



Acupuncture for Hot Flashes in Cancer Patients: Clinical Characteristics and Traditional Chinese Medicine Diagnosis as Predictors of Treatment Response

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Abstract

Background: Acupuncture is a recognized integrative modality for managing hot flashes. However, data regarding predictors for response to acupuncture in cancer patients experiencing hot flashes are limited. We explored associations between patient characteristics, including traditional Chinese medicine (TCM) diagnosis, and treatment response among cancer patients who received acupuncture for management of hot flashes. **Methods:** We reviewed acupuncture records of cancer outpatients with the primary reason for referral listed as hot flashes who were treated from March 2016 to April 2018. Treatment response was assessed using the hot flashes score within a modified Edmonton Symptom Assessment Scale (0-10 scale) administered immediately before and after each acupuncture treatment. Correlations between TCM diagnosis, individual patient characteristics, and treatment response were analyzed. **Results:** The final analysis included 558 acupuncture records (151 patients). The majority of patients were female (90%), and 66% had breast cancer. The median treatment response was a 25% reduction in the hot flashes score. The most frequent TCM diagnosis was qi stagnation (80%) followed by blood stagnation (57%). Older age ($P = .018$), patient self-reported anxiety level ($P = .056$), and presence of *damp accumulation* in TCM diagnosis ($P = .047$) were correlated with greater hot flashes score reduction. **Conclusions:** TCM diagnosis and other patient characteristics were predictors of treatment response to acupuncture for hot flashes in cancer patients. Future research is needed to further explore predictors that could help tailor acupuncture treatments for these patients.

Keywords

acupuncture, hot flashes, traditional Chinese medicine, integrative medicine, cancer, complementary health approaches

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Introduction

Hot flashes are a common symptom among cancer patients, particularly women with breast cancer who receive endocrine therapy or with chemotherapy-induced ovarian failure^{1,2} and men with prostate cancer who undergo androgen-deprivation therapy.³ Hot flashes, though not life-threatening, can adversely affect the quality of life and may result in poor tolerance and early discontinuation of treatment.⁴⁻⁶ Most patients with cancer therapy-related hot flashes are limited to receiving non-hormonally based interventions because hormone replacement therapy is contraindicated

for them. Non-hormonally based drugs such as antidepressants, gabapentinoids, and other centrally acting agents have shown limited benefit compared with estrogen,⁷ as well as considerable side effects.^{8,9}

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Acupuncture, a therapy that has been used for more than 2500 years as part of traditional Chinese medicine (TCM), is now used in at least 103 countries.¹⁰ Many comprehensive cancer centers incorporate acupuncture for cancer symptom management.¹¹ Though the underlying mechanisms of acupuncture are not fully understood, its role in the management of various cancer- and treatment-related symptoms has been well characterized.¹² Our own published experience in an outpatient cancer care setting has demonstrated statistically and clinically significant effects of acupuncture on self-reported symptoms.¹³

Acupuncture has shown promising treatment efficacy for managing hot flashes and a low incidence of adverse effects.¹⁴⁻¹⁶ Mao et al¹⁷ found that the effects of electroacupuncture on hot flashes among women with breast cancer were similar to, but more durable than, those of gabapentin, with fewer side effects. Another large randomized clinical trial found that compared with enhanced usual care alone, the addition of acupuncture was superior in reducing hot flashes and improving quality of life among breast cancer patients.¹⁸

A heterogeneous response rate of acupuncture for hot flashes has been reported by many studies^{12,19,20} and observed by our acupuncture practitioners. This should not be surprising considering well-known variations in disease response to many conventional treatments. However, information about predictors for acupuncture response is much more limited compared with what is known about conventional treatment. One study of 209 perimenopausal and postmenopausal women (age 45-60 years) with hot flashes reported that older age and presence of the TCM diagnosis of *kidney yin deficiency* predicted low acupuncture response rate.²¹ Our study aimed to measure the association of patient characteristics, baseline symptoms, and TCM diagnosis with response to acupuncture for management of hot flashes in cancer patients.

Methods

Study Design and Patients

This retrospective study was approved by The University of Texas MD Anderson Cancer Center's Institutional Review Board in accordance with an assurance filed with, and approved by, the Department of Health and Human Services. Acupuncture records of patients treated from March 2016 to April 2018 were identified through a search of the institutional electronic medical records. The primary reason for acupuncture referral, Patient-Reported Outcomes Measurement Information System (PROMIS)-10 scores, before and after acupuncture treatment scores from a modified Edmonton Symptom Assessment Scale²² (ESAS; 0-10 scale) including scores for hot flashes, and TCM diagnosis were extracted from

acupuncture treatment notes in the medical record. Patients' demographics, vital signs including weight and height at each visit, International Classification of Diseases, Ninth Revision (ICD-9) codes, and pharmacy data were obtained from the institutional data warehouse.

The study included all patients with cancer who received acupuncture treatment for a primary indication of hot flashes. Each acupuncture session was documented indicating the details of the acupuncture treatment, ESAS scores that were collected immediately before and after treatment, and TCM assessment and diagnosis. For each visit, treatment response was calculated: (ESAS hot flashes score before acupuncture treatment – ESAS hot flashes score after acupuncture treatment) × 100/ESAS hot flashes score before acupuncture treatment. Body mass index (BMI) was calculated using the formula weight in kg/(height in m)². Charlson Comorbidity Index was calculated using ICD-9 codes.²³ A patient was considered to be on hormonal treatment if he/she received any of the following drugs: tamoxifen, anastrozole, letrozole, megestrol, medroxyprogesterone, fulvestrant, exemestane, megestrol acetate, or toremifene at the time of acupuncture treatment, or his/her acupuncture treatment was within 3 months following leuprolide or 1 month following goserelin administration. Similarly, non-hormonal pharmacologic management for hot flashes was defined as being on venlafaxine, desvenlafaxine, citalopram, escitalopram, paroxetine, sertraline, fluoxetine, gabapentin, or pregabalin during the time period of receiving acupuncture.

Intervention

Patients referred to the Integrative Medicine Center from within MD Anderson Cancer Center, a large tertiary institution specializing in cancer care and research, were initially evaluated by a physician and referred for acupuncture treatment based on the physician's assessment after reviewing the patients' oncology history and symptoms. Acupuncture treatment was provided in our outpatient center by licensed, experienced (>10 years average) acupuncturists credentialed through the institution's Medical Staff Office. Initial acupuncture visit duration was approximately 1 hour, with follow-up visits of about 30 minutes. The acupuncturists obtained a symptom history from patients, conducted a physical assessment that included pulse palpation and tongue inspection, and then formulated TCM diagnoses and individualized treatment plans outlining acupuncture point selection. The TCM diagnoses and chosen acupuncture points were based on the clinical judgment of the treating acupuncturist following TCM diagnostic principles. One TCM diagnosis usually represents a group of symptoms rather than a single symptom. For instance, symptoms of fatigue, edema, swelling, abdominal distension, cold extremities, and poor memory and appetite in a patient with

hot flashes indicate a diagnosis of *damp accumulation*, while the presence of sensations of heat, especially in the face in the afternoon, sweating, cheek flush, dizziness, poor vision (especially at night), insomnia, palpitations, and irritability is consistent with a diagnosis of *yin deficiency*.²⁴ The symptom of hot flashes can be associated with different diagnoses depending on its accompanying symptoms. The acupuncturists were not under mandates of protocols with predetermined TCM diagnosis or acupuncture point selection for individual referring symptoms. TCM assessment and diagnoses were documented in the medical record as part of the acupuncture encounter. The acupuncture procedure involves inserting small, sterile, solid, stainless steel needles, typically 32 to 40 gauge, into specific acupuncture points on the body. The needles are left in place for 20 to 30 minutes. Manual or electrical stimulation of the needles may be applied to augment the acupuncture effects. No restrictions were placed on treatment frequency, which varied according to patient response, changes of symptoms, and patients' convenience to clinical visits.

Statistical Analysis

The primary outcome was treatment response, defined as $(\text{ESAS hot flashes score before acupuncture treatment} - \text{ESAS hot flashes score after acupuncture treatment}) \times 100 / \text{ESAS hot flashes score before acupuncture treatment}$. We used descriptive statistics to report the frequencies, medians, means, and standard deviations of the study variables for the study cohort. Univariate analysis between patients' characteristics and TCM diagnosis and treatment response was evaluated using the mixed-effects linear regression. Factors with P value below .2 from the univariate analysis were considered for multivariate analysis. Mixed effects linear regression was further applied in the multivariate analysis with variable selection based on conditional Akaike Information Criterion (cAIC) to identify the best set of predictors.²⁵ All statistical analyses were performed using R software (version 3.5.0, The R Foundation, <http://www.r-project.org>).

Results

Figure 1 depicts the flow of patient selection. The final cohort included 151 patients and 558 acupuncture treatment records.

Patient Characteristics

Patient characteristics are reported in Table 1. Women accounted for 89.9% of the study population, and breast cancer 65.8% of all cancer diagnoses. The median age and BMI were 53 years and 27.6 kg/m², respectively. The median ESAS hot flashes score before acupuncture

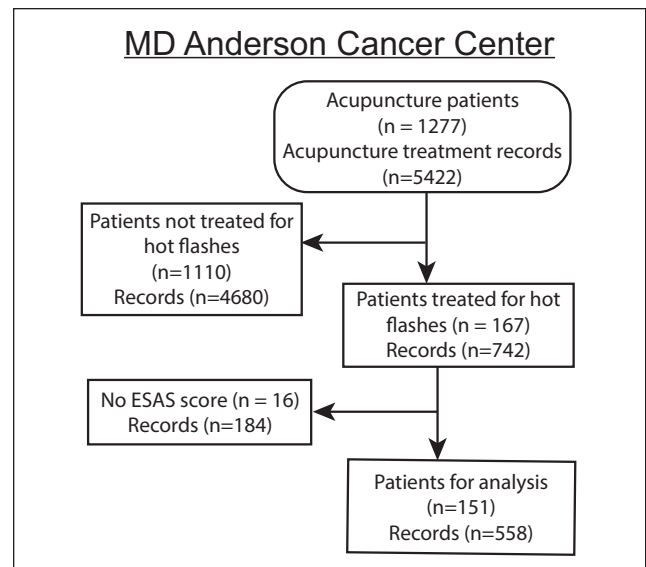


Figure 1. Flow chart of study eligibility.

treatment was 5. A median of 3 acupuncture treatments were received per patient, with a median treatment response of 25% reduction in the hot flashes score. Table 1 lists the 5 most frequent TCM diagnoses in the study patients, with *qi stagnation* being the most common. Each patient may have one or more TCM diagnoses.

Univariate Analysis

Among the clinical and demographic characteristics, only age was significantly correlated with treatment response ($P = .019$), with older age having a greater reduction in the hot flashes score (Table 2). None of the patient self-reported symptoms were associated with reduction in the hot flashes score in response to acupuncture, except anxiety level. Anxiety levels were positively correlated with treatment response ($P = .054$), suggesting the higher the anxiety levels the better the response. A TCM diagnosis of *damp accumulation* was associated with greater reduction in the hot flashes score ($P = .032$). Receiving hormonal/endocrine therapy or a pharmacological intervention for hot flashes did not correlate significantly with treatment response of hot flashes to acupuncture.

Multivariate Analysis

The model selection for multivariate analysis included 5 factors that were $P < .2$ from the univariate analysis. The model achieving the minimum cAIC value indicates the best predictive performance in estimating treatment response. The significant factors are shown in Table 3. Age (1.823; $P = .018$), anxiety level (1.793; $P = .056$), and TCM diagnosis of *damp accumulation* (12.276; $P = .047$) all

Table 1. Patient Demographic, Clinical, and TCM Characteristics.

Characteristic	n (%)
Total	167
Age, median [IQR], years	52 [47-61]
Race	
White	122 (73.1)
Non-White	45 (26.9)
Sex	
Female	150 (89.8)
Male	17 (10.2)
BMI, median [IQR]	27.6 [23.9-32.8]
Charlson comorbidity index, median [IQR]	2 [2-6]
Cancer type	
Breast	102 (65.8)
Prostate	10 (6.5)
Other	55 (35.5)
Pretreatment hot flashes score, median [IQR]	7 [5-8]
Patients with pretreatment TCM diagnosis	
Qi stagnation	135 (80.8)
Blood stagnation	95 (56.9)
Yin deficiency	90 (53.9)
Qi deficiency	76 (45.5)
Damp accumulation	42 (25.1)
Number of acupuncture treatments, median [IQR]	3 [1-6]
Treatment response, median [IQR], percent	25% [0% to 66.7%]

Abbreviations: TCM, traditional Chinese medicine; IQR, interquartile range; BMI, body mass index.

remained associated with larger decrease in hot flashes score in the multivariate analyses. Though *P* value for anxiety was .056 indicating marginal significance, the addition of anxiety in multivariate analysis improved the overall predictive performance for acupuncture response.

Discussion

Our study is the first of its kind as we included a large cohort of cancer patients who received acupuncture treatment for hot flashes and examined the association between changes in hot flashes and multiple common demographic and clinical characteristics such as sex, age, self-reported symptoms, pharmacological factors, and TCM diagnosis. It is also unique that our study evaluated TCM diagnosis and treatment response of each individual acupuncture treatment session. The research methodology was designed to model the TCM clinical practice principle of independently evaluating each acupuncture encounter and to reach a TCM diagnosis that may vary from visit to visit as symptom clusters and clinical assessment change. Our study used a novel

approach to explore correlations between TCM diagnosis and treatment response in a real-world acupuncture practice setting, and our findings suggest future research designs should include TCM diagnosis as predictors of symptom response to acupuncture treatment.

Although older age was previously reported to be associated with more severe vasomotor symptoms of hot flashes²⁶ and to predict a lower acupuncture response rate,²¹ our findings indicated age was associated with greater acupuncture response. The difference could be due to our study population being cancer patients only and/or to differences in the study designs. Future studies are needed to confirm such associations in cancer patients and determine whether these clinical factors affect the immediate and cumulative treatment response to acupuncture differently.

Mood disorders including anxiety are common among cancer patients.²⁷ Anxiety is reported to significantly predict hot flashes in menopausal women as well as in patients with breast cancer and treating anxiety is suggested as an intervention target to reduce hot flashes.^{28,29} Our analysis showed that patient self-reported anxiety level prior to acupuncture treatment was associated with a better treatment response of reducing hot flashes. This interesting observation may not necessarily indicate anxiety as a beneficial predictor of treatment response of hot flashes to acupuncture, but rather is a reflection of the uniqueness of acupuncture as a treatment modality that aims at not only the primary symptom but also the coexisting symptoms. Future studies are needed to further confirm and explore the impact of patient self-reported symptoms on acupuncture treatment response.

Our study patients with the TCM diagnostic category of *damp accumulation* had a more favorable response to acupuncture than those without *damp accumulation*. Predicting acupuncture response by TCM diagnosis has rarely been studied. Avis et al²¹ observed significant differences in TCM diagnosis among women with hot flashes and found *kidney yin deficiency* was associated with less reduction in hot flashes in response to acupuncture. Similarly, our study also observed significant differences in TCM diagnosis for the primary symptom of hot flashes among the patients, but differently, *qi stagnation* was the most frequent TCM diagnosis. The current understanding of the relationship between TCM diagnoses/syndromes and disease pathophysiology by conventional Western medicine is very limited. Nevertheless, similar to conventional Western medicine, TCM diagnosis of bodily dysfunction has significant prognostic value.²⁴ The impact of TCM diagnosis on acupuncture treatment response deserves further investigation.

Our study is unique in its study design modeling TCM principles of assessment and treatment by which diagnosis could vary from one acupuncture visit to another depending on accompanying symptom clusters. The clinical practice of acupuncture is often methodologically different from

Table 2. Univariate Analysis of Treatment Response.

	Factors	Coefficient	P
Clinical characteristics	Age	0.648	.019
	Body mass index	-0.153	.710
	Charlson Comorbidity Index	2.270	.185
	Sex—Male	0.525	.959
	Race—White	-4.938	.468
Patient self-reported symptoms	Anxiety	1.823	.054
	Depression	0.965	.397
	Fatigue	0.725	.388
	Sleep problems	-0.491	.526
	Financial distress	-0.062	.945
	PROMIS PH	-0.315	.805
	PROMIS MH	0.836	.457
TCM diagnosis	Qi stagnation	2.921	.675
	Blood stagnation	1.241	.823
	Yin deficiency	7.356	.190
	Qi deficiency	-3.300	.558
	Damp accumulation	13.263	.032
Pharmacologic intervention	Active hormonal therapy	-0.446	.149
	Active antihot flashes therapy	0.056	.906

Abbreviations: TCM, traditional Chinese medicine; PROMIS PH, Patient-Reported Outcomes Measurement Information System, Physical Health; PROMIS MH, Patient-Reported Outcomes Measurement Information System, Mental Health.

Table 3. Multivariate Analysis of Treatment Response.

Factors	Coefficient	P
Age	0.654	.018
Anxiety	1.793	.056
Damp accumulation	12.276	.047

many acupuncture research, which mostly applies pre-fixed acupuncture points based on presumed diagnosis for the targeted symptom without consideration of accompanying symptom clusters. This retrospective review of associations between patient self-reported symptoms and TCM diagnosis and acupuncture treatment response of hot flashes will enrich the current literature, which lacks reports on real-world acupuncture practice. More clinically relevant research is needed to identify predictors of acupuncture treatment response and treatment individualization.

Our retrospective study shares some methodological challenges that has confronted clinical acupuncture research illustrated in many systematic reviews.^{12,19} First, the association of symptom clusters and TCM diagnosis is not so clearly defined by the TCM diagnostic principles that only an exclusive diagnosis can be concluded from a unique cluster of symptoms. Thus, variations of TCM diagnosis by individual acupuncturists are unavoidable. In addition, the current understanding of biological mechanisms of acupuncture and underlining pathophysiological process of

TCM diagnosis is severely lacking. These challenges faced in acupuncture research as well as real-world practice demand extensive basic and clinical acupuncture research collectively to provide the solutions that can produce a standardized guideline for the practice of this ancient Chinese method globally. Our study has some other limitations to note. It focused only on hot flashes in cancer patients and 90% of patients included in the analysis were women. This limits its generalizability to other symptoms, and it may not be representative of response in males. However, sex was not associated with treatment response. Anxiety, among many factors that are involved in nonspecific (placebo) effects of acupuncture,³⁰ has been reported to affect treatment expectation in patients receiving acupuncture therapy.³¹ Reduction in anxiety is often observed in response to acupuncture that is targeted on other symptoms.^{32,33} Our observation of anxiety predicting acupuncture response may also reflect nonspecific effects of acupuncture treatment. However, age is not known to affect patient expectation about acupuncture. Though the acupuncture treatments for our patients were initiated by the referral physician's suggestions, they are free to decide whether or not to receive or continue the treatments. Self-selection bias may be limited, but cannot be excluded in our study. Furthermore, this was not a randomized controlled trial and a comment on efficacy cannot be made with the current design. The time interval between acupuncture treatments and total number of treatments received by each patient differed between patients. The impact of these factors on acupuncture

response cannot be excluded and the specificity of acupuncture treatment response cannot be determined. Future prospective studies are needed to determine the optimum acupuncture treatment frequency and duration for hot flashes and to confirm the predictive impact of clinical characteristics and TCM diagnosis on the treatment response.

Conclusions

Age, patient self-reported symptoms, and certain features of TCM diagnoses were predictors of treatment response to acupuncture for hot flashes in cancer patients in a large hospital practice. Future research is warranted to further explore predictors that can guide personalization of acupuncture treatment for these patients.

Declaration of Conflicting Interests

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