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Somatic acupressure for the fatigue-sleep disturbance-depression symptom cluster in breast cancer survivors: A phase II randomized controlled trial

Meng-Yuan Li [a], Stephen Wai Hang Kwok [b,c], Jing-Yu (Benjamin) Tan [c], Daniel Bressington [c], Xian-Liang Liu [a], Tao Wang [a,*], Shun-Li Chen [d,**]

[a] School of Nursing, Faculty of Health, Charles Darwin University, Brisbane Centre, 410 Ann Street, Brisbane, QLD, Australia
[b] Murdoch University, Harry Butler Institute, Perth, WA, Australia
[c] School of Nursing, Faculty of Health, Charles Darwin University, Ellengowan Drive, Darwin, NT, Australia
[d] The Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Luzhou, Sichuan, 646000, PR China

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ABSTRACT

Objective: To evaluate the feasibility of the somatic acupressure (SA) for managing the fatigue-sleep disturbance-depression symptom cluster (FSDSC) among breast cancer (BC) survivors and its preliminary effects.
Methods: In this Phase II randomized controlled trial (RCT), 51 participants were randomised evenly into the true SA group, sham SA group, and usual care group. All the participants received usual care. The two SA groups performed additional true or sham self-acupressure daily for seven weeks. The primary outcomes related to the assessment of participants' recruitment and compliance with study questionnaires and interventions. Clinical outcomes assessed the preliminary effects of SA on fatigue, sleep disturbance, depression, and quality of life. Semi-structured interviews were undertaken to capture participants' experiences of participating in this study. The statistical effects of the intervention on the outcomes were modelled in repeated measures ANOVA and adjusted generalized estimating equations.
Results: Forty-five participants completed the SA intervention. No adverse events were reported. Over 85% of the participants could sustain for 25 days or more and 15 min or more per session, but the adherence to the intervention requirement was yet to improve. The group by time effect of the FSDSC and depression were significant ($p < 0.05$). Qualitative findings showed that participants positively viewed SA as a beneficial strategy for symptom management.
Conclusions: The SA intervention protocol and the trial procedures were feasible. The results demonstrated signs of improvements in targeted outcomes, and a full-scale RCT is warranted to validate the effects of SA on the FSDSC.

1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in females globally, with a staggering 2.3 million new cases reported in 2020, and cases are anticipated to reach approximately 4.4 million by 2070 (Soerjomataram and Bray, 2021). The progress in cancer screening, diagnosis, treatment and care has significantly advanced and over 90% of patients with BC are expected to survive at least five years post-diagnosis (Siegel et al., 2022). However, BC survivors often experienced a range of physical and emotional symptoms due to the lengthy cancer experience and adjuvant therapy-related side effects. Depression, fatigue, and sleep disturbance are three commonly reported symptoms and frequently coexist as a cluster among BC survivors, with an incidence of the fatigue-sleep disturbance-depression symptom cluster (FSDSC) being reported of up to 84% (He et al., 2022; Ho et al., 2015). The high prevalence of the FSDSC across the cancer trajectory synergistically impacts the cancer survivors' physical and mental health well-being, deteriorating their QoL, increasing financial burden and

* Corresponding author. School of Nursing, Faculty of Health, Charles Darwin University, Brisbane Centre, 410 Ann Street, Brisbane, QLD, Australia.
** Corresponding author. The Affiliated Hospital of Southwest Medical University, Luzhou No.25 Taiping Street, Jiangyang District, Luzhou City, Sichuan Province, China.
E-mail addresses: mengyuanli@students.cdu.edu.au (M.-Y. Li), stephen.kwok@murdoch.edu.au (S.W.H. Kwok), benjamin.tan@cdu.edu.au (J.-Y.(B. Tan), daniel.bressington@cdu.edu.au (D. Bressington), daniel.liu@cdu.edu.au (X.-L. Liu), alison.wang@cdu.edu.au (T. Wang), chen1054633477@163.com (S.-L. Chen).

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utilization of healthcare resources, as well as impeding their adherence to treatment and follow-up (Bower, 2014; Fiorentino et al., 2011; He et al., 2022; Ho et al., 2015; So et al., 2021).

The adoption of pharmacological interventions to manage the FSDSC can be hindered by a range of major concerns over medication use such as daytime drowsiness, dependence on and tolerance to drugs, risk of falls and fractures, and drug-to-drug interactions with concurrent anti-neoplastic regimens (Fiorentino et al., 2011). Moreover, pharmacologic agents are tailored to manage a limited number of symptoms individually instead of targeting the composite symptom cluster (Chan et al., 2020; Wong et al., 2023). Therefore, efforts have been made to explore some alternative non-pharmacological solutions including the cognitive-behavioral therapy (CBT), complementary and alternative medicine (e.g., acupuncture, yoga), physical activity, mindfulness-based arts interventions (e.g., meditation), which have demonstrated encouraging results in the management of symptom clusters, including the FSDSC (Fiorentino et al., 2011; Jain et al., 2015; Wong et al., 2023). Nonetheless, these non-pharmacological interventions are not without barriers and side effects in their implementations. Such interventions require a substantial amount of time to implement (e.g., yoga, CBT and meditation), and can be costly since they need to be implemented in professional settings and require extensive support by qualified practitioners. Therefore, they are unlikely to be a regular self-practice at home. For invasive interventions such as acupuncture, they carry risks of injuries such as soft tissue infection, pain and subcutaneous ecchymosis, which need clinical care and supervision (Xu et al., 2013). Some interventions (e.g., physical activities) are energy-consuming and can have low participation rates as some cancer survivors who are intolerant of fatigue may not prefer it (Bower, 2014). To improve FSDSC management, an intervention should not only offer promising effects on the symptoms, but also be easy to access, safe, inexpensive, and self-practicable, given the long-term increasing burden of symptoms and finance throughout the illness trajectory of cancer survivors.

Somatic acupressure (SA) has been practiced for centuries and is a form of traditional Chinese medicine (TCM) that applies pressure on acupoints by using the fingers or thumbs (Brown et al., 2009). SA affects various physiological pathways that may be associated with the FSDSC. In TCM, the *yin-yang* theory, the meridians theory and the *zang-fu* organs theory suggest that the stagnation of Qi (life energy) in typical body regions and organs can be alleviated by stimulating specific acupoints distributed along different meridians, restoring *yin* and *yang*, subsequently altering the symptom experience (Weaver, 1985; White and Ernst, 2004). As outlined in inflammatory theory, fatigue (the core symptom of the FSDSC) can be induced by inflammatory cytokines through the autonomic nervous system and/or the hypothalamic-pituitary-adrenal axis (Bower, 2014; Cleeland et al., 2003). The role of SA in regulating proinflammatory cytokines has also been demonstrated in current research, highlighting its potential in managing the FSDSC (Bower et al., 2011). Clinical research (Liu et al., 2020; Tan et al., 2021; Wang et al., 2023) also demonstrated the promising effects of SA on cancer survivors' fatigue, sleep distress, and depressive mood. Studies that have adopted SA to manage symptom clusters, let alone the FSDSC, in cancer survivors are scant. In a recent systematic review conducted by So et al. (2020) on nonpharmacological interventions for symptom cluster management in cancer survivors, only three of the thirteen randomized controlled trials (RCTs) (Jiao et al., 2015; Mao et al., 2018; Yeh et al., 2016) utilized an acupoint stimulation intervention, and none of the three RCTs specifically targeted the FSDSC. In addition, the relevant evidence is limited due to methodological weaknesses. Of the three RCTs, none explored the non-specific (placebo) effects of acupoint stimulation by including a sham comparison. Further, the quality of reporting of the RCTs was unsatisfactory (e.g., there are insufficient details on random sequence generation and allocation concealment procedures).

To develop and evaluate an evidence-based SA intervention for managing the FSDSC in BC survivors, our research team proposed a three-phase research program based on the Medical Research Council Framework for Developing and Evaluating Complex Interventions (Skivington et al., 2021). Phase I involved the protocol development for the SA intervention, taking into account current research evidence, TCM theories, neurophysiological theories, practice standards, and consensus among experts (Tan et al., 2022a). Phase II involved a pilot study with a nested qualitative process evaluation, which aimed to explore the feasibility of a RCT using SA intervention to manage the FSDSC in BC survivors and test the preliminary effects (Wang et al., 2022). A phase III RCT will be undertaken afterwards to assess the SA intervention's clinical efficacy, safety, and cost-effectiveness in managing FSDSC in BC survivors. This paper reports the feasibility outcomes of the SA intervention and the clinical outcomes of the Phase II RCT that could inform the design of the Phase III RCT.

2. Methods

2.1. Study design

This phase II trial was designed as a partially blinded, three-arm, sham-controlled RCT, which included a semi-structured interview after the intervention. Detailed study protocol was reported separately (Wang et al., 2022). Participants were recruited from the outpatient clinic of the Affiliated Hospital of Southwest Medical University in Sichuan Province, China, between February 2021 to March 2022. This trial was approved by both the Clinical Trial Ethics Committee at the study site (KY2019039) and the Human Research Ethics Committee at Charles Darwin University (H19017) and has been registered at Clinicaltrials.gov (NCT04118140).

2.2. Phase II randomized controlled trial

2.2.1. Participants, randomization and blinding

Eligible participants were those who: (1) were adult female patients with BC (stage I- IIIa) without any distant metastasis; (2) have undergone adjuvant chemotherapy for a minimum of one month and a maximum of three years; (3) suffered at least a moderate level of the FSDSC with the fatigue, sleep disturbance and depression all scoring $\geq$4 on a 0–10 point scale (0 = 'no symptom', 10 = 'worst symptom') within the past month; (4) had no scheduled cancer treatment (chemotherapy and radiotherapy) across the study period; and (5) consented to participate in the study (Wang et al., 2022). Participants were ineligible if they: (1) were taking any medications to alleviate fatigue, sleep disturbance and depression; (2) had received acupressure treatment within the past six months; (3) had severe weakness and/or cognitive impairment that prevented them from following study procedures; and (4) were participating in other studies (Wang et al., 2022).

As this pilot study was exploratory and mainly focused on feasibility assessment, twelve participants per group are recommended (Julious, 2005). An attrition rate of 30% was considered according to a similar study (Zick et al., 2016), the sample size was therefore 51 in total, with 17 in each group.

Participants were randomized into three groups (true SA group, usual care group and sham SA group) by a fixed block randomization method with a 1:1:1 ratio. An independent statistician without any involvement in the study was responsible for keeping the computer-generated randomization sequences. Once participants signed consent and completed the baseline assessment, their group assignment was given to the research assistant by the independent statistician. As the recruited participants were SA intervention-naive, group allocation was masked from the participants in the true and sham intervention groups.

The partially blinded outcome assessment for those in the intervention groups was also maintained as the patient-reported questionnaires used in this study were self-rated. The statistical analysis was performed by a neutral statistician who was unaware of group allocation (Wang et al., 2022).

2.2.2. Study intervention

All participants received usual care with an educational booklet. The education booklet providing practical recommendations and management strategies on the cancer-related symptoms (such as nutrition consultation and energy conservation) which was developed based on current evidence-based sources (Berger et al., 2015; Jain et al., 2015; Li et al., 2012). Those participants in the true SA intervention group received a seven-week self-administered SA intervention at eleven acupoints with a daily 36-min session at their convenient time. The participants pressed each acupoint using their fingers for 2 min, evoking the sensation of "*Deqi*". The participants assigned to the sham SA group conducted light self-acupressure at eleven non-acupoints, with the same dosage as the true SA group, but without the sensation of "*Deqi*". Detailed information regarding the intervention was presented in the evidence-based SA intervention protocol paper (Tan et al., 2022a). Prior to the implementation of the intervention, participants allocated to the true and sham SA groups were fully trained until their techniques were fully assessed by the acupuncture practitioner and/or the research assistant. To further support participants' self-acupressure at home, a home learning package with visual materials was provided (Wang et al., 2022).

2.2.3. Study procedures

The research assistant approached the potential participants for eligibility screening, signed consent forms and conducted baseline assessments before the group allocation. Both the participants allocated to the true SA and sham SA groups were required to attend the separate acupressure training sessions provided by the research assistant (Wang et al., 2022). Afterwards, a return demonstration was required to ensure that participants could perform the SA correctly and fluently. During the seven-week SA intervention, each participant was instructed to fill out a daily log detailing the frequency, duration, and side effects of self-acupressure sessions at home. In addition, the research assistant called the participants weekly to remind them to complete the daily intervention, collect information about any adverse events, and answer any questions related to SA practice (Wang et al., 2022). Clinical outcomes were collected by the research assistant using patient-reported questionnaires in a face-to-face way at baseline and telephone surveys immediately after the intervention.

2.2.4. Outcome measures

The feasibility outcomes throughout the study process and the clinical outcomes related to the effects of SA on the FSDSC and QoL were specified in the previous methodological paper (Wang et al., 2022). A summary is presented below.

2.2.4.1. Baseline socio-demographic and clinical data. An investigator-designed questionnaire was used to collect participants' socio-demographic data (e.g., occupation, educational background, age) and medical information (e.g., cancer stage, type of BC surgery).

2.2.4.2. Feasibility outcomes. The primary outcomes were feasibility outcomes throughout the study process, including:

(1) Feasibility of subject recruitment: 1) time taken to complete subject recruitment; 2) eligibility rate; 3) recruitment rate; 4) attrition rate; 5) retention rate; and 6) reasons for participants' withdrawal from the study.
(2) Feasibility of the study questionnaires: percentage of missing value at both item-level and scale-level for each questionnaire used in this study, which included the Hospital Anxiety and Depression Scale (HADS), the Functional Assessment of Cancer Therapy-Breast (FACT-B), the Multidimensional Fatigue Inventory (MFI) and the Pittsburgh Sleep Quality Index (PSQI).
(3) Acceptability of the study intervention: 1) the total duration of SA intervention performance by participants.; 2) the duration of each acupressure session; and 3) participant feedback, satisfaction and experiences related to study participation and the intervention they received were collected through semi-structured interviews after the intervention.
(4) Adverse events of SA were recorded, assessed and managed across the study.

2.2.4.3. Clinical outcomes.

(1) Fatigue: The Chinese MFI (20 items) was used to evaluate fatigue, along with higher scores indicating more severe fatigue. The MFI was demonstrated as a valid and reliable measure of fatigue in Chinese cancer survivors (Tian and Hong, 2012).

(2) Sleep disturbance: The PSQI with 19 items was used to assess sleep disturbance. Each item is graded from 0 to 3, and a higher global score indicates more sleeping difficulty. The Chinese PSQI has shown satisfactory psychometric properties in Chinese BC survivors (Ho and Fong, 2014).

(3) Depression: The depression subscale (HADS-D) of HADS was used to measure depression. Depression is likely to be indicated by a higher score on the seven items of the HADS-D. The HADS-D has been validated as a reliable screening tool for depression in Chinese cancer survivors, with satisfactory psychometric properties. (Li et al., 2016).

(4) QoL: The FACT-B was used to assess QoL. It features a 5-point scale (0–4), and a higher score indicating a better QoL (0–148). The FACT-B has been proven reliable and valid among Chinese BC survivors (Wan et al., 2007).

2.3. Semi-structured interviews

After the completion of the intervention, participants were selected purposefully based on their socio-demographic characteristics (e.g., age, educational background) and different performances (e.g., adherence level to the intervention) in the study intervention. Participants were interviewed individually within a month of completing the intervention based on their voluntary. Due to the COVID-19 pandemic restrictions, the interviews were conducted in a designated hospital room over the phone in Chinese by an experienced research assistant. An interview guide (Wang et al., 2022) with open-ended questions and prompts was used to elicit the participants' overall experience of participating in this study or receiving the SA intervention. Each interview lasted around 30 min. All the interviews were recorded with the participant's consent, and the recordings were transcribed verbatim into written form within 24 h after the interview, which were reviewed by another researcher (TW) to ensure the accuracy and completeness of the content.

2.4. Data analysis

Data analysis was completed using IBM SPSS 25.0. Descriptive statistics were computed to summarize the feasibility outcomes. Fisher's exact tests and Kruskal-Wallis tests were conducted to compare between-group differences in categorical and continuous variables respectively, for the demographic, clinical data at baseline (Wang et al., 2022). The significance level was set at 0.05 in two-tailed test. To generate the FSDSC composite score, the MFI, PSQI, and HADS-D total scores were rescaled into 0–10, respectively; then the average of the three scale scores was taken for each participant (Hoang et al., 2022). Repeated measures ANOVA was used to test the effect of group on outcome variables (MFI, PSQI, HADS-D, FACT-B and FSDSC composite

score) by baseline and post-test. A mixed effects regression model was constructed using Generalized Estimating Equations (GEE), which aimed to examine: (1) group, time and group by time effects on target outcome; (2) estimate the population marginal means of the targeted outcome by groups and time points, while remaining robust for mis-specified working correlation structure (Koper and Manseau, 2009; Wang, 2014). The adjusted GEE model was built to identify the differences in the parameter estimates of outcome variables with regard to group, time, group by time, and the selected covariates. Socio-demographic or clinical characteristics moderately associated with the outcomes were considered potential covariates (Schober et al., 2018). It is deemed "moderate" if the absolute value of the correlation coefficient between two variables is greater than 0.3, and "strong" if it is greater than 0.7 (Schober et al., 2018). Effect sizes were computed for post-tests comparing the true SA group with either the sham SA group or the usual care group. The cut-offs of effect sizes proposed by Cohen (1992) were adopted regarding large (d = 0.8), medium (d = 0.5), and small (d = 0.2) effects.

Thematic analysis was used to analyze the interview data, including the iterative processes of coding, creating categories and abstraction (Braun and Clarke, 2006). The analysis was performed by two authors (MYL and TW). After repeatedly reading each transcript, 16 data sets were coded by MYL manually on the Excel spreadsheet by annotating notes on the participants' sentences and coloring the coding to highlight potential meaning units. Those relevant codes with similar contexts or concepts were grouped to form a range of candidate themes. Then, each potential theme was described in detail and compared at the level of original codes and phrases. Ongoing analysis refined the specific definition of each theme and additional quotes that embody the participants' experiences supporting each subtheme. Necessary discussions were conducted between MYL and TW during the whole data analysis process to achieve consistency.

3. Results

3.1. Clinical trial results

3.1.1. Baseline characteristics

The baseline characteristics of the participants (n = 47) are presented in Table 1. The enrolled participants were 51 (SD = 7.39) years of age on average. Most of the participants (n = 35, 74%) were diagnosed with stage I and II BC, and over 80% (n = 38) had previously undergone regular chemotherapy cycles while the rest had only completed initial adjuvant chemotherapy and did not continue with regular cycles. There were no significant differences in socio-demographic or clinical characters between groups except for participants in the true SA group, who had a higher FSDSC composite score than the usual care group and the sham SA group ($p = 0.038$).

3.1.2. Feasibility outcomes

3.1.2.1. Feasibility of subject recruitment. Three hundred and seventy-two potential participants were assessed for study participation, and 57 met the inclusion criteria during the 13-month recruitment period (57/372, 15.32%). However, six participants refused, and 51 participants were finally included and randomized (51/57, 89.47%). Four of them were removed from the analysis given their conditions deteriorated before the implementation of the SA intervention, and two dropped out due to not returning to the hospital for post-intervention assessment (Fig. 1). Thus, the attrition rate was 11.76% (6/51). The missing posttest values for the two dropouts were imputed by the Last Observation Carried Forward method.

3.1.2.2. Feasibility and acceptability of the study questionnaires. Missing values at item-level were noted in the HADS, MFI and PSQI

Table 1
Demographic and clinical characteristics at baseline.

	True SA (n = 16)	Sham SA (n = 15)	Usual care (n = 16)	Statistics	*p*
Age (Median/IQR)	50 (6.75)	51.5 (9.5)	53.5 (13.25)	2.130[a]	0.345
Education (n, %)					
Primary school	4 (25)	6 (40)	6 (37.5)	3.100[b]	0.842
Junior high school	5 (31.3)	6 (40)	4 (25)		
High school or secondary school	3 (18.8)	2 (13.3)	3 (18.8)		
College, university or above	4 (25)	1 (6.7)	3 (18.8)		
Occupation (n, %)					
Working class	12 (75)	13 (86.7)	13 (81.3)	0.741[b]	0.895
Retired	4 (25)	2 (13.3)	3 (18.8)		
Monthly household income (n %)					
CNY ≤6000	7 (50)	10 (66.7)	6 (37.5)	2.604[b]	0.295
CNY >6000	7 (50)	5 (33.3)	10 (62.5)		
Medical costs payment (n, %)					
Public health care or other	3 (18.8)	3 (20)	2 (12.5)	2.565[b]	0.645
Social medical insurance	6 (37.5)	5 (33.3)	3 (18.8)		
New rural cooperative medical care	7 (43.8)	7 (46.7)	11 (68.8)		
Residential area (n, %)					
Rural	3 (18.8)	6 (42.9)	4 (25)	2.168[b]	0.359
Urban	13 (81.3)	8 (57.1)	12 (75)		
Breast cancer stage (n, %)					
Stage I	7 (43.8)	5 (33.3)	7 (43.8)	0.713[b]	0.986
Stage II	5 (31.3)	6 (40)	5 (31.3)		
Stage III	4 (25)	4 (26.7)	4 (25)		
Surgery type (n, %)					
Modified radical mastectomy	4 (25)	3 (20)	5 (31.3)	3.733[b]	0.772
Breast cancer simple excision	6 (37.5)	5 (33.3)	2 (12.5)		
Conservation Surgery	5 (31.3)	6 (40)	8 (50)		
Other	1 (6.3)	1 (6.7)	1 (6.3)		
Received regular chemotherapy cycles ever (n, %)					
No	3 (18.8)	2 (13.3)	4 (25)	0.741[b]	0.895
Yes	13 (81.3)	13 (86.7)	12 (75)		
Chemotherapy regimens * (n, %)					
AC/ACT	3 (18.8)	3 (20)	3 (18.8)	3.017[b]	0.861
EC/EC-T/ECTX	6 (37.5)	8 (53.3)	8 (50)		
Other	4 (25)	2 (13.3)	1 (6.3)		
NA	3 (18.8)	2 (13.3)	4 (25)		
Received radiotherapy ever (n, %)					
No	8 (50)	5 (33.3)	4 (25)	2.179[b]	0.356
Yes	8 (50)	10 (66.7)	12 (75)		
Family history of disease (n, %)					
No	12 (75)	11 (73.3)	8 (50)	2.610[b]	0.301
Yes	4 (25)	4 (26.7)	8 (50)		
Diabetes (n, %)					
No	13 (81.3)	14 (93.3)	13 (81.3)	1.238[b]	0.671
Yes	3 (18.8)	1 (6.7)	3 (18.8)		
Hypertension (n, %)					
No	13 (81.3)	13 (86.7)	9 (56.3)	3.946[b]	0.173
Yes	3 (18.8)	2 (13.3)	7 (43.8)		
Completed cycles of chemotherapy (Median/IQR) *	8 (4)	8 (2)	8 (7)	0.557 [a]	0.757
FSDSC composite (Median/IQR)	0.60 (0.18)	0.54 (0.15)	0.47 (0.19)	6.540[a]	0.038
MFI –Total (Median/IQR)	51 (8)	50 (8)	48 (4.75)	3.162[a]	0.206

(*continued on next page*)

Table 1 (*continued*)

	True SA (n = 16)	Sham SA (n = 15)	Usual care (n = 16)	Statistics	*p*
PSQI–Total (Median/IQR)	11 (4.75)	10 (5)	9.5 (3.75)	2.767[a]	0.251
HADS-D (Median/IQR)	4.5 (4.75)	4 (4)	3 (3.5)	3.089[a]	0.213
FACT-B-Total (Median/IQR)	108.9 (19.085)	107.67 (8)	116.75 (11.423)	5.830[a]	0.054
Fatigue within last month (Median/IQR)	5 (2)	5 (2)	4.5 (1.75)	0.376[a]	0.829
Sleep disturbance within last month (Median/IQR)	5.5 (2)	5 (2)	4 (1.75)	4.841[a]	0.089
Depression within last month (Median/IQR)	4 (1.75)	4 (1)	4 (1)	2.309[a]	0.315

Note: * For those with regular chemotherapy cycles; SA=somatic acupressure; Chemotherapy regimens: A=Adriamycin, E=Epirubicin, C=Cytoxan, T=Taxol or Taxotere. NA= not applicable; a= Kruskal Wallis test; b=Fisher exact test.

questionnaires at both the baseline and post-intervention assessments, ranging from 2.1% to 8.9%. However, 89.1% of participants at baseline and 97.8% of participants at post-intervention did not respond to one question ("I am satisfied with my sex life") in the FACT-B. More than 80% of the participants completed all items for each questionnaire except the FACT-B questionnaire. The missing items' results at scale-level and item level for each questionnaire are summarized in Table 2.

3.1.2.3. Participants' adherence and acceptability to the study interventions. In both the sham SA and true SA groups, the total number of sessions performed and the duration of each session was far below the specified duration in the intervention protocol (requiring 49 sessions in total, each lasting 36 min). Only 37.5% of participants performed for 30 days or above, while a session of no less than 25 min was only 26.3% in the true group. Similar findings were found in the sham SA group (Table 3).

3.1.2.4. Safety of SA. No adverse events were reported.

3.1.3. Intervention effects on the FSDSC and QoL

In the repeated measures ANOVA (Table 4a), the effect size of FSDSC between the true SA group and the usual care group at posttest was small (partial eta squared = 0.002). The within-subject effect of time on the FSDSC composite score was significant ($p < 0.001$), but there was no significant between-subject effect. After 7 weeks, the improvement of FSDSC in true SA was the greatest as evidenced by the significant group by time effect (True SA by Baseline) in GEE (Table 4b). But the effect size on FSDSC between true SA and control at posttest was small (Cohen's $d = 0.075$) (Table 4c). In all groups, the estimated marginal means of sleep quality (PSQI), depressive symptoms (HADS-D) and fatigue (MFI) decreased, and the QoL (FACT-B) increased (Table 4c). But the improvements in true SA were greater for depression and fatigue as evidenced by the group by time effects in GEE (Table 4b). Yet, the effect sizes (Cohen's d) between groups at posttest were small (Table 4c). Significant improvement in FACT-B over time (B = −4.5, 95%CI [−7.61, −1.4], $p = 0.0045$) indicated an overall improvement in QoL (Table 4b). More severe depressive mood in the last month (0–10-point scale) was associated with worse QoL ($p = 0.0034$), supporting the conceptual framework that depressive mood is associated with lower QoL among BC patients. As expected, the sleep disturbance scores over the last month (0–10-point scale) was associated with worse sleep quality in terms of PSQI ($p < 0.001$). Furthermore, the working class and those who received public health care or other health benefits were associated with less depressive symptoms when compared with the retired class and those covered by new rural cooperative medical care, suggesting that economic factors may have contributed to depressive symptoms among the participants.

3.2. Semi-structured interview findings

Sixteen participants (nine from the true SA group, one from the usual care group and six from the sham SA group) were interviewed (Table 5). Four themes were generated. The first theme "Perceptions of TCM and SA" contained two subthemes, which were "viewing TCM as a promising approach for symptom management with fewer side effects" and "holding high expectations of the effects of SA on FSDSC management". All participants hold a positive attitude toward acupressure in managing cancer-related symptoms: *"I am definitely looking forward to acupressure with 10 score effect, is the best!" [T9]*. The second theme entitled "Perceptions of the SA's effects" encompassed two subthemes, including "SA's effects on fatigue, sleep disturbance and emotional distress" and "SA's effects on other symptoms/health conditions". The theme provided insight into participants' satisfaction with the acupressure for their cancer-related symptoms and health conditions: *"I still believe that acupressure works, and I feel a little comfortable after self-acupressure. It's okay and I can still feel some [symptoms] relief. It's effective." [S6]*. The third theme was "Experience of completing the questionnaires" which comprised four subthemes: "easy to understand and answer", "being burdensome with too many questionnaires' items", "well reflecting the FSDSC", and "completing questionnaires through telephone is acceptable". There were minor complaints about the number of questions in some questionnaires, but overall, the selected questionnaires were feasible and could be easily understood and answered, along with accurately capturing the targeted symptoms*: "These questions (in questionnaires) are exactly described as what I felt, and we have the same problems, and they seem to be saying things directly to my heart." [T6]*. The fourth theme, "Experiences of self-practicing SA," comprised facilitators and barriers to participants' adherence to the intervention. Some barriers were encountered with self-practicing such as unstable acupressure skills, insufficient monitoring strategies, and burdensome daily activities or work. However, facilitators/suggestions were also highlighted by some participants such as using social media and regular reminders: "…. *if there is a WeChat group or something like that, you can remind us frequently or send some pictures of acupoint locations to enhance our skills. I think it would be better, because I feel that my memory is not very good, and no one reminds me for a while and then I forget it." [S1]*. All the themes, sub-themes and interviewees' quotes are detailed in Table 6.

4. Discussion

4.1. Main findings

This study aimed to evaluate the feasibility and preliminary effects of SA intervention protocol for improving the FSDSC in BC survivors through a rigorously designed phase II RCT with sham-SA comparison and partial blinding design. This study was unique that the true and sham SA intervention protocols were developed based on the current best available evidence. The intervention protocol was therefore deemed theoretically feasible in practice. Our findings have demonstrated that it is feasible to conduct a full-scale RCT to further explore whether the SA intervention can improve cancer survivors' outcomes. The findings showed that both the true SA group and sham SA group had improvements in fatigue, sleep disturbance and depressive symptoms independently or as a composite score. The improvement in QoL was also observed. Of which, the true SA group was found superior to sham SA in alleviating all clinical outcomes according to the estimated means in GEE models. The substantial improvements observed in all outcomes

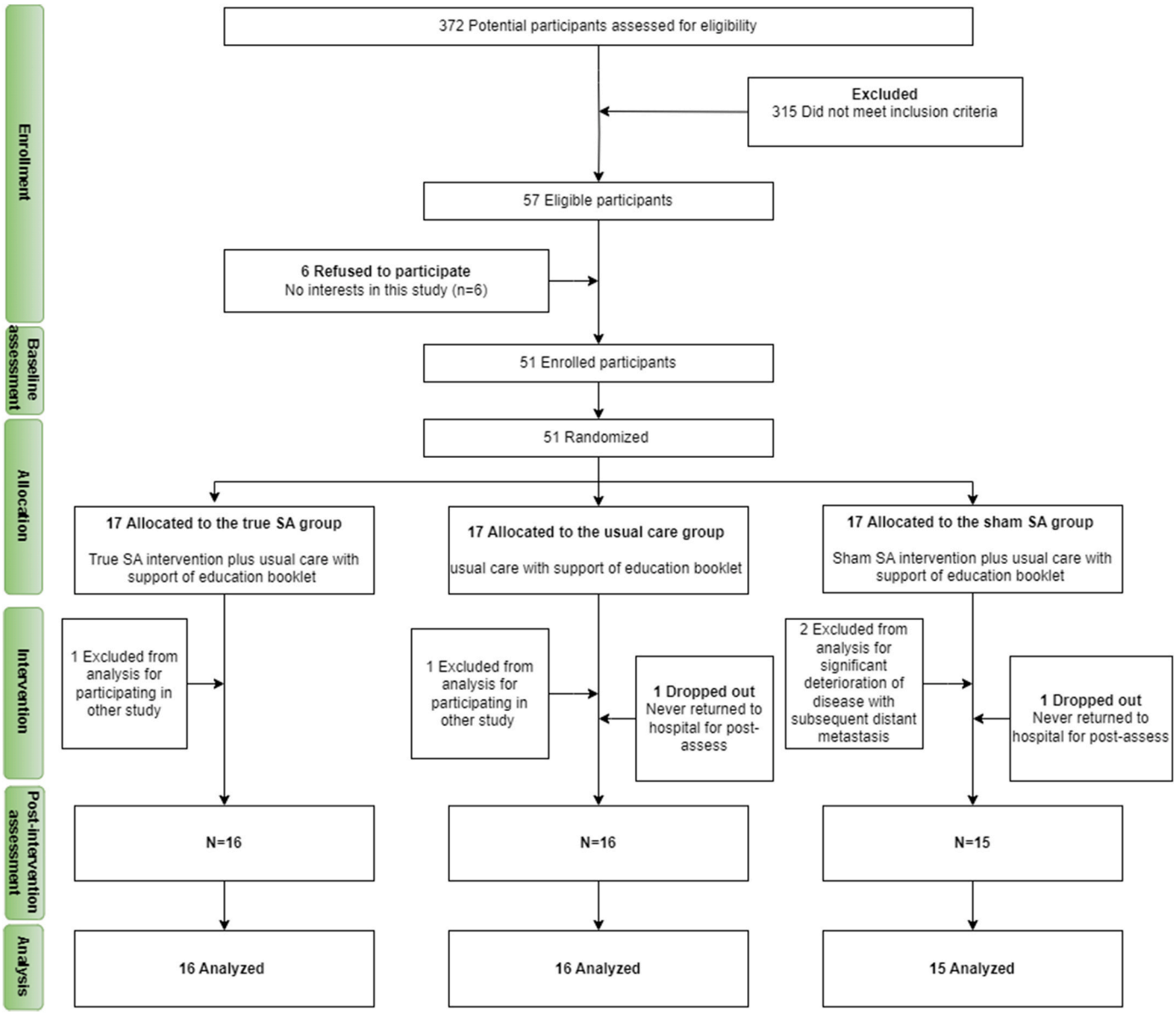

Fig. 1. The Phase II RCT flow chat.

Table 2
Number of items missing and participants responding to all items.

Scales	Baseline (n = 47)			Post-intervention (N = 45)		
	No. of missing value at item-level	No. of subjects responding to all items	No. of missing value at scale-level (n, %)	No. of missing value at item-level	No. of subjects responding to all items	No. of missing value at scale-level (n, %)
FACT-B	9	6	41 (89.1)	2	1	44 (97.8)
HADS	2	45	2 (4.3)	6	39	6 (13.3)
PSQI	5	44	3 (6.4)	2	43	2 (4.4)
MFI	3	45	2 (4.3)	8	37	8 (17.8)

Note: PSQI: Pittsburgh Sleep Quality Index; HADS: Hospital Anxiety and Depression Scale; FACT-B: Functional Assessment of Cancer Therapy-Breast; MFI: Multi-dimensional Fatigue Inventory.

for the true SA group suggest the importance of conducting a full-scale study with a sufficient sample size to examine the SA's effectiveness.

4.2. Attrition

The objectives to test the recruitment procedures and feasibility were achieved. This study's face-to-face recruitment strategy was successful, with a very high recruitment rate even during the COVID period. The high level of retention and low attrition in this study indicated enthusiasm among the BC survivors and their interest in self-practicing acupressure at home, comparable to previous studies using acupressure interventions in the management of cancer-related symptoms

Table 3
Total number of days and Duration of SA intervention in the true AT group and the sham AT group.

Total Number of Days and Duration of SA intervention		True SA group (n = 16)	Sham SA group (n = 15)
No. of days of SA interventions (n, %)	≥30 days	6 (37.5)	3 (20.0)
	25–29 days	8 (50.0)	6 (40.0)
	<25 days	2 (12.5)	6 (40.0)
Average duration of each SA session (%)	≥25 min	26.30	28.01
	15–24 min	72.36	66.33
	<15 min	1.34	5.70

Note: SA: somatic acupressure.

(Cheung et al., 2022; Hoang et al., 2022; Tan, 2017).

4.3. Missing value

The FACT-B, PSQI and HADS-D appeared to be appropriate tools to use and were completed by participants with only a small percentage of missing values except for the question ("I am satisfied with my sex life") in FACT-B. Similar issues with this question in the FACT-B were reported in the literature (Tan, 2017). Chinese conservative attitudes towards discussing sex lives may explain the high missing percentage in this question (Tan, 2017). Another reason might be the instruction ("If you prefer not to answer it, please mark this ballot box symbol and go to the next section") associated with this question (Brady et al., 1997). On the other hand, MFI has relatively high percentage of missing values at both the item-level and scale-level than the other instruments. Considering complaints regarding the burdensome of answering questionnaire items in the qualitative interview, the MFI with 20 items could be exhausting especially for those who suffer from severe fatigue (Mendoza et al., 1999). Instead, the Brief Fatigue Inventory (BFI) was designed specially to assess cancer-related fatigue with few items, making it easier for participants from a variety of educational backgrounds to understand and answer (Mendoza et al., 1999). The Chinese version of the BFI exhibited superior internal consistency and demonstrated satisfactory construct and convergent validity compared with the MFI (Wang et al., 2004). Therefore, the BFI might be more appropriate than MFI for fatigue assessment among BC survivors in the future Phase III RCT.

4.4. Acceptability

Qualitative interview results supported the utilization of the four questionnaires (FACT-B, MFI, PSQI and HADS-D), which were considered "Easy to understand and answer" and "Well reflect the FSDSC" from most participants. Almost all participants in the qualitative interview expressed that they would prefer to recommend self-acupressure to other cancer survivors since they believed that self-acupressure is an acceptable and beneficial treatment for FSDSC in cancer survivors. Additionally, none of the participants in the qualitative interviews complained about the intervention duration and the number of sessions of the intervention. Only one negative response regarding the number of selected acupoints which is hard to perform one session on the required eleven acupoints due to busy work schedules.

4.5. Adherence

The feasibility of the intervention protocol could only be determined as suboptimal given the unsatisfactory participants' adherence. Firstly, due to the COVID-19 pandemic, the study site's restricted policies have made administering participants' self-acupressure more challenging. Secondly, in line with studies of home-based interventions, the most probable explanation probably relates to including insufficient strategies for enhancing participants' self-practice at home (He et al., 2021;

Table 4a
Regression coefficients of repeated measures ANOVA and effect sizes (partial eta squared).

	Time		B [95% CI]	*p*	Partial eta squared
FACT-B total	Baseline	Intercept	115 [110.16, 119.83]	<0.001	0.981
		True SA	−7.85 [-14.69, −1.02]	0.025	0.109
		Sham SA	−6.8 [-13.75, 0.15]	0.055	0.081
		Usual care			
	Post-test	Intercept	119.5 [115.31, 123.69]	<0.001	0.987
		True SA	−4.05 [-9.98, 1.87]	0.175	0.041
		Sham SA	−4.81 [-10.83, 1.21]	0.115	0.056
		Usual care			
PSQI total	Baseline	Intercept	9.56 [8.06, 11.07]	<0.001	0.789
		True SA	1.94 [-0.19, 4.07]	0.073	0.071
		Sham SA	1.24 [-0.93, 3.4]	0.255	0.029
		Usual care			
	Post-test	Intercept	7.81 [6.04, 9.58]	<0.001	0.643
		True SA	1.25 [-1.25, 3.75]	0.320	0.022
		Sham SA	1.65 [-0.89, 4.2]	0.197	0.038
		Usual care			
HADS – D total	Baseline	Intercept	3.19 [2.04, 4.33]	<0.001	0.418
		True SA	1.56 [-0.05, 3.18]	0.058	0.079
		Sham SA	0.88 [-0.76, 2.52]	0.287	0.026
		Usual care			
	Post-test	Intercept	2.25 [1.36, 3.14]	<0.001	0.370
		True SA	−0.25 [-1.51, 1.01]	0.692	0.004
		Sham SA	−0.18 [-1.47, 1.1]	0.775	0.002
		Usual care			
MFI total	Baseline	Intercept	48 [45.26, 50.74]	<0.001	0.966
		True SA	2.87 [-1, 6.75]	0.142	0.048
		Sham SA	1.27 [-2.67, 5.2]	0.520	0.009
		Usual care			
	Post-test	Intercept	42.94 [40.09, 45.78]	<0.001	0.955
		True SA	−0.37 [-4.4, 3.65]	0.852	0.001
		Sham SA	−0.07 [-4.16, 4.02]	0.972	<.001
		Usual care			

(*continued on next page*)

Table 4a (*continued*)

	Time		B [95% CI]	*p*	Partial eta squared
FSDSC Composite	Baseline	Intercept	0.45 [0.38, 0.52]	<0.001	0.780
		True SA	0.13 [0.03, 0.23]	0.014	0.130
		Sham SA	0.07 [-0.03, 0.18]	0.169	0.043
		Usual care			
	Post-test	Intercept	0.32 [0.24, 0.4]	<0.001	0.582
		True SA	0.01 [-0.1, 0.13]	0.797	0.002
		Sham SA	0.03 [-0.09, 0.15]	0.612	0.006
		Usual care			

Note: ANOVA: analysis of variance; B: regression coefficient; 95% CI: 95% confidence interval; *p*: p value; SA: somatic acupressure; FACT-B: The Functional Assessment of Cancer Therapy – Breast; PSQI: The Pittsburgh Sleep Quality Index; HADS-D: Hospital Anxiety and Depression Scale – Depression; MFI: Multidimensional Fatigue Inventory; FSDSC Composite: Composite score of MFI, PSQI, and HADS-D.

Kawi et al., 2022). Qualitative feedback from participants revealed that personal reasons (e.g., busy work, burdensome housework, and poor memory), as well as insufficient maintenance and monitoring strategies for participants' self-acupressure at home may account for their poor compliance. Meanwhile, most participants suggested that the use of audio-visual materials in a home learning package and the most frequently utilized WeChat App would help address the above barriers and motivate them to perform SA at home. The WeChat platform was widely used in cancer management and the follow-up strategy with a telephone plus WeChat group has proven to be highly effective in adherence and satisfaction of cancer survivors (Qiao et al., 2019; Sui et al., 2020). A recommendation for future trial is therefore to have daily WeChat reminders to self-administer the SA and weekly personalized contact via WeChat or telephone over participants' preference for additional training and ongoing monitoring.

4.6. Clinical outcome analysis and sample size

The sample size for regression analysis in this study was finally 47. According to the literature (Li and Redden, 2015), a sample size larger than 40 was deemed adequate for regression and GEE. Moreover, GEE can demonstrate desirable properties when the sample size exceeds 40 in cluster-randomized trials (Li and Redden, 2015). When the sample size exceeds this threshold, the GEE estimator for the marginal mean approximately follows a multivariate normal distribution (Li et al., 2019). However, when the sample size is below 40, there could be inflated type I errors in the standard covariance estimator (the empirical sandwich estimator) of GEE (Teerenstra et al., 2010). To maintain the type I error rate at 5%, a sample size of around 30 ~ 40 for mixed models and 40 ~ 50 for GEEs is recommended (Leyrat et al., 2018).

In our GEE models, after controlling for confounders, the time effect is commonly seen as significant, which means the score improved over time in general; the group-by-time effect was significant for HADS and FSDSC and was borderline significant for MFI. It indicates that there are significant improvements in depressive symptoms (HADS) and the symptom cluster (FSDSC), as well as borderline significant improvements in fatigue (MFI). The baseline differences, e.g., in FSDSC ($p < 0.05$), FACT-B-Total, and Sleep disturbance ($p < 0.01$) after block randomization could not be taken into account in Cohen's d at posttest. With a small sample, block randomization is difficult to balance unobserved confounders (Efird, 2011; Suresh, 2011), and a small sample is

Table 4b
Regression coefficients of GEE models with respect to the effects on outcome variables.

		B [95% CI]	*p*
FACT-B total	(Intercept)	136.3 [125.68, 146.92]	<0.001
	Sleep disturbance score, last month (0–10)	−0.48 [-2.02, 1.06]	0.54
	Depressive mood score, last month (0–10)	−3.14 [-5.23, −1.04]	0.0034
	True SA	−2.82 [-8.42, 2.79]	0.32
	Sham SA	−5.8 [-12.15, 0.56]	0.074
	Baseline	−4.5 [-7.61, −1.4]	0.0045
	True SA by Baseline	−3.8 [-9.78, 2.18]	0.21
	Sham SA by Baseline	−1.99 [-8.33, 4.35]	0.54
PSQI total	(Intercept)	1.96 [-2.48, 6.4]	0.39
	Completed cycles of chemotherapy	0.28 [-0.28, 0.84]	0.32
	Sleep disturbance score, last month (0–10)	0.84 [0.36, 1.32]	<0.001
	Received regular chemotherapy cycles ever: No	0.47 [-4.12, 5.05]	0.84
	Chemotherapy regimen: AC/ACT	0.8 [-2.15, 3.75]	0.6
	Chemotherapy regimen: EC/EC-T/ECTX	−0.02 [-2.57, 2.53]	0.99
	True SA	0.41 [-2.04, 2.86]	0.74
	Sham SA	0.78 [-1.3, 2.87]	0.46
	Baseline	1.75 [0.38, 3.12]	0.012
	True SA by Baseline	0.72 [-1.51, 2.95]	0.53
	Sham SA by Baseline	−0.42 [-2.45, 1.62]	0.69
HADS – D total	(Intercept)	3.37 [2.1, 4.63]	<0.001
	Working class	−1.34 [-2.41, −0.27]	0.014
	Public health care or other	−1.17 [-2.15, −0.19]	0.02
	Social medical insurance	0.62 [-0.38, 1.63]	0.22
	True SA	−0.38 [-1.6, 0.84]	0.54
	Sham SA	−0.27 [-1.59, 1.04]	0.68
	Baseline	0.94 [0.098, 1.78]	0.029
	True SA by Baseline	1.81 [0.48, 3.14]	0.0076
	Sham SA by Baseline	0.99 [-0.36, 2.34]	0.15
MFI total	(Intercept)	42.94 [40.03, 45.84]	<0.001
	True SA	−0.38 [-4.16, 3.41]	0.85
	Sham SA	−0.37 [-4.48, 3.75]	0.86
	Baseline	5.06 [2.32, 7.81]	<0.001
	True SA by Baseline	3.25 [-0.17, 6.67]	0.063
	Sham SA by Baseline	1.44 [-2.47, 5.34]	0.47
FSDSC Composite	(Intercept)	0.1 [-0.1, 0.3]	0.33
	Fatigue score, last month (0–10)	0.021 [-0.0095, 0.052]	0.17
	Sleep disturbance score, last month (0–10)	0.024 [-0.00083, 0.048]	0.058
	True SA	−0.011 [-0.12, 0.093]	0.83
	Sham SA	0.0087 [-0.11, 0.13]	0.89
	Baseline	0.13 [0.065, 0.2]	<0.001
	True SA by Baseline	0.12 [0.019, 0.21]	0.019
	Sham SA by Baseline	0.043 [-0.052, 0.14]	0.38

Note: reference categories are control group, post-test, received chemotherapy ever: yes, chemotherapy regimen: other, retired, new rural cooperative medical care; B: regression coefficient; 95% CI: 95% confidence interval; *p*: p value; SA: somatic acupressure; Chemotherapy regimen: A: Adriamycin, E: Epirubicin, C: Cytoxan, T: Taxol or Taxotere; FACT-B: The Functional Assessment of Cancer Therapy – Breast; PSQI: The Pittsburgh Sleep Quality Index; HADS-D: Hospital Anxiety and Depression Scale – Depression; MFI: Multidimensional Fatigue Inventory; FSDSC Composite: Composite score of MFI, PSQI, and HADS-D.

associated with low power and non-significant results (Button et al., 2013; Serdar et al., 2021). Our original sample size calculation followed the conclusion by Julious (2005) which was based only on visual interpretation of sample size by "gain in precision" for a two-group scenario, taking into account neither repeated measures nor hypothetical effect size. Besides, the objective of this pilot study is mainly to focus on the feasibility assessment rather than to calculate the effect size for future main study's sample size calculation as the sample size of the pilot study was small in each group. Thus, the sample size calculation based on the effect size obtained in our pilot study might not be satisfactory. However, given that there were significant improvements as per the statistical results and the good feasibility results of the pilot study, a main study is needed. Given together, it would be more appropriate to calculate the main study's sample size based on other published similar studies. The effect size (Cohen's d) retrieved from current similar studies on self-acupressure for cancer-related fatigue (the core symptom of the FSDSC) was at least 0.32 conservatively (Cheung et al., 2022; Khanghah et al., 2019; Zick et al., 2016). Given the $\alpha = 0.05$, $\beta = 0.2$ for three groups and three-time points, the sample size will be 108, allowing the attrition rate to be 25% (Ling et al., 2014) in a repeated measures regression (ANOVA) (Faul et al., 2007). Restricted randomization will be considered to obtain more balanced groups by time and ensure better blinding by using randomly permuted block sizes. Also, the frequency and duration of the intervention will be included in the data analysis.

4.7. Placebo effect

Research evidence has implicated that acupoint stimulation produced both specific and non-specific effects (placebo effects) (Tan et al., 2015, 2022b). As such, it is recommended to simultaneously use both active (attention control) and inert controls (no treatment at all) in clinical trials to differentiate between the non-specific and specific effects of an intervention (Molassiotis et al., 2012). Our study findings showed that both the true SA group and sham SA group had improvements in FSDSC at cluster level and single symptom level as well as the QoL. Of which, the true SA group was found superior to sham SA in alleviating all clinical outcomes despite the between-group differences did not achieve statistical significance. Therefore, the alleviation of FSDSC has been deemed a mixture of specific and placebo effects of SA, given that both the true and sham SA effectively alleviated FSDSC with relatively stronger symptom alleviation identified by using the true SA. Given that the study sample size was relatively small and the absence of power-based sample size estimation, the statistical analysis is likely underpowered. Nevertheless, the presence of placebo effects of SA intervention cannot be ruled out. Future studies should continue to use a sham comparison and a usual care comparison to test the size of both the non-specific and specific effects of the SA intervention.

Table 5
Characteristics of the interviewees.

Demographic and Clinical data		Numbers (%)
Study groups (n = 16)	True SA group	9 (56.25)
	Sham SA group	6 (37.5)
	Usual care group	1 (6.25)
Age (years) (n = 15)	40–49	5 (33.3)
	50–59	9 (60.0)
	60–69	1 (6.67)
Education Background (n = 16)	Primary school	3 (18.75)
	Junior high school	6 (37.5)
	High school or secondary school	4 (25)
	College, university or above	3 (18.75)
Occupation (n = 16)	Working class	12 (75)
	Retired	4 (25)
Monthly household income (n = 15)	CNY ≤6000	6 (40)
	CNY >6000	9 (60)
Residential area (n = 16)	Rural	5 (31.25)
	Urban	11 (68.75)
Breast cancer stage (n = 16)	Stage I	6 (37.5)
	Stage II	5 (31.25)
	Stage III	5 (31.25)
Days of performing the SA (n = 15)	≥30 days	5 (33.3)
	<30 days	10 (66.7)

Note: SA: somatic acupressure; CNY: Chinese Yuan.

Table 4c
Estimated marginal means of outcome variables by group and time with effect sizes at post-test.

		True SA	Sham SA	Control	True SA vs Sham SA	True SA vs Control
		Mean [95% CI]	Mean [95% CI]	Mean [95% CI]	Cohen's d [95% CI]	Cohen's d [95% CI]
FACT-B total	Baseline	108.27 [103.48, 113.07]	107.1 [102.81, 111.4]	114.89 [111.57, 118.21]		
	Post-test	116.58 [113.2, 119.96]	113.6 [108.67, 118.52]	119.39 [115.23, 123.55]	0.356 [-0.363, 1.056]	0.364 [-0.343, 1.053]
PSQI total	Baseline	11.48 [9.53, 13.43]	10.72 [9.13, 12.32]	10.36 [8.65, 12.07]		
	Post-test	9.01 [6.36, 11.67]	9.39 [7.53, 11.24]	8.61 [6.52, 10.69]	0.08 [-0.626, 0.783]	0.084 [-0.612, 0.775]
HADS – D total	Baseline	4.89 [3.8, 5.98]	4.17 [3.05, 5.29]	3.45 [2.66, 4.25]		
	Post-test	2.14 [1.37, 2.91]	2.24 [1.32, 3.16]	2.52 [1.55, 3.49]	0.061 [-0.646, 0.764]	0.211 [-0.489, 0.901]
MFI total	Baseline	50.88 [48.09, 53.66]	49.07 [46.08, 52.06]	48 [45.82, 50.18]		
	Post-test	42.56 [40.14, 44.98]	42.57 [39.66, 45.48]	42.94 [40.03, 45.84]	0.002 [-0.703, 0.706]	0.069 [-0.626, 0.76]
FSDSC Composite	Baseline	0.57 [0.5, 0.64]	0.52 [0.45, 0.59]	0.47 [0.42, 0.51]		
	Post-test	0.32 [0.26, 0.38]	0.34 [0.26, 0.42]	0.33 [0.25, 0.42]	0.142 [-0.567, 0.844]	0.075 [-0.62, 0.767]

Note: SA: somatic acupressure; Mean: estimated marginal mean; 95% CI: 95% confidence interval; Cohen's d: effect size; FACT-B: The Functional Assessment of Cancer Therapy – Breast; PSQI: The Pittsburgh Sleep Quality Index; HADS-D: Hospital Anxiety and Depression Scale – Depression; MFI: Multidimensional Fatigue Inventory; FSDSC Composite: Composite score of MFI, PSQI, and HADS-D.

Table 6
Main themes, sub-themes and descriptions.

Themes	Sub-themes	Descriptions
Perceptions of Traditional Chinese Medicine (TCM) and SA	Viewing TCM as a promising approach for symptom management with fewer side effects	*"Treat us [symptoms] with TCM … I think the side effects are less than western medicine." (S1)*
		"Yes, I am treated with TCM. I think it is reasonable for Chinese people to use TCM. TCM has a history of thousands of years." (T3)
	Holding high expectations of the effects of SA on FSDSC management	*"It should be at least a score of 8 or 9 [rate the expectations of SA effects using 0–10 score]." (S1)*
		"I am definitely looking forward to it with 10 score effect, is the best." (T9)
Perceptions of the SA's effects	SA's effects on fatigue, sleep disturbance and emotional distress	*"When I heard my ward mates said they can't sleep well, I prefer to recommend acupressure to them." (S3)*
		"I think the positive effect of acupressure should be due to a variety of factors. If I can insist on practice well along with an improvement of mood, it (symptoms) should be improved." (S1)
	SA's effects on other symptoms/health conditions	*"Yes, I performed it (acupressure), I felt more relaxed" (T1)*
		"I still believe that acupressure works, and I feel a little comfortable after self-acupressure. It's okay and I can still feel some [symptoms] relief. It's effective." (S6)
Experience of completing the questionnaires	Easy to understand and answer	*"I can understand your questions (in the questionnaires) …." (C1)*
		"Yes, it is good and easy to understand." (T3)
	Being burdensome with too many questionnaires' items	*"There are quite a lot of questions in some (questionnaires), a little bit verbose (for me)." (S5)*
		"Some are still a bit too much, I forgot about them (questions)." (S4)
	Well reflect the FSDSC	*"These questions (in questionnaires) are exactly described as what I felt, and we have the same problems, and they seem to be saying things directly to my heart." (T6)*
		"I think those questions (in questionnaires) are detailed about our symptoms." (T4)
	Completing questionnaires through telephone is acceptable	*"I am very happy when you call to me as I can feel you care about me, I am very thankful." (T8)*
		"This approach (completing questionnaires through telephone) is good and appropriate. It (this method) is good because I feel you care about me." (T7)
Experienceof self-practicing SA	Facilitators toward adherence	*"You can teach us regularly in case we forget it, such as WeChat videos, or WeChat groups, send to us some pictures and remind us regularly." (S6)*
		" …. if there is a WeChat group or something like that, you can remind us frequently or send some pictures of acupoint locations to enhance our skills. I think it would be better, because I feel that my memory is not very good, and no one reminds me for a while and then I forget it." (S1)
		"That's right. When we gather, and everyone reminds each other, it may be easier to insist (self-acupressure) and the motivation (for self-practice) will be greater." (T3)
	Barriers toward adherence	*"I forgot, sometimes I forgot when I sleep better." (S3)*
		"Hmm … sometimes I entertain with my mobile phone and then forget to press (the acupoints). Sometimes I would like to press (the acupoints) when feeling a little numb with my hand." (T8)
		"I may not be able to locate the correct acupoints by myself possibly …" (T9)
		"Mainly because I am too busy, sometimes I feel too tired, but I have to go to work as well, so I feel that I have no time to [to press]." (S1)

Note: S: sham; T: true; SA: somatic acupressure; FSDSC: fatigue-sleep disturbance-depression symptom cluster.

4.8. Limitations

This study has some limitations. Group balance in characteristics after block randomization was not evident given the small sample size, which perhaps contributes to low statistical power in analysis, the statistical findings should be interpreted with caution. Future studies should ensure sufficient sample size and a better randomization strategy. Besides, blinding among participants was not possible with regard to the intervention or control status, although intervention groups might not differentiate between true or sham SA. In addition, participating in similar activities in personal life, and palliative methods or medication for alleviating the symptoms, were unobserved confounders. Without effective randomization, these effects might not be balanced out between groups. Finally, the composite score of fatigue, sleep disturbance, and depressive symptoms was computed from three items, which is different from a psychometric instrument with sufficient items for constructing validity tests such as factor analysis.

5. Conclusion

This Phase II RCT demonstrated that the study protocol and the SA intervention were feasible for BC survivors with the FSDSC. Feasibility findings regarding the subject recruitment process and study questionnaires were satisfactory, although there were recognized challenges with BC survivors' adherence to the SA protocol. The preliminary results suggested the potential treatment effects of SA in improving the FSDSC. It would be prudent to conduct a trial with an alternative sample size estimation to address the limitations and to identify the definite effects of SA on the FSDSC and QoL among BC survivors.

Trial registration

ClinicalTrials.gov (NCT04118140).
The study protocol has been published.

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CRediT authorship contribution statement

Meng-Yuan Li: study design, data interpretation, and manuscript drafting and revision. **Stephen Wai Hang Kwok:** statistical analysis, data interpretation, and manuscript revision. **Jing-Yu (Benjamin) Tan:** study conception and design, data interpretation, and manuscript drafting and revision. **Daniel Bressington:** study design and data interpretation, and manuscript revision. **Xian-Liang Liu:** study design data interpretation, and manuscript revision. **Tao Wang:** study conception and design, trial administration and implementation, data interpretation, and manuscript revision. **Shun-Li Chen:** study coordination, data collection, and quality assurance.

Declaration of competing interest

The authors declare that they have no competing interests.

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