron et al., 2016 [31], Brazil	Manual acupuncture	NR	<b>Duration:</b> 10 weeks <b>Frequency:</b> weekly, lasting 30 min	Zhongji (CV3), Yinlingquan (SP9), Zusani (ST36), Fulin (KI7), Taichong (LR3), Jianjin (GB21), Jianyu(LI15), HT14, Chize (LU5), Hegu (LI4), Tiaokou (ST38), Kunlun (BL60) 5 paraspinal (T1, T2, T3, T4, T5), Hegu (LI4), 2–3 trigger points in the trapezius muscle, two upper sternal middle points
S9: Minchom et al., 2016 [32], UK	Manual acupuncture	NR	<b>Duration:</b> 2 weeks <b>Frequency:</b> NR	Specific treatments for each patient
S10: Quinlan-Woodward et al., 2016 [33], USA	Manual acupuncture	Acupuncturist	<b>Duration:</b> as many as 2 times during post-surgery hospitalization <b>Frequency:</b> about 36 min per time	
S11: Liu et al., 2016. [34], China	Manual acupressure	NR (but not self-acupressure)	<b>Durations:</b> 7 days (from 2 days before the surgery to 5 days after the surgery) <b>Frequency:</b> twice per day, lasting 15–20 min	Taiyang (EX-HN5), Yintang (EX-HN3), Baihui (DU20), Sishencong (EX-HN1), Neiguan (PC6), Hegu (LI4), Shenmen (HT7), Sanyinjiao (SP6), Zusani (ST36), and Taichong (LR3)
S12: Beikmoradi et al., 2015 [35], Iran	Manual acupressure	Researcher (qualification NR)	<b>Duration:</b> 10 sessions (10 days) <b>Frequency:</b> daily, lasting 25–30 min	Hegu (LI4), Shousanli (LI10), Shenmen (H7), Taiyuan (Lu9), Baihui (DU20), Qihai (CV6), Yintang (EX-HN3), Feishu (UB13), and Shenmen (ear)
S <sup>a</sup> 13: Bao et al., 2014 [36], USA	Manual acupuncture	Acupuncturists	<b>Duration:</b> 8 weeks + 4 weeks follow-up <b>Frequency:</b> weekly	Guanyuan (CV4), Qihai (CV6), Zhongwan (CV12), Hegu (LI4) Master of Heart 6 (MH6), Yanglingquan (GB34), Zusani (ST36), Taixi (KI3), and Shugu (BL65)
S14 Tang et al., 2014 [37], Taiwan	Manual acupressure	Self-administrated at home after trained by research assistants	<b>Duration:</b> 5 months (around 20 weeks) <b>Frequency:</b> daily, every acupoint for 1 min, and 6 min in total	Hegu(LI4), Zusani(ST36), Sanyinjiao (SP6)
S15: Molassiotis et al., 2014 [38], UK	Manual acupressure	Patients wear elastic wristbands with a button	<b>Duration:</b> 4 chemotherapy cycles, and lasting 7 days per cycle (from the morning of chemotherapy day to the flowing 6 days)	Neiguan (PC6)
S16: Deng et al., 2013 [39], USA	Manual acupuncture	Acupuncturists	<b>Duration:</b> 6 weeks <b>Frequency:</b> weekly, lasting 20 min per time	Qihai (CV6), Guanyuan (CV4), Taixi (KI3), Zusani (ST36), Sanyinjiao (SP6), Quchi (LI11), Yinxi (HT6), and an auricular point (anti-depression)
S17: Molassiotis et al., 2012 [40], UK	Manual acupuncture	Acupuncturists	<b>Duration:</b> 6 weeks <b>Frequency:</b> weekly, lasting 20 min	Zusanli (ST36), Sanyinjiao (SP6), Hegu (LI4) (if the points could not be punctured, 2 alternative points were selected including Yanglingquan [GB34] and Yinlingquan [SP9])
S18 Feng et al., 2011 [41], China	Manual acupuncture	Acupuncturists	<b>Duration:</b> 30 days <b>Frequency:</b> daily, lasting 20–30 min	Fenglong (ST40), Yinlingquan (SP9), Xuehai (SP10), Sanyinjiao (SP6), Yintang (EX-HN3), Baihui (DU20), Sishencong (EX-HN1), Neiguan (PC6), Shenmen (HT7)
S19 Cheung et al., 2019 [42], Hong Kong	Manual acupressure	Self-administrated	<b>Duration:</b> 4 weeks + 4 weeks follow-up <b>Frequency:</b> twice a day, lasting 15 min	Neiguan (PC6), Zusani (ST36), Sanyinjiao (SP6), Baihui (DU20), and another two following additional acupoints [Shenmen (HT7), Hegu(LI4), Taichong (LR3), Taixi (KI3), Fengchi (GB20) Qihai (CV6), Guanyuan (CV4), and Shenshu (BL23)]
S20 Li et al., 2020 [43], China	Manual acupuncture	Acupuncturists	<b>Duration:</b> 20 weeks + 4 weeks follow-up <b>Frequency:</b> weekly, lasting 30 min	Specific treatments for each patient
S21 Hoang et al., 2021 [44]	Manual acupressure	Self-administrated	<b>Duration:</b> 4 weeks + 4 weeks follow-up <b>Frequency:</b> weekly, lasting around 28 min	Baihui (GV20), Yintang (EX-HN3), Fengchi (GB20), Neiguan (PC6), Shenmen (HT7), and Taichong (LR3)
S22, D'Alessandro et al., 2022 [45]	Manual acupuncture	Acupuncturist	<b>Duration:</b> 10 weeks <b>Frequency:</b> weekly, lasting 20 min	Fengfu (GV 16), Baihui (GV 20), Shenshu (BL 23), and Qihai (CV 6)

**Table 4**

Risk of bias (quality) assessment of included studies.

Study	Criteria											
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12
S1 [23]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
S2 [24]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
S3 [25]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
S4 [27]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
S5 [28]	Yes	Unclear	Unclear	No	Unclear	Yes	Yes	Yes	Yes	NA	Yes	Unclear
S6 [29]	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Unclear
S7 [30]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
S8 [31]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear
S9 [32]	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
S10 [33]	Yes	Unclear	No	No	No	Yes	No	Yes	No	Unclear	Yes	Unclear
S11 [34]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
S12 [35]	Yes	Unclear	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Unclear
S13 [36]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
S14 [37]	Yes	Unclear	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
S15 [38]	Yes	Yes	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S16 [39]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
S17 [40]	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
S18 [41]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
S19 [42]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
S20 [43]	Yes	Unclear	Yes	No	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes
S21 [44]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S22 [45]	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes

S: Study. Yes: low risk of basis; No: high risk of basis; unclear: unclear risk of basis. NA: Not applicable. \*: for participants in the true and sham groups. Item 1: "Was the method of randomization adequate?"; Item 2: "Was the treatment allocation concealed?"; Item 3: "Was the patient blinded to the intervention?"; Item 4: "Was the care provider blinded to the intervention?"; Item 5: "Was the outcome assessor blinded to the intervention?"; Item 6: "Was the drop-out rate described and acceptable?"; Item 7: "Were all randomized participants analysed in the group to which they were allocated?"; Item 8: "Are reports of the study free of suggestion of selective outcome reporting?"; Item 9: "Were the groups similar at baseline regarding the most important prognostic indicators?"; Item 10: "Were co-interventions avoided or similar?"; Item 11: "Was the compliance acceptable in all groups?"; Item 12: "Was the timing of the outcome assessment similar in all groups?"; and Item 13: "Are other sources of potential bias unlikely?" [Direct quotation from the original source (ref 22, p1665)].

group, and some studies [29,39] also emphasised that the non-acupoints were a few millimetres off the meridians. The intervention duration varied across studies. Two used single intervention session during [28] or after [33] surgery. Intervention durations in other studies ranged from one week to five months. Details of the SAS protocols are summarised in Table 3.

### 3.4. Methodological quality of the included journal articles

Methodological quality of the included studies is presented in Table 4. All the included studies mentioned randomization, and 19 [23–25,28–30,32,33,35–45] detailed the generation of random sequence by using computer-generated sequence, applying random number table, or rolling a dice. Adequate allocation concealment was only described in eight studies [25,29,32,38–40,42,44]. Eight studies adopted blinding design for patients (n = 8) [24,36–39,43–45], intervention provider (n = 3) [24,25,38], and/or outcome assessor (n = 10) [24,29,35–39,42,44,45]. All the studies reported drop-out of patients and the attrition rate was deemed acceptable. Most of the studies (n = 15) [23–25,27,28,30,32,34,36–39,41,42,44]analysed all the randomized patients, for instance, using the intention-to-treat analysis. Pre-defined outcomes were analysed and reported in all the included studies. For the majority of the included studies, baseline data and the timing of the outcome assessment were similar among the study groups.

### 3.5. Effects of somatic acupoint stimulation

Effects of SAS on anxiety and depression were synthesized based on the included journal articles, and the meta-analysis results and the relevant evidence level are summarised in Table 5 and Table 6, respectively. For the effects of SAS on QoL, descriptive analysis was used given different QoL measures used across studies with insufficient data for synthesis.

#### 3.5.1. Overall assessment of the effects of somatic acupoint stimulation

**3.5.1.1. Somatic acupoints simulation versus standard methods of treatment/care.** Thirteen studies [25,27,28,30,32–35,38,40,42–44] explored the effects of SAS on anxiety by comparing the SAS with standard methods of treatment/care. Data syntheses were performed for ten studies (n = 803) as the data of three studies [32,38,43] was unavailable for synthesis. The pooled results with moderate quality of evidence showed that SAS can significantly decrease anxiety in cancer patients [random effect model, SMD = -0.83, 95% CI = -1.13 to -0.53, p < 0.00001]. For depression, eleven out of fifteen [23–25,27,30–32,34,38,40–45] studies (n = 899) were used for data syntheses (four studies [32,38,43,45] were excluded due to unavailable data for analysis); the pooled results favoured the intervention [random effect model, SMD = -1.33, 95% CI = -1.93 to -0.73, p < 0.00001], with the quality of evidence rated as moderate. Eight studies [23,25,27,32,38,40,42,44] assessed the effects of SAS on QoL by comparing the SAS with standard methods of treatment/care. Apart from the study conducted by Molas-siotis et al. [38], Cheung et al. [42], and Hoang et al. [44], the remaining five studies [23,25,27,32,40] showed significant improvement of QoL after a period of intervention (between-group comparison).

**3.5.1.2. Somatic acupoint simulation versus sham comparisons.** Eight [28,29,35–37,39,43,44] and seven [29,36,37,39,43–45] studies compared the effects of SAS with sham comparisons for anxiety and depression, respectively. Of which, two [36,43] exploring anxiety and three [36,43,45] exploring depression was excluded for data synthesis as the type of data cannot be transformed for data synthesis with other studies. Six [28,29,35,37,39,44] and four [29,37,39,44] studies on anxiety and depression, respectively, were therefore used for meta-analysis. The pooled results indicated that the between-group differences did not reach statistical significance for both anxiety (six trials with 392 patients) [random effect model, SMD = -0.26, 95% CI = -0.55 to -0.04, p = 0.09] and depression (four trials with 277 patients) [random effect

**Table 5**  
Summary of meta-analysis.

Outcomes	Trials No.	Patients No.	Statistical Method	Effect estimate	Test for overall effect		Heterogeneity	
					Z	P	P	I [2]
<b>Acupoints stimulation versus standard methods of treatment/care</b>								
Depression	2	11	899 Std. Mean Difference (IV, Random, 95% CI)	-1.33 [-1.93, -0.73]	4.32	<0.00001	<0.00001	>50%
Anxiety	10	10	803 Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.13, -0.53]	5.36	<0.00001	0.0001	>50%
<b>Acupoints stimulation versus sham acupoints stimulation</b>								
Depression	4	4	277 Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.42, 0.31]	0.30	0.76	0.09	>50%
Anxiety	3	6	392 Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.55, -0.04]	1.69	0.09	0.06	50%
<b>Subgroup analysis on stimulation types</b>								
• <b>Acupuncture:</b> acupuncture versus standard methods of treatment/care								
Depression	5	5	507 Std. Mean Difference (IV, Random, 95% CI)	-1.26 [-2.08, -0.44]	3.01	0.003	<0.00001	>50%
Anxiety	2	2	264 Std. Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.79, -0.24]	3.71	0.0002	0.50	0%
• <b>Acupuncture:</b> acupuncture versus sham acupoints stimulation								
Depression	2	2	161 Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.78, 1.54]	0.64	0.52	0.65	0%
Anxiety	2	2	161 Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.09, 1.06]	0.03	0.98	0.62	0%
• <b>Acupressure:</b> acupressure versus standard methods of treatment/care								
Depression	9	6	392 Std. Mean Difference (IV, Random, 95% CI)	-1.42 [-2.41, -0.42]	2.79	0.005	<0.00001	>50%
Anxiety	8	8	539 Std. Mean Difference (IV, Random, 95% CI)	-0.89 [-1.25, -0.52]	4.73	<0.00001	0.0002	>50%
• <b>Acupressure:</b> acupressure versus sham acupoints stimulation								
Depression	11	2	116 Mean Difference (IV, Fixed, 95% CI)	-1.03 [-3.02, 0.96]	1.01	0.31	0.03	>50%
Anxiety	12	4	231 Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.89, 0.15]	1.40	0.16	0.01	>50%
<b>Subgroup analysis based on treatment duration</b>								
• <b>≤4 weeks (including 4 weeks):</b> acupoints stimulation versus standard methods of treatment/care								
Depression	6	5	326 Std. Mean Difference (IV, Random, 95% CI)	-1.40 [-2.51, -0.30]	2.48	0.01	<0.00001	>50%
Anxiety	5	6	327 Std. Mean Difference (IV, Fixed, 95% CI)	-0.74 [-0.97, -0.52]	6.40	<0.00001	0.006	>50%
• <b>≤ weeks (including 4 weeks):</b> acupoints stimulation versus sham acupoints stimulation								
Depression	10	2	140 Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.99, 1.59]	0.46	0.65	0.72	0%
Anxiety	7	4	247 Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.59, 0.22]	0.88	0.38	0.05	>50%
• <b>4–8 weeks (including 8 weeks):</b> acupoints stimulation versus standard methods of treatment/care								
Depression	4	4	403 Std. Mean Difference (IV, Random, 95% CI)	-1.78 [-3.08, -0.48]	2.69	0.007	<0.00001	>50%
-Acupuncture	2	2	287 Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.79, -0.27]	3.95	<0.00001	0.70	0%
-Acupressure	2	2	116 Mean Difference (IV, Fixed, 95% CI)	-2.92 [-3.19, -2.65]	21.33	<0.00001	0.42	0%
Anxiety	3	3	386 Mean Difference (IV, Fixed, 95% CI)	-1.96 [-2.38, -1.54]	9.12	<0.00001	0.81	0%
• <b>4–8 weeks (including 8 weeks):</b> acupoints stimulation versus sham acupoints stimulation								
Depression	2	2	121 NR	NR	NR	NR	NR	NR
Anxiety	2	2	121 NR	NR	NR	NR	NR	NR
• <b>&gt;8 weeks:</b> acupoints stimulation versus standard methods of treatment/care								
Depression	3	3	218 Std. Mean Difference (IV, Fixed, 95% CI)	-0.47 [-0.74, -0.20]	3.41	0.0007	0.99	0%
Anxiety	1	1	90 NR	NR	NR	NR	NR	NR
• <b>&gt;8 weeks:</b> acupoints stimulation versus sham acupoints stimulation								
Depression	1	1	40 NR	NR	NR	NR	NR	NR
Anxiety	1	1	40 NR	NR	NR	NR	NR	NR

model, SMD = -0.06, 95% CI = -0.42 to 0.31, p = 0.76], however, the relevant quality of the evidence was rated as low for anxiety or very low for depression. Four studies [36,38,39,44] reported QoL, and all of which showed that there was no significant difference between the true and sham SAS. However, two studies [39,44] demonstrated significant within-group difference on QoL in true SAS group before and after the intervention.

### 3.5.2. Subgroup analysis based on different types of somatic acupoint stimulation

To minimize the clinical heterogeneity of each comparison, subgroup synthesis was performed based on the types of SAS (acupuncture and acupressure), and intervention duration (short-term [ $\leq 4$  weeks], mid-term [4–8 weeks], and long-term [ $> 8$  weeks]) (Table 5).

#### 3.5.2.1. Somatic acupuncture

**3.5.2.1.1. Acupuncture versus standard methods of treatment/care.** Effects of acupuncture on anxiety and depression were reported in three [33,40,43] and seven [23,24,31,40,41,43,45] studies, respectively. Of which, two studies [43,45] were excluded for data synthesis as the type of data (reported change scores only) cannot be transformed for data synthesis with other studies. Acupuncture was found to be superior for both anxiety (two trials with 264 patients) [random effect model, SMD = -0.52, 95% CI = -0.79 to -0.24, p = 0.0002] and depression (5 trials with 507 patients) [random effect model, SMD = -1.26, 95% CI = -2.08 to -0.44, p = 0.003], with the quality of the evidence being

moderate and low, respectively. For QoL, three studies [23,32,40] explored the effects of acupuncture, and the descriptive analysis supported that acupuncture can significantly improve cancer patients' QoL when compared with standard methods of treatment/care (all at  $p < 0.05$ ).

**3.5.2.1.2. Acupuncture versus sham comparison.** Effects of acupuncture on anxiety and depression were compared with sham acupuncture in three [29,39,43] and four studies [29,39,43,45], respectively. Two [29,39] of which were used for data synthesis, and the pooled results of meta-analysis favoured the true intervention group in relieving anxiety (two trials with 161 patients) [Fixed effect model, MD = -0.01, 95% CI = -1.09 to 1.06, p = 0.98] and depression (two trials with 161 patients) [Fixed effect model, MD = -0.38, 95% CI = -0.78 to 1.54, p = 0.52] but did not reach statistical significance. However, the quality of evidence generated from the data synthesis was rated as very low. In terms of QoL, two studies [36,39] reported that there was no significant difference between the true and sham acupuncture group after intervention. One study [39] demonstrated significant within-group difference on QoL for both the true and sham SAS groups before and after the study intervention.

#### 3.5.2.2. Somatic acupressure

**3.5.2.2.1. Acupressure versus standard methods of treatment/care.** Eight studies [25,27,28,30,34,35,42,44] reported the effects of acupressure on anxiety by comparing with standard methods of treatment/care. Moderate evidence indicated that acupressure can

**Table 6**

Summary of the quality of evidence based on each comparison.

Outcomes	GRADE					Quality
	Limitation	Inconsistency	Indirectness	Imprecision	Publication Bias	
<b>Overall assessment of the effects of anxiety</b>						
SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	0	0	⊕⊕⊕O MODERATE
SAS VS sham comparisons	-1 <sup>1,2</sup>	-1 <sup>3</sup>	0	0	0	⊕⊕OO LOW
<b>Subgroup analysis based on different types of somatic acupoint stimulation for anxiety</b>						
Somatic acupuncture VS standard methods of treatment/care	-1 <sup>1,2</sup>	0	0	0	0	⊕⊕⊕O MODERATE
Somatic acupressure VS sham comparisons	-1 <sup>2</sup>	-1 <sup>3</sup>	0	-1 <sup>4</sup>	0	⊕OO VERY LOW
Somatic acupressure VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	0	0	⊕⊕⊕O MODERATE
Somatic acupressure VS sham comparisons	0	-1 <sup>3</sup>	0	-1 <sup>4</sup>	0	⊕⊕OO LOW
<b>Subgroup analysis of intervention duration of somatic acupoint stimulation for anxiety</b>						
Short-term duration: SAS VS standard methods of treatment/care	-1 <sup>1,2</sup>	0	0	0	0	⊕⊕⊕O MODERATE
Short-term duration: SAS VS sham comparisons	-1 <sup>1,2</sup>	-1 <sup>3</sup>	0	0	0	⊕⊕OO LOW
Mid-term duration: SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕⊕OO LOW
<b>Overall assessment of the effects of depression</b>						
SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	0	0	⊕⊕⊕O MODERATE
SAS VS sham comparisons	-1 <sup>2</sup>	-1 <sup>3</sup>	0	-1 <sup>4</sup>	0	⊕OO VERY LOW
<b>Subgroup analysis based on different types of somatic acupoint stimulation for depression</b>						
Somatic acupuncture VS standard methods of treatment/care	-1 <sup>1,2</sup>	0	0	-1 <sup>5</sup>	0	⊕OO LOW
Somatic acupuncture VS sham comparisons	-1 <sup>2</sup>	-1 <sup>3</sup>	0	-1 <sup>4,5</sup>	0	⊕OO VERY LOW
Somatic acupressure VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕OO LOW
Somatic acupressure VS sham comparisons	0	-1 <sup>3</sup>	0	-1 <sup>4</sup>	0	⊕OO LOW
<b>Subgroup analysis of intervention duration of somatic acupoint stimulation for depression</b>						
Short-term duration: SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕⊕OO LOW
Short-term duration: SAS VS sham comparisons	-1 <sup>1,2</sup>	-1 <sup>3</sup>	0	-1 <sup>4</sup>	0	⊕OO VERY LOW
Mid-term duration: SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕OO LOW
Mid-term duration: Somatic acupuncture VS standard methods of treatment/care	-1 <sup>2</sup>	0	0	0	0	⊕⊕O MODERATE
Mid-term duration: Somatic acupressure VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕⊕OO LOW
Long-term duration: SAS VS standard methods of treatment/care	-1 <sup>1</sup>	0	0	-1 <sup>5</sup>	0	⊕⊕⊕O MODERATE

**Note:** The included reviews were biased in terms of randomization, allocation concealment, and blinding method [2]; incomplete reports and outcome events and selective outcome bias (including adverse reactions, negative results, etc.) were not presented or explained [3]; the confidence intervals of different studies overlapped greatly, and the combined result of heterogeneity was larger [4]; the invalid value (RR = 1.0) was included in the confidence interval [5]; significant benefits or harms were included in the confidence interval (RR < 0.75 or RR > 1.25 were the criteria).

significantly relieve patients' anxiety (eight trials with 539 patients) [random effect model, SMD = -0.89, 95% CI = -1.25 to -0.52, p < 0.00001]. Six studies [25,27,30,34,42,44] with 392 patients on depression were used for data synthesis and the results showed that acupressure was superior for depression relief [random effect model, SMD = -1.42, 95% CI = -2.41 to -0.42, p = 0.005]; Of note, the quality of the evidence was low. Five studies [26,27,38,42,44] investigated the effects of acupressure on QoL by comparing with standard treatment/care, and the results were inconsistent. Of which, four [25,27, 42,44] reported significant improvement of QoL after receiving acupressure (within-group) while the other study [38] showed no significant improvement after the intervention (within-group).

**3.5.2.2.2. Acupressure versus sham comparison.** Acupressure was compared with sham acupressure for anxiety relief in four studies [28, 35,37,44], and acupressure was not found to be superior in reducing anxiety (four trials with 231 patients) [random effect model, SMD = -0.37, 95% CI = -0.89 to 0.15, p = 0.16], with the quality of evidence rated as low. For depression, two studies [37,44] (n = 116) explored the effects of acupressure by comparing with sham acupressure, and no significant difference was found between the true and sham acupressure group [fixed effect model, MD = -1.03, 95% CI = -3.02 to 0.96, p = 0.31]. There were two studies [38,44] comparing the true acupressure with sham acupressure in terms of QoL, and no significant difference was identified between groups as well.

### 3.5.3. Subgroup analysis on intervention duration

#### 3.5.3.1. Short-term duration ( $\leq 4$ weeks)

**3.5.3.1.1. Somatic acupoints stimulation versus standard methods of treatment/care.** Seven [28,32–35,42,44] studies examining the effects of SAS on anxiety and six studies [28,32,34,35,42,44] on depression by using a short-term intervention. Of which, one [32] reported the change scores of anxiety and depression, and indicated that acupuncture in combination with morphine can significantly decrease patients' anxiety when compared with morphine only. Data synthesis was performed for the remaining studies. The pooled results favoured the SAS group for both the anxiety (six trials with 327 participants) [fixed effect model, SMD = -0.74, 95% CI = -0.97 to -0.52, p < 0.00001] and depression (five trials with 326 participants) [random effect model, SMD = -1.40, 95% CI = -2.51 to -0.30, p = 0.01], with the evidence quality rated as moderate and low, respectively. QoL assessment was performed in four studies [32,36,42,44] following the short-term intervention but data synthesis was not performed due to different types of data. Of which, two studies<sup>32,36</sup> showed that SAS group had better QoL than the control group with standard treatment/care after intervention (between-group comparison).

**3.5.3.1.2. Somatic acupoint stimulation versus sham comparison.** Five [28,29,35,36,44] and three [29,36,44] studies compared true SAS with sham comparison and reported the effects on anxiety and depression after a short-term intervention, respectively. For anxiety, meta-analysis was performed for four studies (n = 247) [28,29,35,44], and the results

did not favour the true intervention with no statistical significance [random effect model, SMD = -0.18, 95% CI = -0.59 to -0.22, p = 0.38]. For depression, data synthesis was performed two studies (n = 140) [29,44], and the no significant statistical significance was identified [fixed effect model, MD = -0.30, 95% CI = -0.99 to 1.59, p = 0.65]. Of note, the quality of the evidence was rated as low for anxiety and very low for depression. Two studies [36,44] explored the QoL, and the result also supported that there was no statistically significant difference between groups.

### 3.5.3.2. Mid-term duration [4–8 weeks (including 8 weeks)]

**3.5.3.2.1. Somatic acupoints stimulation versus standard methods of treatment/care.** Three studies [25,30,40] reported the effects of SAS on anxiety after a mid-term intervention. The pooled effects (three trials with 386 patients) supported that patients in the intervention group had less anxiety following the intervention than those in the control group [fixed effect model, SMD = -1.96, 95% CI = -2.38 to -1.54, p < 0.00001]. In terms of depression, four studies [25,30,31,40] were used for data synthesis, and SAS was found to be more effective in relieving depression [random effect model, SMD = -1.78, 95% CI = -3.08 to -0.48, p = 0.007]. However, significant heterogeneity (p < 0.00001,  $I^2 = 96\%$ ) was identified for depression. To minimize the heterogeneity and improve the evidence quality, further sub-group analysis was performed based on the types of acupoints stimulation (acupuncture and acupressure). Data synthesis was conducted for two acupuncture studies [31,40] (n = 287) and two acupressure studies (n = 116) [25,30], respectively, and pooled effect supported the superiority of acupuncture (moderate evidence) [fixed effect model, SMD = -0.53, 95% CI = -0.79 to -0.27, p < 0.0001] and acupressure (low evidence) [fixed effect model, MD = -2.92, 95% CI = -3.19 to -2.65, p < 0.0001] in relieving cancer-related depression. Two studies [25,40] reported patients' QoL after a mid-term SAS (6 weeks) intervention, and the results showed that patients in the intervention group had better QoL following the intervention than those in the control group.

**3.5.3.2.2. Somatic acupoints stimulation versus sham comparison.** Effects of SAS on anxiety and depression after a mid-term intervention was reported in two studies [36,39] by comparing true and sham SAS, but only descriptive analysis was performed due to unavailable data for synthesis [36]. No significant difference was detected for both anxiety and depression between the true and sham groups [36,39]. While for the within-group comparison, the anxiety and depression scores decreased in both groups [39]. For QoL, only one study reported the QoL

assessment without any statistically significant between-group difference but only a within-group difference in either true or sham intervention group.

### 3.5.3.3. Long-term duration [>8 weeks]

**3.5.3.3.1. Somatic acupoints stimulation versus standard methods of treatment/care.** Effects of long-term SAS on anxiety were reported in two [27,43] studies. One study [27] showed that SAS can decrease cancer patients' anxiety significantly (p < 0.05). While for the other study [43], obvious trend of anxiety alleviation was found without statistical difference. Effects of long-term SAS on depression were reported in five [24,27,31,43,45] studies. However, due to the different types of data among studies, only three studies (n = 218) [24,27,31] were used for data synthesis, and the results with a moderate level of evidence indicated that SAS can significantly decrease cancer patients' depression [fixed effect model, SMD = -0.47, 95% CI = -0.74 to -0.20, p = 0.0007]. One study [27] explored patients' QoL after a 12-week intervention, and the results indicated that patients in the intervention group had better QoL than those in the control group after the intervention (p < 0.05).

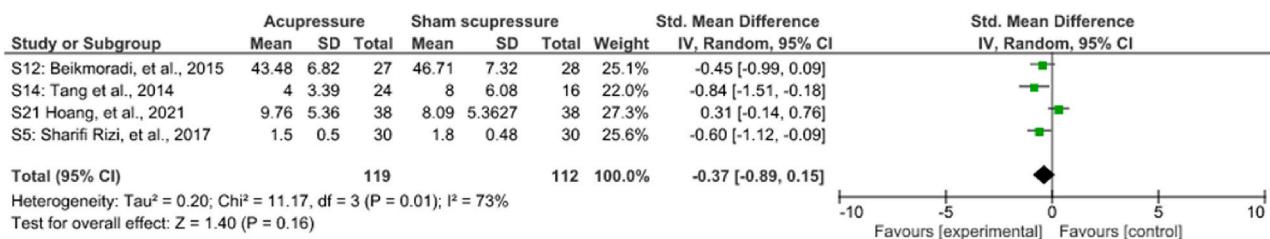
**3.5.3.3.2. Somatic acupoints stimulation versus sham comparison.** Effects of SAS on anxiety and depression following the completion of a long-term intervention were measured in two studies [37,43], and three studies [37,43,45], respectively. Two studies [37,43] showed that patients in the true SAS group reported lower anxiety and depression score than those in the sham group, but the difference did not achieve statistical significance. While another study [45] showed that true SAS could significantly improve depression compared to the sham group (P < 0.001). No study reported patients' QoL assessment results.

### 3.5.4. Sensitivity analysis

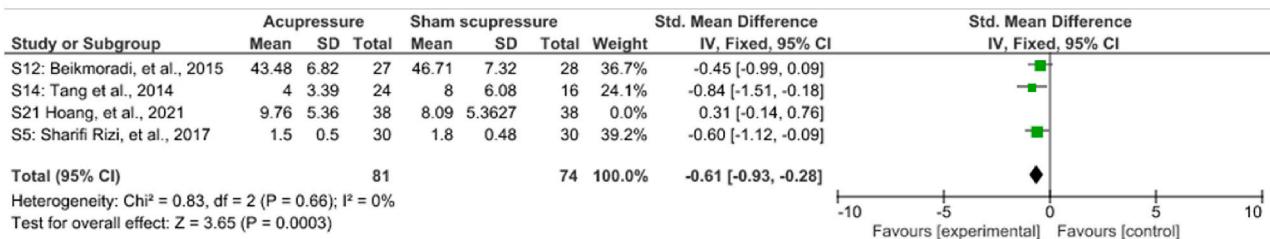
For comparisons with three studies or above, a sensitivity analysis was performed to identify the stability and reliability of the findings, as well as to preliminarily locate the potential sources that contribute to such heterogeneity (Table 7). Except for the comparisons of "acupressure versus sham acupressure (anxiety)" (Fig. 2), the pooled effects of all other comparisons were shown as stable after excluding the dubious studies, which included "acupuncture versus standard methods of treatment/care (depression)" (Fig. 3), "acupressure versus standard methods of treatment/care (anxiety)" (Fig. 4), "short-term duration: SAS versus standard methods of treatment/care (depression)" (Fig. 5), "short-term duration: SAS versus standard methods of treatment/care

**Table 7**  
Sensitivity analysis.

Outcomes & Number of Trials	Before sensitivity analysis		Removal of Studies	Number of Trials	After sensitivity analysis	
	SMD (Model) 95% CI	Heterogeneity $I^2$			SMD/MD (Model) 95% CI	Heterogeneity $I^2$
<b>• Acupuncture: acupuncture versus standard methods of treatment/care</b>						
Depression: 5	-1.26 (Random) [-2.08, -0.44]	>50%	Removing Deng & Xu, 2019 [23] and Feng et al., 2011 [41]	3	-0.51 (Fixed) [-0.74, -0.29]	0%
<b>• Acupressure: acupressure versus standard methods of treatment/care</b>						
Depression: 6	-1.42 (Random) [-2.42, -0.42]	>50%	Removing Zick et al., 2018 [25], Feng & Sun, 2018 [27], Cheung et al., 2020 [42] and Hoang et al., 2021 [44]	2	-1.54 (Fixed) [-1.93, -1.16]	>50%
Anxiety: 8	-0.89 (Random) [-1.25, -0.52]	>50%	Removing Zick et al., 2018 [25] Liu et al., 2016 [34], and Hoang et al., 2021 [44]	5	-0.77 (Fixed) [-1.01, -0.53]	0%
<b>Acupressure: acupressure versus sham acupressure</b>						
Anxiety: 4	-0.37 (Random) [-0.89, 0.15]	>50%	Removing Hoang et al., 2021 [44]	3	-0.61 (Fixed) [-0.93, -0.28]	0%
<b>• ≤4 weeks (including 4 weeks): acupoints stimulation versus standard methods of treatment/care</b>						
Depression: 5	-1.40 (Random) [-2.51, -0.30]	>50%	Removing Deng & Xu, 2019 [23], Cheung et al., 2020 [42], and Hoang et al., 2021 [44]	2	-8.14 (Fixed) [-9.71, -6.58]	24%
Anxiety: 6	-0.74 (Fixed) [-0.97, 0.52]	>50%	Removing Hoang et al., 2021 [44]	5	-0.97 (Fixed) [-1.23, -0.70]	29%
<b>• 4–8 weeks (including 8 weeks): acupoints stimulation versus standard methods of treatment/care</b>						
Depression: 4	-1.78 (Random) [-3.08, -0.48]	>50%	Removing Zick et al., 2018 [25]	3	-0.65 (Fixed) [-0.89, -0.41]	>50%

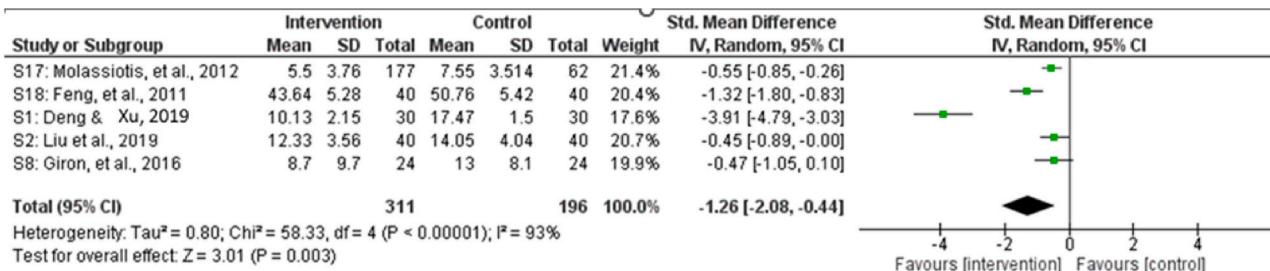


a Forest plots before removing S21 (Hoang, et al., 2021)

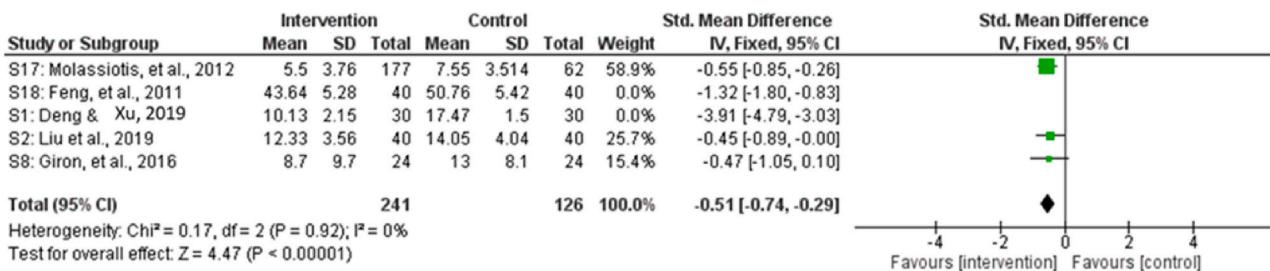


b Forest plots after removing S21 (Hoang, et al., 2021)

Fig. 2. Forest plots for the comparisons of “acupressure versus sham acupressure (anxiety)”.



a Forest plot: before removing S1 (Deng &amp; Xu, 2019) and S18 (Feng, et al., 2011)



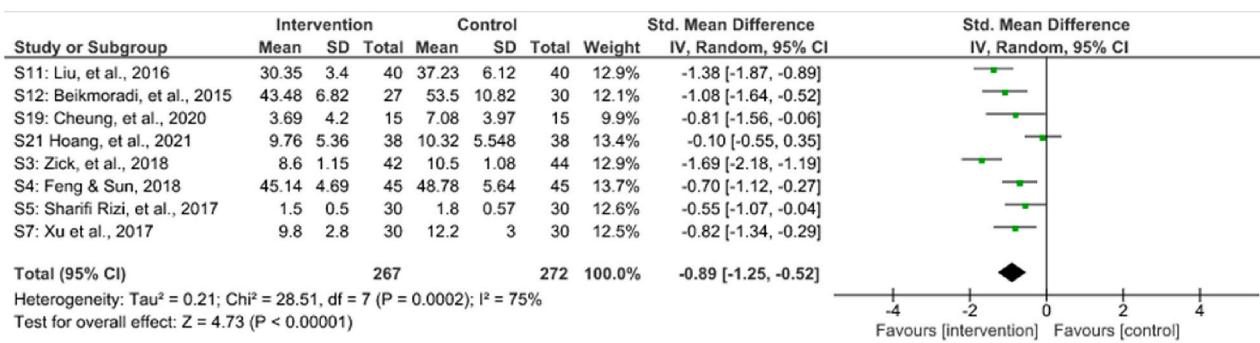
b Forest plot: after removing S1 (Deng &amp; Xu, 2019) and S18 (Feng, et al., 2011)

Fig. 3. Forest plots for the comparisons of “acupuncture versus standard methods of treatment/care (depression)”.

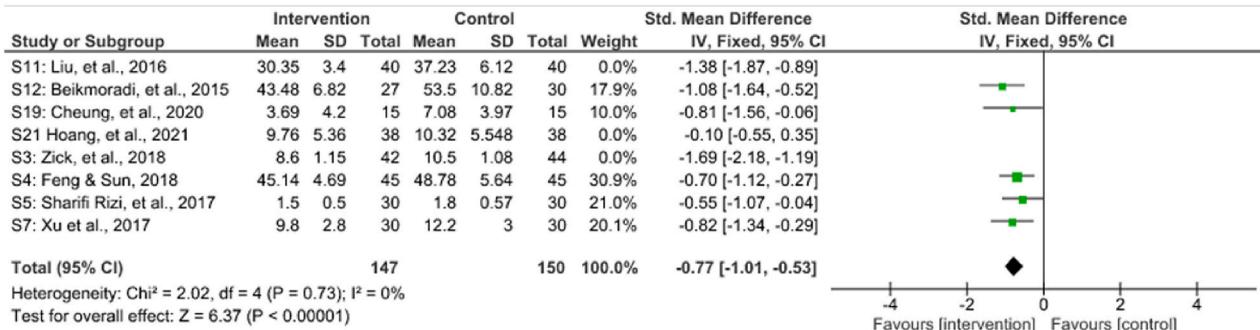
(anxiety)” (Fig. 6), “acupressure versus standard methods of treatment/care (depression)” (Fig. 7) and “mid-term duration: SAS versus standard methods of treatment/care (depression)” (Fig. 8). Besides, except for the comparisons of “acupressure versus standard methods of treatment/care (depression)” (Fig. 7) and “mid-term duration: SAS versus standard methods of treatment/care (depression)” (Fig. 8),  $I^2$  was decreased considerably after excluding the dubious studies. The study conducted by Zick et al. [25] was the most frequently identified study that contributes to the heterogeneity, in which the intervention was implemented by the patients (self-administrated acupressure at home) rather than the SAS practitioners.

### 3.5.5. Adverse events

Potential adverse events were assessed as a safety outcome in eleven studies [23–25,28,29,32,36,39,40,43,44]. Of which, four [23,28,29,36] reported that no SAS-related adverse events occurred during the study period. One study [40] monitored SAS-related adverse events without reporting the details. One study [39] reported a total of 11 adverse events happened during the intervention, such as small bowel obstruction, low blood counts and renal failure, but none of them were deemed related to SAS as the author had identified apparent alternative explanations for those events. The remaining five studies [24,25,32,43,44] reported some adverse events including mild bruising and/or pain at stimulation sites, skin irritation due to acupuncture, and dizziness and headache. The causality between the SAS and reported adverse events

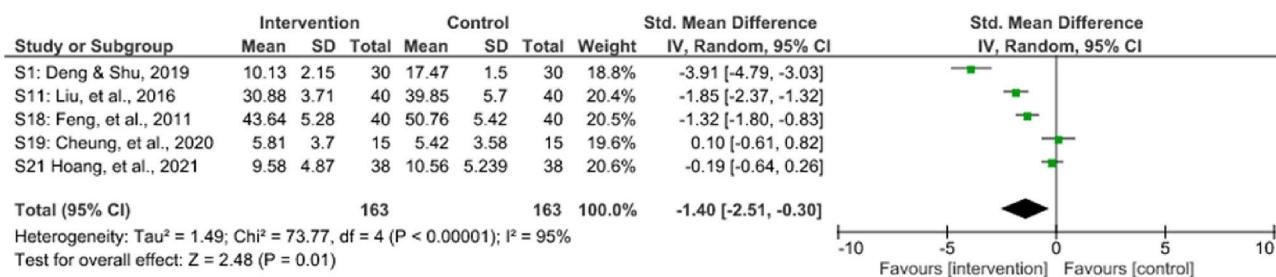


a: Forest plot: before removing S3 (Zick, et al., 2018), S11 (Liu, et al., 2016), and S21 Hoang, et al., 2021

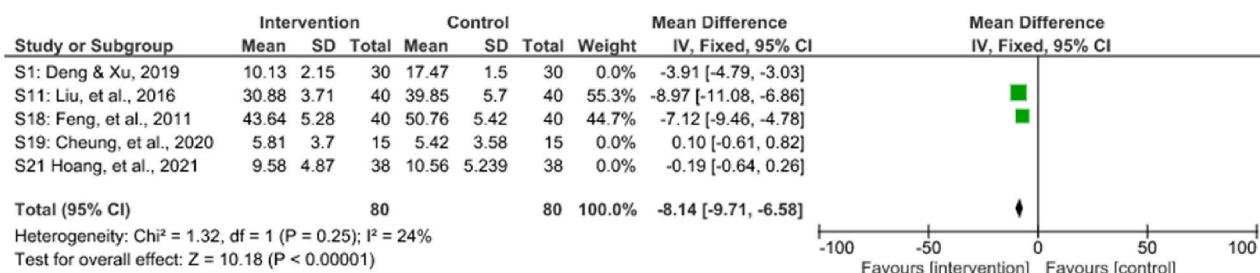


b: Forest plot: after removing S3 (Zick, et al., 2018), S11 (Liu, et al., 2016), and S21 (Hoang, et al., 2021)

Fig. 4. Forest plots for the comparisons of “acupressure versus standard methods of treatment/care (anxiety)”.

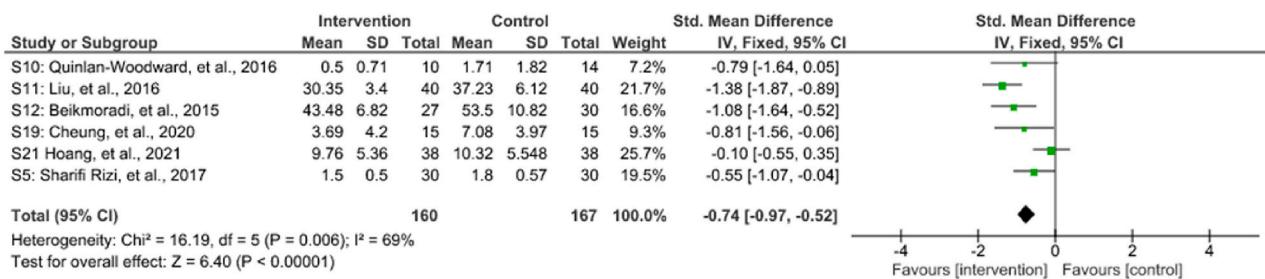
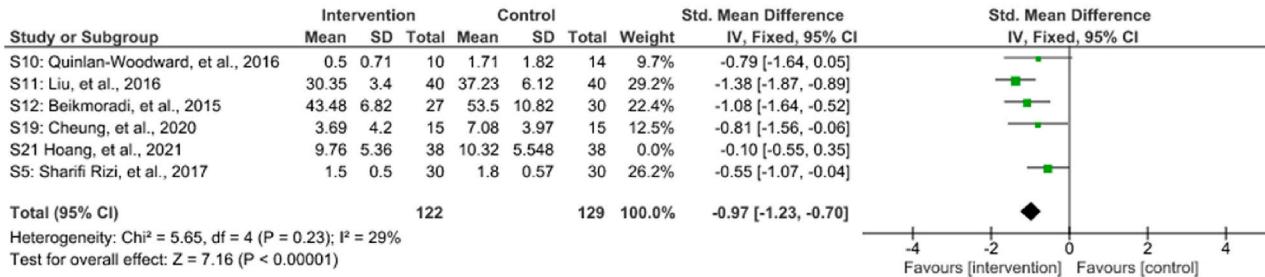
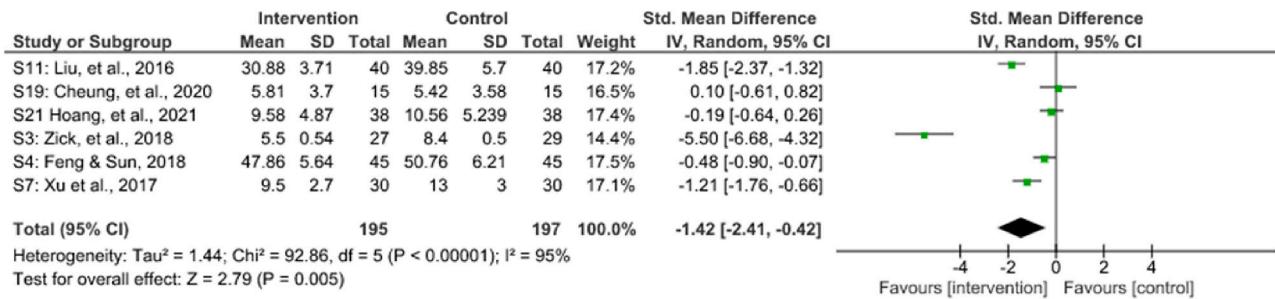
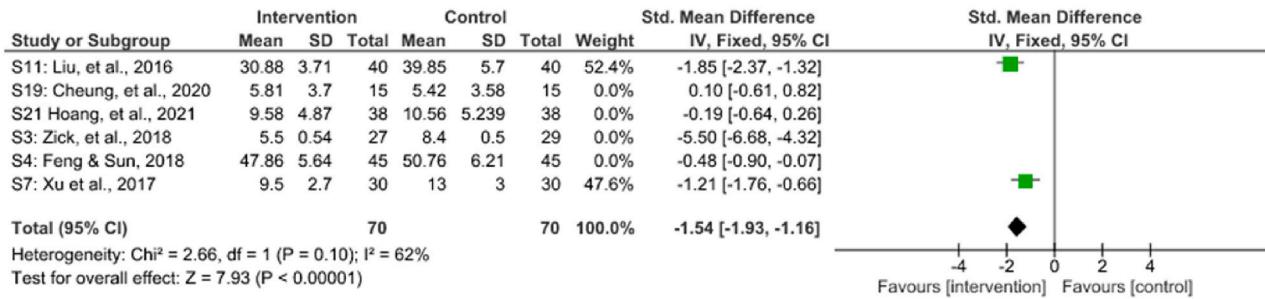


a: Forest plot: before removing S1 (Deng &amp; Xu, 2019), S19 (Cheung, et al., 2020), and S21 (Hoang, et al., 2021)



b: Forest plot: after removing S1(Deng &amp; Xu, 2019), S19 (Cheung, et al., 2020), and S21 (Hoang, et al., 2021)

Fig. 5. Forest plots for the comparisons of “short-term duration ( $\leq 4$  weeks): SAS versus standard methods of treatment/care (depression)”.

**a:** Forest plot: before removing S21 (Hoang, et al., 2021)**b:** Forest plot: after removing S21 (Hoang, et al., 2021)**Fig. 6.** Forest plots for the comparisons of “short-term duration ( $\leq 4$  weeks): SAS versus standard methods of treatment/care (anxiety)”.**a:** Forest plot: before removing S3 (Zick, et al., 2018), S4 (Feng & Sun, 2018) and S19 (Cheung, et al., 2020)**b:** Forest plot: after removing S3 (Zick, et al., 2018), S4 (Feng & Sun, 2018) and S19 (Cheung, et al., 2020)**Fig. 7.** Forest plots for the comparisons of “acupressure versus standard methods of treatment/care (depression)”.

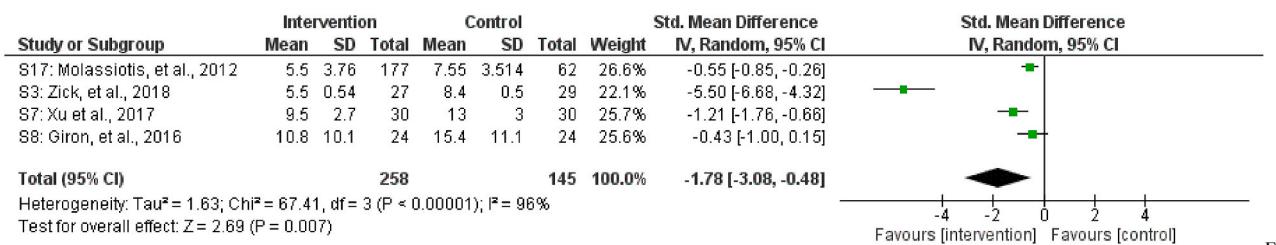
was not assessed in any of the included studies.

#### 4. Discussion

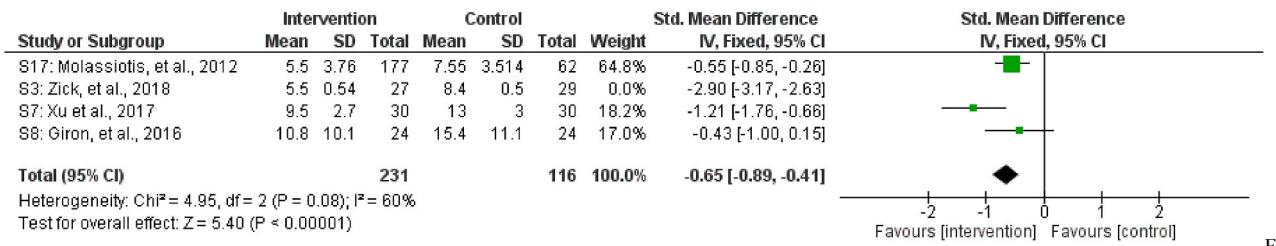
Findings from the systematic review indicated that SAS might be a promising approach for anxiety and depression management in cancer patients. It seems that the positive effect of SAS was not affected by the types of intervention and treatment duration. SAS, regardless of the modality of stimulation and the duration of intervention, can significantly decrease cancer-related anxiety and depression when compared with standard methods of treatment/care. However, due to reasons such

as the relatively small sample size and clinical heterogeneity in some sub-group comparisons and methodological flaws identified in some studies, the levels of evidence quality were suboptimal, the review findings therefore should be prudently interpreted, and research evidence on SAS for anxiety and depression management in cancer patients is not fully conclusive.

This systematic review identified positive effects of SAS on cancer-related emotional distress, which could be explained by some biological mechanisms [52]. It has been suggested that SAS can affect the secretion of Neuropeptide Y which is released by the sympathetic nervous system, which is believed to play a vital role in decreasing emotional distress



Fig

**a: Forest plot: before removing S3 (Zick, et al., 2018)**

Fig

**b: Forest plot: after removing S3 (Zick, et al., 2018)****Fig. 8.** Forest plots for the comparisons of “mid-term duration (4–8 weeks): SAS versus standard methods of treatment/care (depression)”.

[53]. SAS can also increase the release of adrenocorticotropic hormone,  $\beta$ -endorphins, neurotransmitters serotonin, norepinephrine and dopamine, all of which are key targets in the treatment of emotional distress including anxiety and depression [54,55].

This study showed that variations in modality and treatment duration of SAS did not contribute to any significant difference in the treatment effects for both anxiety and depression when compared with standard methods of treatment/care. Given the limited number of studies, the SAS was only categorised into two modalities including acupressure (therapists-led acupressure and patient-administrated acupressure) and acupuncture for the subgroup analysis. According to the sensitivity analysis, the modality of patient-administrated acupressure may partly contribute to the sub-group comparison statistical heterogeneity as the  $I^2$  value for some comparisons decreased obviously after removing Zick et al.’ [25], Cheung et al.’ [42], and Hoang et al.’ [44] study which implemented patient-administrated acupressure at home. Well-maintained intervention fidelity is crucial for achieving satisfactory outcomes in interventional studies. Relevant strategies should be reported to assure the intervention is performed as designed, particular for the patient-administrated intervention [56].

Previously published clinical trials and systematic reviews [21, 57–59] have proved that true acupoints stimulation was more effective than the sham comparisons in improving patient outcomes, which supported the specific therapeutic effects of true SAS. However, sub-group comparisons in this review did not reveal statistically significant difference between the true and sham SAS. Design of the sham comparisons might partially contribute to the insignificant between-group difference. To distinguish the specific therapeutic effects of SAS from its non-specific effects, ten studies included in this review [28,29,35–39,43–45] explored the placebo effect of SAS by using a sham comparison, which indicated faked acupoints stimulation [57]. All the nine studies located the sham acupoints (the “non-acupoints”) away from the true acupoints used in the true SAS group. However, it was difficult to ensure that all the selected non-acupoints are properly identified given only two studies clearly stated that the sham points were located away from meridians.

Safety of SAS has been well analysed in a previous systematic review [60], which suggested that serious acupuncture-related side events were rare, however, acupuncture is not entirely risk-free in practice. Comparing with acupuncture, acupressure is easily accepted given its non-invasive nature with less side effects [57]. In this systematic review, the reported side effects were mild reactions such as skin irritation and

dizziness. Although dizziness is generally a mild adverse event, potential risks (e.g., accidental falls) associated with dizziness should be noted especially for elderly patients and patients who receiving treatment in clinical settings as they would leave soon after the treatment. The assessment of adverse events was unsatisfactory as half of included studies failed to include safety assessment as one of the outcomes. Approaches used for collecting and analysing the events were also seldom reported in the included studies. All the included studies did not assess the causality between the adverse events and the intervention.

This systematic review findings provided the most updated research evidence that SAS can play a promising role in managing emotional distress in cancer patients. However, a definite conclusion cannot be drawn due to the suboptimal evidence quality and the limitations of this review itself. Firstly, some methodological issues exist in some of the analysed studies, for example, description of the random assignment sequence in some studies were ambiguous; and the credibility assessment of blinding after the completion of the trial was not reported in almost all the studies with sham group design. All of which may affect the strength of the evidence as effects size of the analysed studies would be overestimated with the unsatisfactory methodological quality [61]. Meanwhile, language bias cannot be excluded as only English and Chinese articles were included. In addition, within each subgroup analysis, further sub-group analysis (e.g., measures for anxiety and depression, frequency of the intervention) was not performed due to the limited quantity of available studies.

## 5. Implication for future research and practice

Firstly, more details of the SAS protocols should be elaborated, including the stimulation modality, practitioner, intervention dosage (duration, frequency and number of sessions), and the selection of acupoints and its rationales, for both the true and sham interventions. Secondly, design of sham SAS should be more reasonable. The design of sham comparison should be determined by considering the study objectives, participants and the nature of health outcomes to be assessed [57]. For example, if a study aimed to examine the specific effects of some particular acupoints, the protocols of true and sham group should be the same except for acupoint formula. Moreover, apart from the subjective outcomes (e.g., questionnaires and scales), some objective measures like biomarkers [62] could be considered in future studies as patients’ expectations to treatment could affect the results of subjective outcomes, particular for studies without adequate blinding

and/allocation concealment [63]. Although blinding of practitioner is difficult to reach in clinical trials using manual SAS, a double-blind design for patients and outcome assessors is feasible. Credibility of blinding should be examined in future studies. Finally, adverse events as a safety outcome, as well as the causality between adverse events and SAS should be assessed and reported in future studies by following relevant guidelines such as the Guidelines for Case Reported of Adverse Events Related to Acupuncture [64].

## 6. Conclusion

This systematic review provided updated research evidence that SAS might be a promising approach to improving anxiety and depression in cancer patients. Given the methodological concerns identified in some included studies as well as the significant clinical heterogeneity and relatively small sample size for some sub-group analyses, current evidence on SAS for cancer-related emotional distress is not fully conclusive. More rigorously designed RCTs with appropriate sham comparisons are needed to generate high-quality evidence.

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## Authors' contributions

**Wang T:** study conception and study design, literature search, data extraction and analysis, and manuscript drafting and revision; **Tan JY:** study conception and design, data interpretation, and manuscript drafting and revision; **Yao LQ:** literature search, data extraction, and manuscript revision; **Cheng HL, Zhao I, Eliseeva S and Polotan MJ:** study conception and design, and manuscript revision; study conception and design, and manuscript revision.

## Data availability

Data analysed in this review were all extracted from the original published studies (those included in this review). All data relevant to the study are included in the article.

## Patient and public involvement

No patient involved.

## Declaration of competing interest

The authors declare that there is no any conflict of interests regarding the publication of this paper.

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