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CAN ACUPUNCTURE BE A PART OF THE TREATMENT FOR BREAST CANCER-RELATED LYMPHEDEMA? A SYSTEMATIC REVIEW OF THE SAFETY AND PROPOSED MODEL FOR CARE

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ABSTRACT

Acupuncture is a potential therapy for breast cancer-related lymphedema (BCRL). Despite a recent meta-analysis on efficacy, data on acupuncture safety in BCRL are lacking. Current clinical guidelines recommend avoiding needling in the upper extremity affected by lymph node dissection. We undertook a systematic review focusing on acupuncture safety and treatment protocols in clinical trials for BCRL. Literature searches were conducted in PubMed, Ovid, CINAHL, and Cochrane library. Eight clinical trials on acupuncture for BCRL were analyzed. The Standards of Acupuncture intervention (STRICTA 2010) and Cochrane risk of bias (RoB2 2019) were applied to assess methods for acupuncture interventions within Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. Quantity and severity of adverse events (AE) were reviewed. A total of 189 subjects participated in 8 clinical trials with 2965 acupuncture treatments. No serious adverse events (SAE) were reported regardless of treatment laterality or protocol, with only a single grade 2 skin infection in 2,965 total treatments (.034%), including 1,165 bilateral and 225 ipsilateral treatments. Our comprehensive review of clinical trials of acupuncture for BCRL demonstrated no significant adverse events in 2,965 treatments, including 1,390 in the affected limb. An approach for routine integration of acupuncture into BCRL maintenance therapy is proposed.

Keywords: Acupuncture, lymphedema, safety, breast cancer, complete decongestive therapy

Breast cancer and breast cancer treatment can cause breast cancer-related lymphedema (BCRL) a secondary lymphedema that develops due to impaired lymphatic drainage from lymph node dissection, radiation therapy, and/or neoplastic disease causing the obliteration of lymphatic vessels (1,2). This complication can involve the upper extremity, hand, and ipsilateral breast and trunk (3). The risk of lymphedema remains lifelong for individuals having undergone breast cancer treatments such as surgery or radiation treatment (4). Breastcancer.org reports that there over 3.8 million breast cancer survivors as of January 1, 2021 (5,6). Published incidence rates for breast cancer-related lymphedema range from 2-65%. This significant variance in incident rates is due to a lack of standardization of measurement techniques and diagnostic criteria for lymphedema. It has been estimated that about 20% of women who undergo axil-

lary lymph node dissection and about 6% of women who have sentinel lymph node biopsy for breast cancer will develop arm lymphedema (7,8). The standard treatment for BCRL is complete decongestive therapy (CDT) which includes manual lymphatic drainage, compression garments, multilayer bandaging, and skincare (1-3,7). Significantly reduced health-related quality of life outcomes related to physical functioning, psychological well-being, and social well-being are well documented. Numerous publications report reasons for impaired quality of life which include limited daily activity and severe body image issues associated with having a single enlarged limb (4,9-12).

According to Rodrick et al, a limited number of qualified clinical professionals can provide CDT treatment. CDT can be costly and time-consuming. Because of this, patients are frequently unable to maintain treatment. Thus, the need for additional lymphedema treatment modalities and broader access to maintenance support warrants investigation (13). Acupuncture is one of these modalities. Acupuncture treatment has been practiced in Asian countries for over 2,000 years (14). The safety of acupuncture has been demonstrated for a variety of conditions when performed by a licensed acupuncturist (15-18). Acupuncture stimulation is thought to work by activating the somatic afferent nerve system stimulating a response from the spinal cord, midbrain, and thalamus. The possible responses from acupuncture stimulation are analgesic effects, anti-inflammatory effects, and neuro-immunological regeneration of lymphatic vessel obstruction. However, a specific mechanism of acupuncture for BCRL is not understood (19-29).

For the last decade, the general recommendation for acupuncture treatment of lymphedematous limbs has been strict avoidance – no puncturing of the skin (needling) in the affected area to avoid exacerbation of swelling and potential infection. This guideline, however, is not based on clinical evidence and remains theoretic (30-32).

The primary purpose of this review is to evaluate the safety of acupuncture treatment for BCRL by systematically reviewing published clinical trials, as this has not been previously addressed in the literature. The secondary aim is to create a framework by which to best assess efficacy of past and future trials by formally evaluating the study design, acupuncture intervention, and outcome measures.

METHODS

Search Strategy

PubMed, Ovid, Cochrane Library, and CINAHL electronic database systems were queried thru December 10, 2019, keyword search (lymphedema OR oedema OR "extremity lymphedema" OR "limb lymphedema" OR "Early Onset Lymphedema") AND ("Breast Cancer" OR "Breast Neoplasms" OR "Breast Tumors") AND (acupuncture OR electroacupuncture OR moxibustion OR "warm needle" OR "acupuncture and moxibustion" OR needling OR moxa) in the English language. Reference lists were reviewed to recruit more clinical studies.

Data Extraction and Quality Assessment

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines were structured for all the studies to evaluate the safety of acupuncture treatments. STRICTA 2010 (The Standards Clinical Trials of Acupuncture) and Cochrane Risk of Bias (RoB2 2019) guidelines were used to review selected studies.

STRICTA 2010 assesses the standardization of acupuncture interventions and RoB 2 2019 evaluates the quality of randomized controlled trials (RCT). STRICTA 2010 guidelines were developed to standardize acupuncture intervention in research protocols. STRICTA 2010 considers acupuncture rationale, precise needling placement and type, specific treatment regimen, additional treatment interventions (moxa, e-stim, etc.), practitioner background, and comparator intervention details (33,34).

Two independent reviewers (JK, CL) evaluated all studies and compared the results for consistency and consensus.

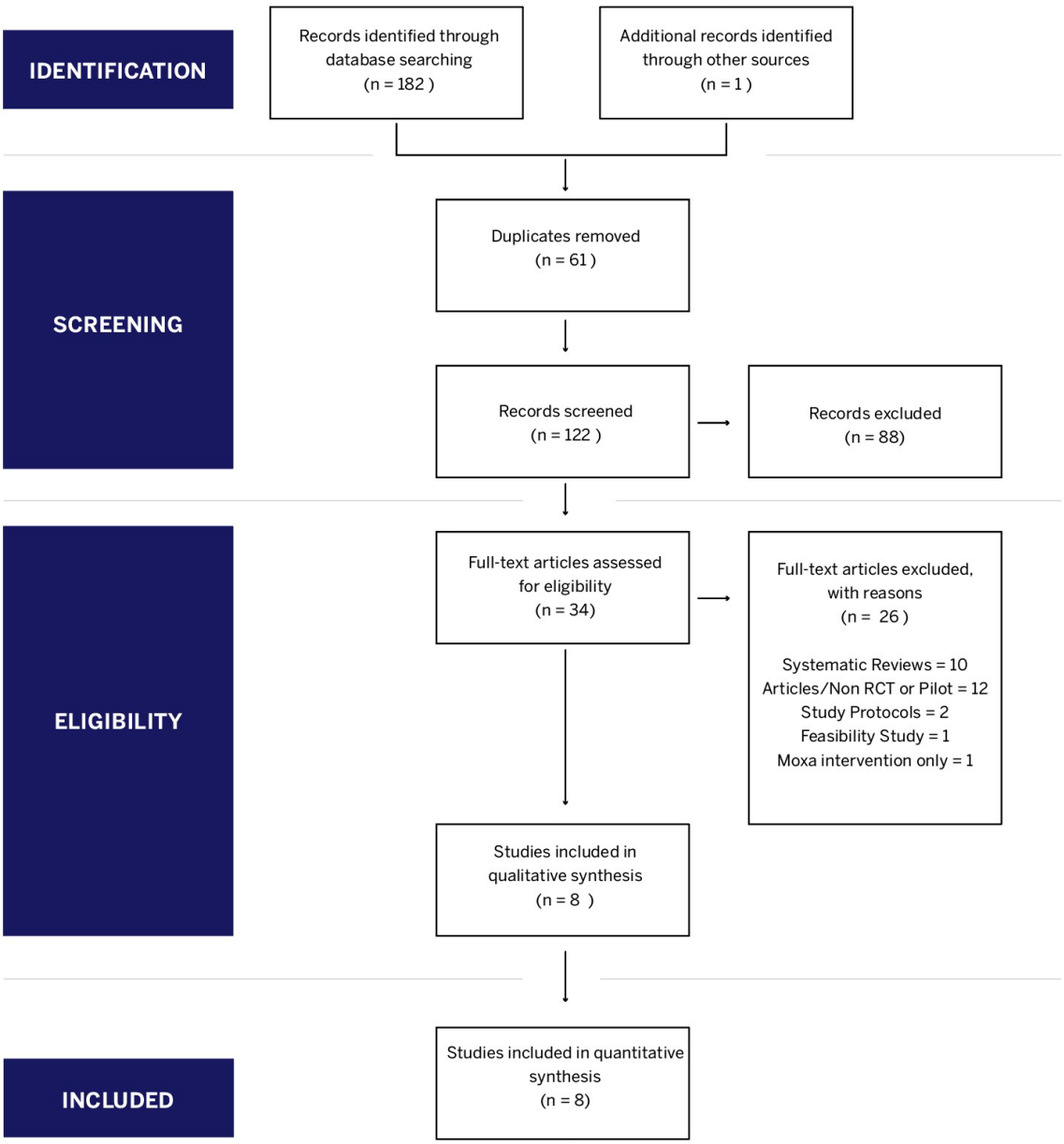

Fig.1. Diagram outlining selection of trials for inclusion in review on acupuncture for BCRL

Eligibility Criteria

Only prospective interventional studies in English and RCT were included in the systematic review. Participants must have had a breast cancer diagnosis with BCRL following breast surgery, and acupuncture interventions specifically for extremity lymphedema were required.

RESULTS

Study Selection

An initial 183 selected articles with the inclusion of one pilot study were found from the reference lists. Sixty-one duplicated articles and 88 articles after a thorough review of the title and abstract were excluded. Ten systematic reviews were also removed from analysis as there was a lack of specific patient demographic data (breast cancer stage, lymphedema stage, chronicity of lymphedema, specific treatment methods and protocols, etc.) and records of AEs. The studies were not sufficient in data provided to assess the safety of acupuncture in treating BCRL as they evaluated mixed methods for aggregate assessment of efficacy. Within those systematic reviews, however, the individual trials that did have sufficient data were included in this analysis. Twelve non-clinical trials, 2 study protocols, 1 case report study, and 1 moxa-only intervention study were eliminated from the remaining 34 articles. Ultimately, 3 randomized control trials (RCT) and five pilot interventional studies were selected to review for the safety of acupuncture treatments (*Fig. 1*).

Participants' Characteristics and Inclusion Criteria

Inclusion criteria and patient characteristics among the clinical trials varied substantially. Mean age across studies was 58.4 years. Half reported BMI or height and weight (range 27.9- 29.2). All participants were stable without evidence of active cancer (*Table 1*).

The majority of participants had lymphedema for 6 months to 5 years (54%). Twenty-eight percent of participants (53/189) had lymphedema stage indicated (36,39,41), and 74% of participants (some participants had both stage and arm measurements) reported a 2~3 cm discrepancy between affected and unaffected arms. Although 5 of 8 studies did not specifically state the stage of lymphedema, data summarized in *Table 2* indicates most participants had at least stage 2 BCRL even if not specified. Stage 0 (3%) and stage 1 (8%) were rare, and no insertion of needles in the affected arm were reported in subjects with stages 0 and 1 lymphedema.

STRICTA 2010 and RoB 2 2019 Evaluation

All the clinical trials were evaluated by STRICTA 2010 for standardization and quality of acupuncture intervention. Of the 17 criteria, 5 of 8 clinical studies met more than 80% of guidelines (36,37,39,41). All randomized control trials were also evaluated based on Cochrane Risk of Bias (RoB). The risk of bias was evaluated by examining multiple domains: The randomization process, deviations from intended interventions, missing outcome data, outcome measurements, and the selection of the reported results. Each study was then scored and stratified as having either "low risk," "some concerns," or "high risk" of bias as for each RoB category. Three randomized controlled trial studies (38,40,41) were reviewed by ROB2 (2019). The Bao study was deemed low risk of bias; however, Smith et al scored as 'some concern' and Yao et al at 'high risk' of bias (11,12,33-41). Detailed itemized study analysis is listed in the supplemental tables for STRICTA and ROB2 2019 (*Tables 3,4,5*).

Safety Review Based on Laterality and Region of Acupuncture Treatments

A total of 189 subjects participated in the combined eight clinical trials. 2,697 acupuncture treatments were performed in total. 51% of subjects (97/189) had received contralateral treatment on the unaffected side, 41% (78/189) of subjects had bilateral treatment, and 8% (15/189) on the affected side only. All study

TABLE 1
Inclusion Criteria and Number of Participants Across all Eight Studies

		2008 Alem et al. n=29	2011 Cassileth et al. n=9	2012 De Veloid et al. SI n=25	2013 Cassileth et al. n=33	2014 Smith et al. n=9	2016 Jeong et al. n=9	2016 Yao et al. n=15	2018 Bao et al. n=36	Total (Percentage) n=189
Length of LE	>3 months			49						49 (26%)
	> 6 months					9				9 (5%)
	5 years > > 6months		9		33		9	15	36	102 (54%)
	> 6 months after surgery	29								29 (15%)
Stage	0	6								6 (3%)
	1	10					5			15 (8%)
	2	5					4		36	53 (28%)
	3	8								
	Not Indicated But it seems more than stage 2		9	49 (Mild to moderate)	33	9		15		115(61%)
Intervention	Acupuncture		9			9	9		5	32 (17%)
	Acupuncture & Moxibustion							15		15 (8%)
	Acupuncture and Standard care	29			33				31	93 (49%)
	Acupuncture-Moxibustion with Standard care			49						49 (26%)
Phase	Active									
	Stable					9		15		24 (13%)

TABLE 2
Summary of Study Treatment Laterality and Number of Acupuncture Treatments

		Participants in acupuncture group	Contra-lateral	Bilateral	Affected area	Treatment/ person	Total treatments
Alem et al.		29	696			24	696
De Valois et al.	S1	25	420			7	420
	S2	24				6	
Cassileth et al		9		73		8	73
Cassileth et al		33		255		8	255
Smith et al		AG 9	108			12	108
Young J Jeong et		9	162			18	162
C Yao et al		15			225	15	225
Bao et al		AG 36/40		837		10	837
		189	1386	1165	225		2965

methods and findings are summarized in *Supplemental Table 1*. No significant adverse events (SAE) were reported. There was one grade-2 skin infection reported in a total of 2,965 treatments (0.034%). The most common minor adverse reaction reported was minor bruising found in Cassileth 2013 (36%, 12/33) and Bao's 2018 study (58%, 45/78). Two incidences of lymphangitis (with prior history of lymphangitis) were reported in Jeong's 2015 study. All other studies either reported no MAE (Minor adverse events) or noted but did not quantify these minor events (36) (11,12,36-40,42).

Outcomes and Efficacy Measures

Studies were divided by treatment laterality; contralateral only, bilateral, and ipsilateral (affected arm).

Contralateral:

About half of the treatments (1,386) were contralateral only. There was no uniform measure of efficacy across studies which precluded a meta-analysis for efficacy. Outcomes of 1,386 contralateral treatments were evaluated with various methods such as perceived improvement of range of motion, BIS (Bio Impedance spectroscopy), circumference tape measurement, and self-assessment tools such as VAS (Visual analog scale), MYMOP (Measure Yourself Medical Outcome Profile), PANA (The Positive and Negative Affect Schedule) SF-36 (Simple Form 36). Reduction of swelling measurements varied widely and could not be evaluated in a standardized fashion but are summarized in *Supplemental Table 2* (12,36, 38,39).

Alem et al measured lymphedema with arm circumference measurement, VAS score of hardening and tightening, and ROM. The participants with the following stage of lymphedema (Stage 0: 6, Stage 1: 10, Stage 2: 5, Stage 3: 8). The result of measurement showed improvement of the degree of lymphedema ($p=0.016$), Mean VAS Scores of heaviness and tightening ($p<0.001$), Mean ROM deficit ($p<0.001$). For circumferential measurements of the arm, forearm, and wrist, no significant

TABLE 3
STRICTA Evaluation of Interventional Studies with Notation as Specified (S) or not Specified (NS)

		2018 Bao et al	2015 Yao et al RCT	2014 Jeong et al	2014 Smith et al RCT	2013 Cassileth et al	2011 De Valois et al	2011 Cassileth et al	2008 Alem et al
Acupuncture rationale	Style	S	S	S	S	S	S	S	S
	Reasoning	S	S	S	NS	S	S	S	S
	Variation	S	U	S	S	S	S	S	S
Details of needling	Number of needles	U	U	S	U	S	NS	U	S
	Names of points	S	S	S	S	S	NS	S	S
	Depth	NS	NS	S	NS	S	NS	S	S
	Response sought	S	NS	S	S	NS	NS	S	NS
	Stimulation (manual, e stim)	S	S	S	S	S	NS	S	S
	Retaining time	S	S	S	S	S	NS	S	S
	Needle type	S	S	S	S	S	NS	S	S
Treatment Regime	Number of treatments	S	S	S	S	S	S	S	S
	Frequency and duration	S	S	S	S	S	S	S	S
Other components of treatments	Details of other intervention	U	S	S	S	NS	S	NS	NS
	Description of discussion setting for designing	S	NS	S	NS	S	S	S	NS
Practitioner background	Description of background	S	NS	S	S	S	S	S	S
Control or comparator interventions	Rationale for the control or comparator in the context	S	S	NA	S	NA	NA	NA	NS
	Precise description of control or comparator	S	S	NA	S	NA	NA	NA	NS

TABLE 4
Cochrane Risk-of-Bias Tool (RoB2 2019) for Randomized Trials for the 3 RCT Studies

	Randomizing process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Risk of Bias
Smith et al	Away from null	High	Low	Low	Low	Some concern
Yao et al	Unpredictable	Some concern	Unpredictable	Away from null	Low	High
Bao et al	Low	Some concern	Low	Low	Low	Low

TABLE 5
Percentage Meeting the Guidelines of STRICTA and Risk of Bias Estimation RoB2

	2018 Bao et al	2015 Yao et al RCT	2014 Jeong et al	2014 Smith et al RCT	2013 Cassileth et al	2011 De Valois et al	2011 Cassileth et al	2008 Alem et al
STRICTA 2010	**82%**	**65%**	100%	76%	87%	53%	87%	80%
ROB 2 2019	Low	High		Some concern				

improvement between the different treatment periods was observed (36).

De Valois et al evaluated the result of treatment through self-assessment tools such as Measure Yourself Medical Outcome Profile (MYMOP), The Medical Outcomes Study Short Form (SF-36), The Positive and Negative Affect Schedule (PANAS). The participants were 1.28 points improvement ($p<0.0001$) in MYMOP. Changes in some (Bodily pain, Vitality) SF-36 scores for the participants were significant to 4 weeks after treatment in bodily pain and vitality (12).

Smith et al utilized BIS (Bio Impedance Spectroscopy) to measure the whole arm. The acupuncture group ranged from an increase of 0.01 to a decrease of 0.30. However, in the control group, the BIS ratio changed from an increase of 0.28 to a decrease of 0.43. There was no change in the quality of life or any patient-reported outcome measurement that assessed symptoms related to their lymphedema. No study participant experienced an increase in swelling of >10% (38).

Jeong et al reported stages of the lymphedema, VAS, arm circumference measurement, and SF-36. The severity of lymphedema at the end of treatment demonstrated a significant reduction in the average VAS score ($p<0.001$). Average edema rates of the elbow and the forearm at the end of treatment ($P = 0.021$ and $P < 0.001$, respectively). However, the lymphedema stage did not change during treatment or follow-up evaluation (4 weeks after last treatment). As for quality-of-life measure, the SF-36 health status score improved significantly at the end of the treatment ($p=0.018$) (39).

Item	Detail
1. Acupuncture rationale	1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc.)
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate
	1c) Extent to which treatment was varied
2. Details of needling	2a) Number of needle insertions per subject per session (mean and range where relevant)
	2b) Names (or location if NS standard name) of points used (uni/bilateral)
	2c) Depth of insertion, based on a specified unit of measurement or on a particular tissue level
	2d) Response sought (e.g., *de qi* or muscle twitch response)
	2e) Needle stimulation (e.g., manual, electrical)
	2f) Needle retention time
	2g) Needle type (diameter, length, and manufacturer or material)
3. Treatment regimen	3a) Number of treatment sessions
	3b) Frequency and duration of treatment sessions
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group (e.g., moxibustion, cupping, herbs, exercises, lifestyle advice)
	4b) Setting and context of treatment, including instructions to practitioners and information and explanations to patients
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice
	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.

Fig.2. STRCTA guidelines utilized and the details for each item.

Bilateral:

A total of 1,165 bilateral treatments were performed. 15/42 participants had a reported 30% or greater reduction in arm size with bilateral treatment in the two pilot studies conducted from the same group at Memorial Sloan Kettering (Cassileth et al 2011, 2013) with bilateral treatment. [(Largest pretreatment difference - Same site post-treatment difference)/ Largest pretreatment difference *100%)]. However, the bilateral acupuncture protocol in the more recent randomized trial by Bao et al found no significant difference between groups for arm circumference difference (0.38 cm greater reduction in AC vs. WL, 95% CI – 0.12 to 0.89, p=0.14) or bioimpedance difference (1.06 greater reduction in AC vs. WL, 95% CI – 5.72 to 7.85, p=0.8). There was also no difference in the proportion of responders: 17% AC versus 11% WL (6% difference, 95% CI – 10 to 22%, p=0.5). (Wait list received usual care only) (11,37,41).

Ipsilateral:

Yao's study of 225 unilateral treatments on the affected side (45) utilized the Index of Effectiveness: [(upper arm circumference before treatment-upper arm circumference after treatment)/ (upper arm circumference of the affected arm before treatment-upper arm circumference of the unaffected arm before treatment)] x 100%. They reported 51.46% reduction in the treatment group over 26% control group treated with diosmin alone ($p < 0.00001$). Compared with baseline, the range of motion (ROM) of the affected shoulder joint

at 4th week showed significant improvement in both groups ($p<0.05$). However, the experimental group reported ROM improvement from 1st week. All participants in the experimental group improved in quality of life (average rating: satisfied); in contrast, participants in the control group showed some persisting impairments in quality of life. The differences between the treatment groups were significant ($p<0.05$) (40).

DISCUSSION

Despite significant differences in treatment design and outcome measures, all pilot studies and RCTs consistently demonstrated no significant adverse events (SAE), and any minor adverse events such as bruising, mild pain, or hematoma were very infrequent, with only a single grade 2 skin infection, a rate of .034%.

Importantly in this review of 1,390 collective acupuncture treatments needling in the affected limb, there were no SAEs, providing the first comprehensive data countermanding the standing contraindication of performing acupuncture on an edematous limb or ipsilateral arm from breast cancer. Our analysis provides supporting evidence that needles may be safely placed the affected limb, but Bao's randomized trial suggested there may not be additional efficacy by treating the affected limb. In addition, the Yao study had a RoB2 2019 high risk of bias and a small sample size limiting generalizability (40). Thus the question of efficacy, specifically in affected limbs remains unanswered and requires future study following the more stringent design outlined in this paper.

Five systematic reviews and meta-analyses were published more recently in 2019 and 2020. In the multiple studies where acupuncture treatment was conducted in conjunction with moxibustion, arm circumference and range of motion demonstrated improvement. However, it is important to note that these studies did all had limitations regarding baseline participants' demographics, risk of bias, and small sample size (*Supplemental Table 2*). Furthermore, safety was not fully evaluated in some of the RCTs and systematic reviews. Though STRICTA guidelines were followed, however, a notable limitation to these guidelines is that there is no category for evaluation of adverse events (43-47). While acupuncture as an intervention for lymphedema demonstrates safety and feasibility, evaluation with a well-designed study following STRICTA guidelines but also with larger and better-defined treatment populations, and specific adverse events measurements is warranted. Authors note a limitation to this review is that we were only able to review studies written in English and thus excludes contributions from many Asian countries where acupuncture is a mainstay of clinical treatment for many conditions.

Standard primary methods of outcome measurement of BCRL vary greatly across current studies, limited assessments of efficacy and true meta-analysis of data. According to the American Physical Therapy Association, the clinical practice guidelines for measuring upper quadrant lymphedema secondary to cancer should include bioimpedance analysis and volumetric measurements (circumferential measurements, water displacement, perometer). The measurement method varies based on the staging of lymphedema set by the International Society of Lymphology staged from 0-3 (1). In stages 0-1, measurement protocols recommend bio-impedance and volumetric measurements, but volumetric measurements are better suited as bioimpedance is considered less useful in stages 2-3 (48). Thus all prior studies of efficacy are challenged by variable stages of disease and measurements of response.

Quality of Life (QoL), measured using questionnaires, provides important subjective and qualitative data. Both types of data are essential for inclusion when analyzing the efficacy and value of treatment, and thus QoL improvement is the primary concern for most patients and should therefore be a uniform and consistent outcome measure in acupuncture intervention trials (12,40).

Proposed Model for Care of Breast Cancer Related Lymphedema Including Acupuncture

Prior studies have all focused on stable recalcitrant disease rather than prevention or early-stage intervention. An analysis of the trends and fluctuations in lymphedema, measuring the earliest onset and progression, is essential for improving patient quality of life by interventions before disfiguring and recalcitrant lymphedema has set in. Capturing the initial onset of BCRL and measuring its status over time with bioimpedance and/or limb volume assessment and the utilization of patient-reported outcome tools provides data to compare the efficacy of current standard care and acupuncture or a combination of acupuncture and the standard care options.

At our community-based hospital, we address lymphedema needs and concerns through our established breast cancer pre-rehabilitation program. Lymphedema risk surveillance, onset, and treatment are incorporated into this model of care to achieve successful self-management.

Incorporating acupuncture into the self-management phase of this model of care offers an opportunity to assess acupuncture treatment's possible benefits. PT and OT follow-up with these patients would yield data regarding limb volume changes, UE function, and lymphedema status as assessed with the QUICK DASH (The Disabilities of the Arm, Shoulder, and Hand) and LLIS (Validation of the Lymphedema Life Impact Scale), respectively.

Currently, there are no published or NCI-listed clinical trials using acupuncture intervention for early post-operative care, and as a prevention with subclinical lymphedema of breast cancer patients. Further clinical trials for post-operative care and subclinical care with acupuncture is warranted, as this may be an excellent opportunity in risk reduction of progression to functional impairment for women being treated for breast cancer.

CONCLUSION

Acupuncture treatments for BCRL patients demonstrate a high degree of safety throughout 2,965 treatments. 1,390 out of 2,965 acupuncture treatments inserted needles in the affected arm and in the lymphedematous region without adverse event providing substantial support that acupuncture does not increase the risk for infection or progression of breast cancer-related lymphedema. A clinical care model including acupuncture in the maintenance phase of treatment based on experience in a comprehensive breast cancer lymphedema program is proposed, and an active clinical trial design within this model is warranted to assess the efficacy and ideal timing of acupuncture in the treatment journey for patients with BCRL.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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SUPPLEMENTARY TABLE 1
Summarization of Preliminary Clinical Intervention Studies

	Participants					Intervention	Comparator	Outcome		
STUDY	# of subjects interven-tion Comp-arator	Inclusion Criteria	Exclusion Criteria	Duration of LE	Mean Age & BMI	Intervention group protocol and plan (# of total treatments)	Control Group Protocol and Plan (# of total treatments)	Outcome measuring method	Result	Adverse Reaction Notes
2008 Alem, Pilot	29	Unilateral breast cancer surgery with axillary lymph node dissection at least 6 months prior to study Lymphedema with 2cm or greater difference in circumference limbs and/or restriction of 20 degrees or more in flexion and/or abduction ROM Stage 0: 6 Stage 1: 10 Stage 2: 5 Stage 3: 8	Patients with tumor recurrence or active disease, vascular abnormalities or bone or joint changes in the upper limb ipsilateral to surgery, or other morbidities that cause alteration in tactile sensation,	not stated	Age: 61.9(11.6) BMI Kg/m^2: Not indicated	CV12, CV3, CV2, LI 15. TE 14. LU5, TE5, LI4, ST36. SP9, SP6 (24 per patient 1x/weekly,	N/A	Degree of lymphedema with an arm circumference VAS score hardening and tightening ROM	Mean degree of lymphedema (p=0.016) Before: 1.9 6months 1.1 Mean VAS Scores (p<0.001) *Heaviness:* Before 5.5 6 months 2.1 *Tightening* Before 3.7 6 months 0.4 Mean ROM deficit (p<0.001) *Flexion* Before 50.8 6 months 16.9 *Abduction* Before 60.5 6 months 18.6 For circumferential measurements of the arm. forearm and wrist, no significant improvement between the different periods of treatment was observed	non stated
2011 Cassileth , Pilot	9	Women 18 or older w/ lymphedema as a result of surgery and/or radiation therapy for BC Clinical dx of lymphedema for at least 6 months and no more than 5 years affected arm >2 cm circumference than unaffected	No previous acupuncture treatment for lymphedema No current use of diuretics	MEAN NOT STATED at least 6 months, no more than 5 years	Age: 54(9.9) BMI Kg/m^2: 30.4 (5.1)	Acupuncture twice a week for consecutive weeks 8 treatments per patient 73 total treatments LI15, LI4, TE14, RN12, RN3, LU5, SP6, ST36	N/A	Arm circumference and 6 months follow up call for information about side effects	Four women showed at least a 30% reduction in the extent of lymphedema at 4 weeks when compared with their respective baseline values.	No SAE
2012 DE Valois, Pilot	BC S1: n=25 BC S2: n=24	male or female patients with mild to moderate uncomplicated lymphoedema, age 18 or over, under the care of the lymphoedema service for at least two (HNC) or three (BC) months	No active cancer No acupuncture treatment within the previous 6 months Patients with advanced cancer disease and bilateral BC patients	MEAN BC 50(30.1), BC - 3 months or more	Age: 57.5 [9.3] BMI: Not indicated	Treatments and plans of care are individualized to meet the patient's specific needs Treatment frequency was once weekly for seven sessions (S1), and participants could choose a further six sessions (S2) for a possible total of 13 treatments. 420 treatments were administered, with a mean of 12 per participant Other interventions included lifestyle advice, offered as appropriate to the ' 'individual's needs and capacity for taking advice, and included advice for healthy dietary habits, rest, exercise, and maintaining a sensible weight. The acupuncturists encouraged participants to adhere to the self-care programs prescribed by the nurse specialist	N/A	Measure Yourself Medical Outcome Profile (MYMOP) The Medical Outcomes Study Short Form (SF-36) The Positive and Negative Affect Schedule (PANAS)	Mean MYMOP: BC participants were 1.28 points improvement (p<0.0001) S1 HNC change scores were 2.29 points improvement and 0.94 for S2 Changes in some (Bodily pain, Vitality) SF-36 scores for BC participants were significant to 4 weeks after treatment. Bodily pain: S1 p<0.04, S2 p<0.005, 4 weeks follow up p< 0.003, 12 weeks follow up p<0.2 Vitality: S1 p<0.005, S2 p<0.041, 4 weeks follow up p<0.027, 12 weeks follow up p<0.6	Bruising and/or bleeding at the needle site, tiredness after treatment, pain on needling portion, 1 BC reported a lightheaded sensation 1 BC reported headaches No SAE found

SUPPLEMENTAL TABLE 1 (CONTINUED)

	Participants					Intervention	Comparator	Outcome		
STUDY	# of subjects interven-tion Comp-arator	Inclusion Criteria	Exclusion Criteria	Duration of LE	Mean Age & BMI	Intervention group protocol and plan (# of total treatments)	Control Group Protocol and Plan (# of total treatments)	Outcome measuring method	Result	Adverse Reaction Notes
2013 Cassileth, Pilot	33	women aged ≥18 years with unilateral lymphedema, defined as ≥2 cm in a circumference difference between affected and unaffected arms resulting from surgery and/ or radiation therapy for breast cancer Clinical dx of lymphedema for at least 6 months and no more than 5 years 6 months post-surgery time frame allowed for any surgically related non-lymphedema swelling to subside months and a cap of 5 years Maintenance treatment for lymphedema such as exercise, massage or compression garments were included.	Previous acupuncture treatment for lymphedema Using diuretics metastatic cancer, history of autoimmune or fibroproliferative disorders, history of primary lymphedema or bone marrow transplant, or current treatment with corticosteroids or myelosuppressive or stimulatory drugs.	MEAN NOT STATED at least 6 months, no more than 5 years	Age: 55 BMI Kg/m^2: 30.4 (26.7-35.4)	TE14, LI15, LU5, CV12, CV3, LI4, ST36, SP6 30-minutes sessions 2x weekly for 4 consecutive weeks 255 total treatments Twenty-five patients (76%) received all 8 sessions, 7 (21%) missed 1 treatment session, and 1 (3%) missed 2 treatment sessions	N/A	reduction in arm circumference difference 2-point measures with a 5% circumference change threshold has high sensitivity and specificity (80% and 71%, respectively)	mean reduction in the extent of BCRL was 0.90 cm (95% CI, 0.72-1.07 cm; P<.0005 Eleven patients (33%) exhibited a reduction of ≥30% after acupuncture treatment	9 of the 33 patients reported mild bruising (27%), minor pain, Edema (transient increase in lymphedema in the axilla) 1/33 (3%), Nausea 1/33 (3%), Neuropathy 1/33 (3%), Pain 2/33 (6%) within 4 weeks treatment period (255 acupuncture treatment) 1/33 (3%) extremity pain at 4th week through 6 months follow up
2014 Smith, RCT	Intervention: 9 Comparator: 10	Women ≥18 years Stable unilateral intransient lymphedema present for at least 6 months ranged from those with the localized early presentation to women with severe longstanding symptoms.	no use of intensive therapy within the past 3 months, no infections in the lymphedematous limb requiring antibiotics within the past 3 months, no recent exacerbation of symptoms that led to change in daily activities, and exceeding the previously determined threshold for lymphedema with bioelectrical impedance spectroscopy (BIS) for at least one 10 cm segment	MEDIAN Control 24 months, Acupuncture 87 months At least 6 months for intervention	Age: "Late 50's early 60's" BMI Kg/m^2: 26.8 (2.9)	Individualized treatments are based on individual diagnoses. Practitioners selected 3 standardized points from: (1) CV12, CV3, CV2 (2) LI15, TE4, LU5, LI4 - unaffected side (3) ST36, SP9, SP6 Other additional points used based on dx Women received 12 treatments administered over 8 weeks, twice weekly for 4 weeks then once weekly for 4weeks Total # of overall Tx:	a regular routine for management of their lymphedema	BIS and arm circumference measures BIS (SFB7 instrument, ImpediMed, Brisbane, Australia), Measuring 10 cm segment from wrist	The change in whole arm BIS ratio in the acupuncture group ranged from an increase of 0.01 to a decrease of 0.30 whereas, in the control group, the BIS ratio changed from an increase of 0.28 to a decrease of 0.43 No study participant experienced an increase in swelling of >10%. There was no change in the quality of life or any patient-reported outcome measurement that assessed symptoms related to their lymphedema	No major and minor adverse reported
2015 Jeong, Pilot	9	Lymphedema in UE as a result of breast cancer ≥2 cm difference in circumferential measurement of the affected upper limb in comparison to the contralateral limb Stage 1 (5/9), Stage 2 (4/9) Clinical dx of lymphedema for at least 6 months Karnofsky performance score of >60 Voluntary participation follow up for the duration of the study Cessation of other pharmacologic or alternative Tx including exercise, compression sleeves, for at least 1 week before trial	(1) primary or secondary lymphedema caused by other diseases (2) other pharmacologic or alternative treatments, such as exercise and compression sleeves/ gloves for lymphedema, for lymphedema during the trial (3) progressive or metastatic breast cancer (4) serious medical or psychiatric conditions that made the patient unsuitable to participate in the trial.	MEAN 67.44 (SD 38.12) in months	Age: 58.4 years BMI Kg/m^2: Not indicated Hight: 155.75cm (5.36) Weight: 57.89kg (11.13)	Sa'am style acupuncture, individualized per patient (Unaffected side treatment) 18 sessions of acupuncture, delivered 3 times per week, for 6 weeks	N/A	Stage, VAS Arm Circumference SF-36	Stages are not changed during treatment and follow up evaluation (4 weeks after last treatment) Repeated-measure one-factor analysis showed a significant reduction in the average VAS score for severity of lymphedema at the end of treatment ($p<0.001$) Repeated-measure one-factor analysis revealed a significant reduction in the average edema rates of the elbow and the forearm at the end of treatment ($P = 0.021$ and $P < 0.001$, respectively) SF-36 Health status score was significantly improved at the end of the treatment ($p=0.018$)	2 patients experienced lymphangitis (also had a prior history of lymphangitis) No minor and serious adverse events

SUPPLEMENTAL TABLE 1 (CONTINUED)

	Participants					Intervention	Comparator	**Outcomes**		
STUDY	# of subjects interven-tion Comp-arator	Inclusion Criteria	Exclusion Criteria	Duration of LE	Mean Age & BMI	Intervention group protocol and plan (# of total treatments)	Control Group Protocol and Plan (# of total treatments)	Outcome measuring method	Result	Adverse Reaction Notes
2016 Yao, RCT	30 total Intervention: 15 Comparator: 15	30-80 years old Unilateral lymphedema (defined as more than a 3 cm difference in circumference between the affected and unaffected arms) BCA had met the clinical diagnostic criteria for between 6 months and 5 years. At least 2 months stable BCRL UL lymphedema symptoms including stiff or hard skin and impaired ROM in shoulder joint	Receiving other Tx for lymphedema (exercise, massage, compression garments, etc.) Had BCA recurrence; other internal organ metastasis; other cancer; heart failure; kidney failure; liver disease	MEAN Intervention: 8.82 Comparator: 8.81	Age: Intervention 56.2 Comparison 55.8 BMI Kg/m^2: Not indicated	LI10, LI11, LI14, LI15, SJ5, SJ14 Moxa sticks for warm acupuncture on top of SJ5, LI15, and SJ14 (total # of Tx unclear - maybe 15 per patient and 225 total, not clearly stated)	900 mg diosmin tablets orally 3x daily for 30 days	- Effective index for UL Lymphedema (measure circumference) - ROM in shoulder joint - QOL self-reported modified European Org for Research and Treatment of Cancer's QLQ-30 - Monitor clinical safety w/ routine blood tests, electrocardiography	Effective Index Overall: ($p<0.00001$) Week1: Control 8.42, Intervention 19.80 Week2: Control 15.18, Intervention 30.31 Week3: Control 19.98, Intervention 43.51 Week4: Control 26.76, Intervention 25.35 ROM: ($p<0.05$) Baseline: Control 92.74, Intervention 91.22 Week4: Control 95.06, Intervention 96.34 QOL: ($P<0.05$) Baseline: Control 2, Intervention 2.01 Week4: Control 1.07, Intervention 0	No adverse events were reported during treatment, and no local burns, bleeding, ecchymosis, or inflammation events occurred
2018 Bao, RCT	Intervention: 36 AC Comparator: 37 WL	Women 18≥ Stage 2 lymphedema or higher, chemotherapy, and/or radiation for breast cancer for 6 months and no more than 5 years Arm circumference > 2cm larger than the unaffected arm	Women with bilateral lymphedema; prior acupuncture treatment; concurrent diuretic use; history of primary lymphedema, pregnancy; or history of an implanted electronically charged medical device were ineligible	MEAN AC 2.5 WL 2.26	Age: Acupuncture: 65 (54, 71) Control: 55.8 (5.02) BMI Kg/m^2: Not indicated	Acupuncture treatment group-lymphedema assessments after 6 weeks of acupuncture treatment and 3 months after the conclusion of treatment. TE14, LI15, LU5, CV12, CV3, LI4, ST36, SP6 12 total treatments 2/week for 6 weeks / Acupuncture and Lymphedema therapy (85%)	Wait-list control group, Lymphedema therapy (79%)-	Lymphedema staging was based on the International Society of Lymphology (ISL) staging system and performed by a Certified Lymphedema Therapist (CLT) Arm circumference measurements were performed by trained research staff 10 cm above and 5 cm below the olecranon process using non-stretch tape. measured bio impedance using the Impedimed L-Dex U400	Arm Circumference: AC 4.74 (2.23) 4.29 (2.67) WL 4.82 (2.32) 4.76 (2.68) Difference: − 0.38 (− 0.89, 0.12) $p< 0.14$ Bioimpedience: AC 38.6 (30.4) 35.9 (27.4) WL 42.2 (32.2) 40.3 (35.6) Difference: − 1.06 (− 7.85, 5.72) $p< 0.8$	Bruises: 45 (58%) Hematoma 2 (2.6%) Pain: 2 (2.6%) Skin infection:1 (1.3%)

SUPPLEMENTAL TABLE 2
Summary of Recent Systematic Review and Meta-Analysis

Studies	Studies included	Efficacy evaluation and results	Adverse effect report
2019 Chien et al	Bao 2018 Yao 2016 Jeoung 2015 Smith 2014 Cassileth 2011, 2013	Arm circumference shows favorable in Bao and Yao et al. 95% CI=-5.39 to 1.59, P =.29 Bao 2018 (Acupuncture treatment vs Standard lymphedema treatment) Yao 2016(Warm acupuncture vs Diaosim tablets)	not stated
2019 Hou et al	Jiang 2008 Zhan 2017 Jin 2017 Jiang 2015 Zhao 2012 Yang 2017 Feng 2018 Huang 2014 Jiao 2017 Bao 2018 Yao 2016 Wu 2018 Smith 2014	Total effective rate Odds ratio=4.62; 95% CI=[2.61-8.17] Test for overall effect: Z=5.27 (P,0.00001) Degree of swelling The variation of the affected arm circumferences (MD=0.79; 95% CI [0.57-1.01] Test for overall effect: Z=7.11 (P,0.00001)) Feng 2018 (Acupuncture and cupping vs Hydrochlorothiazide) Yang 2017 (Moxibustion vs Air-cycle driving therapy) The variation of the elbow joint diameters in the affected arm 1 (MD 6.68; 95% CI [5.27-8.08] Test for overall effect: Z=9.33 (P<0.00001) Huang 2014 (Suspended moxibustion with acupuncture & functional exercise vs Hydrochlorothiazide, spironolactone, functional exercise and living nurse) Jiao 2017 (Acupuncture and suspended moxibustion vs Comprehensive conventional treatment) Zhao 2012 (Suspended moxibustion vs comprehensive conventional therapy) The variation of the elbow joint diameters in the affected arm 2 (MD 6.0; 95% CI [5.03-6.97] Test for overall effect: Z=12.08 (P<0.001)) Huang 2014 (Suspended moxibustion with acupuncture & functional exercise vs Hydrochlorothiazide, spironolactone, functional exercise and living nurse) Jiao 2017 (Acupuncture and suspended moxibustion vs comprehensive conventional therapy) Zhao 2012 (Suspended moxibustion vs comprehensive conventional therapy) The variation of the circumference difference in the contralateral arm (MD 1.69; 95% CI [-1.80- -0.91] p<0.001) Jiang 2015 (Thunder fire moxibustion & air wave pressure vs air wave pressure) Bao 2018 (Acupuncture treatment vs Standard lymphedema treatment) Wu 2018 (Acupuncture & functional exercise vs Functional exercise) Zhan 2017 (Acupuncture and functional exercise vs Functional exercise) The variation of the circumference difference in the contralateral arm (in the midpoint positions of the upper limbs) (MD -1.69; 95% CI [-1.89- -1.49] Test for overall effect: Z=16.40(P<0.001))	No SAE was reported Two studies reported minor adverse effects The upper arm receiving moxibustion showed flushing, itching and no blisters, treatment was discontinued 45 bruises, hematoma 2 times, pain 2 times and skin infection 1 time but not treatment related
Zhang et al 2019	Yao 2016 Smith 2014 Huang 2014 Jin 2017 Zhao 2012 Bao 2017	Diameter of elbow joint (WMD 6.0; 95%CI 5.11-6.89; p<0.001) Huang 2014 (Suspended moxibustion with acupuncture & functional exercise vs Hydrochlorothiazide, spironolactone, functional exercise and living nurse) Zhao 2012 (Suspended moxibustion vs Usual care) Effect rate of reduction in upper lymphedema (RR1.4; 95% CI 1.17-1.67; p<0.001) Huang 2014 (Suspended moxibustion with acupuncture & functional exercise vs Hydrochlorothiazide, spironolactone, functional exercise and living nurse) Zhao 2012 (Suspended moxibustion vs usual care) Effect rate of lymphedema reduction index (WMD 23.34, 95% CI 10.74-35.94 p<0.001) Jin 2016 (Laser acupuncture vs Usual care) Yao 2018 (Warm acupuncture vs Diaosim tablets)	Bao et al reported adverse events such as bruising, hematoma and pain in patients who received acupuncture. No adverse events were reported in other studies
Yu et al 2020	Yao 2016 Fen 2018 Huang 2014 Jiao 2017 Xin 2018 Yang 2017 Zhao 2012 Bao 2018	Effective rate (OR4.23; 95% CI 2.1-8.49; Z=4.07 p<0.001) Fen 2017 (Acupuncture with cupping and Hydrochlorothiazide vs hydrochlorothiazide) Huang 2014 (Suspended moxibustion with acupuncture & functional exercise vs Hydrochlorothiazide, spironolactone, functional exercise and living nurse) Xin 2018 (Acupuncture with shiatsu & conventional nursing vs conventional nursing) Zhao 2012 (Moxibustion with acupuncture vs Comprehensive conventional exercise) The range of Motion Flexion (MD 0.19; 95% CI; -3.68 – 4.06; Z=0.09, p=0.92) Yang 2017(2) (Electroacupuncture and PT vs PT) Yao 2018 (Warm acupuncture needle vs Diosmin) Extension (MD 0.42; 95% CI 12.22 – 3.06; Z=0.31. =0.75) Volume increased 397.2 ±9.3 ml (Treatment group) and 562.6 ±12.3 ml (Control group) p<0.05	4 out of 8 RTCs assessed adverse events. Only one study reported pain (2.6%), skin infection (1.3%) and hematoma (2.6%).