Effectiveness of Acupuncture in Relieving Chemotherapy-induced Leukopenia in Patients With Breast Cancer: A Systematic Review With A Meta-Analysis and Trial Sequential Analysis

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Abstract

Background: Breast cancer is one of the most common cancers and a major cause of death in women worldwide. Chemotherapy is mainly used to treat and control the progression of breast cancer. Leukopenia is the most common side effect of chemotherapy which may decrease immune function and further lead to serious fatal infections. The purpose of this study was to evaluate the effect of acupuncture on regulating hematopoietic function in chemotherapy-induced leukopenia among patients with breast cancer. **Methods:** PubMed, Embase, Cochrane Library, CINAHL Plus, Web of Science, and Chinese articles in the Airiti Library and China National Knowledge Infrastructure (CNKI) databases were searched to August 2021 for papers to include in a systematic review and meta-analysis. A random-effects model was applied. The effect size was calculated by Hedges' g. Heterogeneity was determined using Cochran's Q test. Moderator analyses were performed to examine potential sources of heterogeneity. A trial sequential analysis (TSA) was conducted to determine whether the current sample size was sufficient. **Results:** Ten randomized controlled trials involving 650 participants were eligible for inclusion. Analysis by the random-effects model showed a significant effect by acupuncture of ameliorating leukopenia during chemotherapy. Levels of white blood cells (WBCs) were increased (Hedges' $g = 0.70$, $P < .001$, $I^2 = 34\%$), neutrophil counts (Hedges' $g = 0.80$, $P < .001$, $I^2 = 0\%$) were significantly enhanced. Moreover, regardless of the manner through which acupuncture was applied, overall values of WBCs increased. **Conclusions:** The current meta-analysis supports acupuncture possibly ameliorating chemotherapy-induced leukopenia, as WBC and neutrophil values significantly increased after acupuncture in patients undergoing chemotherapy. Additionally, regardless of the type of acupuncture, values of WBCs increased. These findings are actionable and support both the clinical use of acupuncture to relieve chemotherapy-induced leukopenia and further research regarding the use of acupuncture in patients experiencing immunosuppression when undergoing chemotherapy.
Trial Registration: PROSPERO-CRD42020215759.

Keywords

leukopenia, chemotherapy, acupuncture, breast cancer, meta-analysis

Background

Breast cancer is one of the most common cancers and a major cause of death in women worldwide. Chemotherapy is the most effective therapeutic approach for treating cancer. It is administered as adjuvant or neoadjuvant therapy for early-stage breast cancer and is also administered for palliative purposes for metastatic breast cancer.[1] Many patients are treated with moderate to high toxicity chemotherapy, including doxorubicin/epirubicin, paclitaxel/docetaxel, and cyclophosphamide with or without 5-fluorouracil. Although it is an effective way to manage cancer cells, it is also harmful to the hematopoietic system.[1,2]

Previous clinical trials demonstrated that taxane and cyclophosphamide, 2 chemotherapeutic drugs, are the main regimens for breast cancer. They can cause bone marrow

suppression (leukopenia, thrombocytopenia, and anemia)[1,3] and severe immunosuppression, which may lead to serious and fatal infections, including respiratory infections and sepsis.[4]

Once leukopenia occurs, treatment schedules should be interrupted and the treatment course may even be discontinued. In the clinic, granulocyte colony-stimulating factor (G-CSF) is the most common administered to reduce the risks of leukopenic complications associated with chemotherapy.[5] However, it can result in many problems, such as aching in the bones and muscles, dyspnea, chest pain, nausea, hypoxemia, anaphylaxis, syncope, and flushing.[6,7] And also, the G-CSF injection is conditional only for patients with a white blood cell (WBC) count of $<1000/\mu L$ or an absolute neutrophil count (ANC) of $<500/\mu L$.[8] Therefore, using a subcutaneous injection of G-CSF to prevent or treat chemotherapy-induced leukopenia cannot benefit all oncologic patients.

With regard to G-CSF, there are some other therapeutic approaches toward improving chemotherapy-induced leukopenia, such as mistletoe extracts,[9] Chinese herbal medicine decoctions (Sijunzi Tang),[10] chamomile,[11] Wenshen Shengbai decoction with moxibustion[12] and also acupuncture. Furthermore, acupuncture is the most commonly used as a complementary therapy in patients with leukopenia during chemotherapy.[13]

Acupuncture is a traditional Chinese medicine (TCM) based approach for treating a wide variety of symptoms by triggering specific acupoints on the skin with needles, which has been observed to alleviate adverse effects of surgery or chemotherapy for cancer patients, including postoperative arm lymphedema,[14] chemotherapy-induced nausea and vomiting,[15,16] and chemotherapy-induced peripheral neuropathy[17,18] and leukopenia.[19,20] It is strongly suggested to provide a comprehensive review of the effect of acupuncture in relieving chemotherapy-induced leukopenia in patients with breast cancer. Nevertheless, as of today, there was only one systematic review focused on the breast cancer population for acupoint stimulation-managed treatment-related side-effects in breast cancer,[21] although there are published academic studies evaluating the association between acupoint injection/acupuncture and chemotherapy related complications in patients with lung cancer regardless of the tumor type.[13,19,22] There has been no systematic review with a meta-analysis study that has evaluated the association between the effects of acupuncture and chemotherapy-induced hematopoietic suppression in patients with breast cancer so far. Therefore, the purpose of this systematic review with a meta-analysis was to evaluate the effects of acupuncture on chemotherapy-induced hematopoietic suppression in patients with breast cancer, including changes in blood counts, and further, to use a trial sequential analysis (TSA) to determine whether the sample size is sufficient in the current study.

Methods

This review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines. This review was registered with PROSPERO (International Prospective Register of Systematic Reviews: CRD42020215759).

Literature Sources and Search Strategy

Studies were identified by a comprehensive literature search of the following electronic databases up to August 2021: PubMed, Embase, Cochrane Library, CINAHL Plus, Web of Science, and Chinese articles in the Airiti Library and China National Knowledge Infrastructure (CNKI). The search was restricted to human populations, and only in the English or Chinese language, and there was no time restriction on publications. We also reviewed references, government publications, and recommendations from the included studies.

The strategy combined or separated Medical Subject Heading (MeSH) terms and all fields of white blood cell, bone marrow suppression, breast cancer and acupuncture. The detailed search strategy for PubMed is shown in Supplemental Table 1.

Inclusion Criteria

All RCTs in English or Chinese were included without a time restriction. Participants of any race or gender and who were at least 18 years old with a diagnosis of breast cancer at any stage and under chemotherapy were included.

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Interventions of studies which evaluated any type of invasive (with/without electrical stimulation) or non-invasive acupuncture (moxibustion) were included. A study had to include a hematopoietic outcome indicator such as WBCs.

Exclusion Criteria

Observational, cohort, and case-control studies, case reports, qualitative studies, non-RCTs, review articles, and laboratory (animal) studies were excluded. Also, studies with participants with a disease of the hematopoietic system or immune deficiency, or with participants duplicated from other included studies were excluded.

Data Extraction and Quality Assessment

Two investigators (Y.W.S. and J.Y.S.) independently identified titles and abstracts of articles obtained using the above described search strategy and extracted the general characteristics of eligible studies. Discrepancies were resolved by discussion with a third investigator (H.T.T.).

Studies for further review were selected on the basis of the following inclusion criteria: (1) humans who had been diagnosed with breast cancer at any stage and were undergoing chemotherapy; (2) with an RCT study design; (3) studies that used acupoint stimulation as the intervention, such as, acupuncture, moxibustion, which are invasive or non-invasive interventions; and (4) studies that investigated regulation of hematopoietic indicator, for example WBCs.

Evaluation of the methodological quality of the included studies was based on the Cochrane risk of bias tool (RoB).[23] The following elements in trials were assessed: random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias. The tool ranks evidence from research studies as having "high," "low," or "unclear" levels of bias. The rank of high risk of bias is interpreted as bias that may affect the research results dramatically; for low risk of bias, the bias does not affect the research results dramatically; for unclear of bias, there is insufficient information to assess whether an important risk of bias exists.[24] This assessment tool also is appropriate for the evaluation of the methodological quality of RCTs.[23,24] Two investigators (Y.W.S and J. Y. S.) independently extracted data from the studies (Table 1), and any disagreements were resolved by discussion or consultation with a third independent reviewer (H.T.T.).

Statistical Analysis

Two-sided *P* values were calculated, with $P < .05$ set as the level of statistical significance. First, pre- to post-test changes in scores were derived for the intervention group and control group from each included study.[23] Then, the effect size for the difference between the intervention and control groups was calculated for each study. Hedges' g was used as the effect size index using the formula: $g = d(1-(3/(4(n_1 + n_2)-9)))$.[23,25] Results are expressed as the effect size (Hedges' g) with the 95% confidence interval (CI). A Hedges' g value of 0.2 to 0.4 represents a small effect size, 0.5 to 0.7 a moderate effect size, and ≥ 0.8 a large effect size.[25] A random-effects model was chosen because all included study characteristics differed: stage of cancer, different cancers, type of acupuncture (manual acupuncture or electro-acupuncture), theoretical principles of acupuncture points selected (fixed or unfixed points), total treatment dose (min), and the quality of the study.

Heterogeneity was determined using Cochran's *Q* test, with statistical significance at $P < 0.1$, and the I^2 statistic was used to determine the proportion of total variance in the pooled effect size that was caused by heterogeneity among studies. An I^2 value of 0% indicates no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and $\geq 75\%$ high heterogeneity.[26]

Moderator analyses were performed to examine potential sources of heterogeneity. Once heterogeneity was detected, subgroup analyses and meta-regression analyses were conducted to determine the possible influences of certain effects.[23] Evaluation of publication bias using funnel plots was performed if the number of studies more than 10.[27] Comprehensive Meta-analysis (CMA) vers. 3.0 was used for all statistical analyses.

TSA is a methodology in which the evidence required is quantified, providing a value for the required information size. We applied a TSA to determine whether the sample size was sufficient to detect the specific effect, which can only be calculated using three or more trials. TSA was performed at the level of an overall 5% risk of a type I error and with 80% power. In the TSA, if the cumulative Z curve entered the futility area or crossed the trial sequential monitoring boundary, the anticipated intervention effect might reach a sufficient level of evidence, and further trials would not need to be included in the current meta-analysis.[28] We calculated the required information size based on the mean difference and variance in change of blood cell count levels. The TSA was conducted using TSA vers. 0.9 beta software.

Results

Study Selection

In total, 73 studies were identified from an initial search, and additional records identified initial searches other sources (n=3), 10 duplicate articles were excluded. Records were screened for 66 articles, and a further 15 articles were excluded due to the following reasons: conference or editorial (n=2), animal/cell studies (n=4), meta-analyses or reviews (n=9). In total, there were 51 studies remaining for full manuscript

Table 1. Characteristics of the Included Studies.

No	Authors	Country	No. of subjects in each arm (experimental:control)	Chemotherapy drug	Acupuncture group Acupoints	Acupuncture group Intervention	Intervention dose (mins)	Control group intervention	Assessment of outcomes
1	Beith et al[29]	Australia	14:16	AC FEC	PC6/IL4/ST36	Electro-acupuncture	80	Sham Electro-acupuncture	Nausea and vomiting/WBC/Neutrophil
2	Hu and Zhao[31]	China	30:30	TAC	ST36/SP6/SP10/BL23	Acupuncture	150	Western medicine routine	WBC/Neutrophil
3	Ji et al[38]	China	48:44	Anthracycline-taxane	ST36/SP6/CV8/ST35/ST41	Moxibustion	2400	Without moxibustion	WBC/ANC
4	Li[36]	China	36:36	Anthracycline-taxane	ST36/SP6/CV8/CV4/CV6	Moxibustion	2835	Western medicine routine	WBC/QoL/Neutrophil
5	Lu et al[34]	China	30:30	n/a	BL20/BL24/CV12/CV4	Moxibustion	420	Routine care	WBC/BFI
6	Liu[35]	China	50:50	TEC	CV12/CV4/ST36/CV6/SP10/BL20/BL21/BL17	Moxibustion	320	Western medicine routine	WBC/vomiting
7	Meng and Lü[30]	China	27:27	CAF	ST36/ST25/BL21/BL17/CV6/SP6/SP4/HT7	Acupoint catgut-embedding + moxibustion	10080	Western medicine routine	WBC/ nausea/vomiting
8	Shi[37]	China	30:28	n/a	GV20/CV12/CV4/CV6/CV3/GV4/GV3/GV2	Electro-acupuncture	210	Sham Electro-acupuncture	WBC/Neutrophil nausea/vomiting
9	Xie et al[33]	China	23:23	FEC	ST36/BL23	Acupoint catgut-embedding	NA	Western medicine and Chinese decoction	WBC/ Neutrophil
10	Zhu et al[32]	China	40:38	CAT, CET	ST36/SP10/BL26/SP6/BL23/BL18	Acupuncture	150	Western medicine	WBC

Abbreviations: BFI, brief fatigue inventory; n/a, not mentioned; CAF, cyclophosphamide/Adriamycin/5-fluorouracil; FEC, 5-Fluorouracil/Epirubicin /cyclophosphamide; AC, Adriamycin/Cyclophosphamide; TAC, Taxotere/Adriamycin/Cyclophosphamide; TAC, Taxotere/Adriamycin/cyclophosphamide; TEC, Taxotere/epirubicin/cyclophosphamide; CAT, cyclophosphamide/Adriamycin/Taxotere; CET, cyclophosphamide/epirubicin/Taxotere.
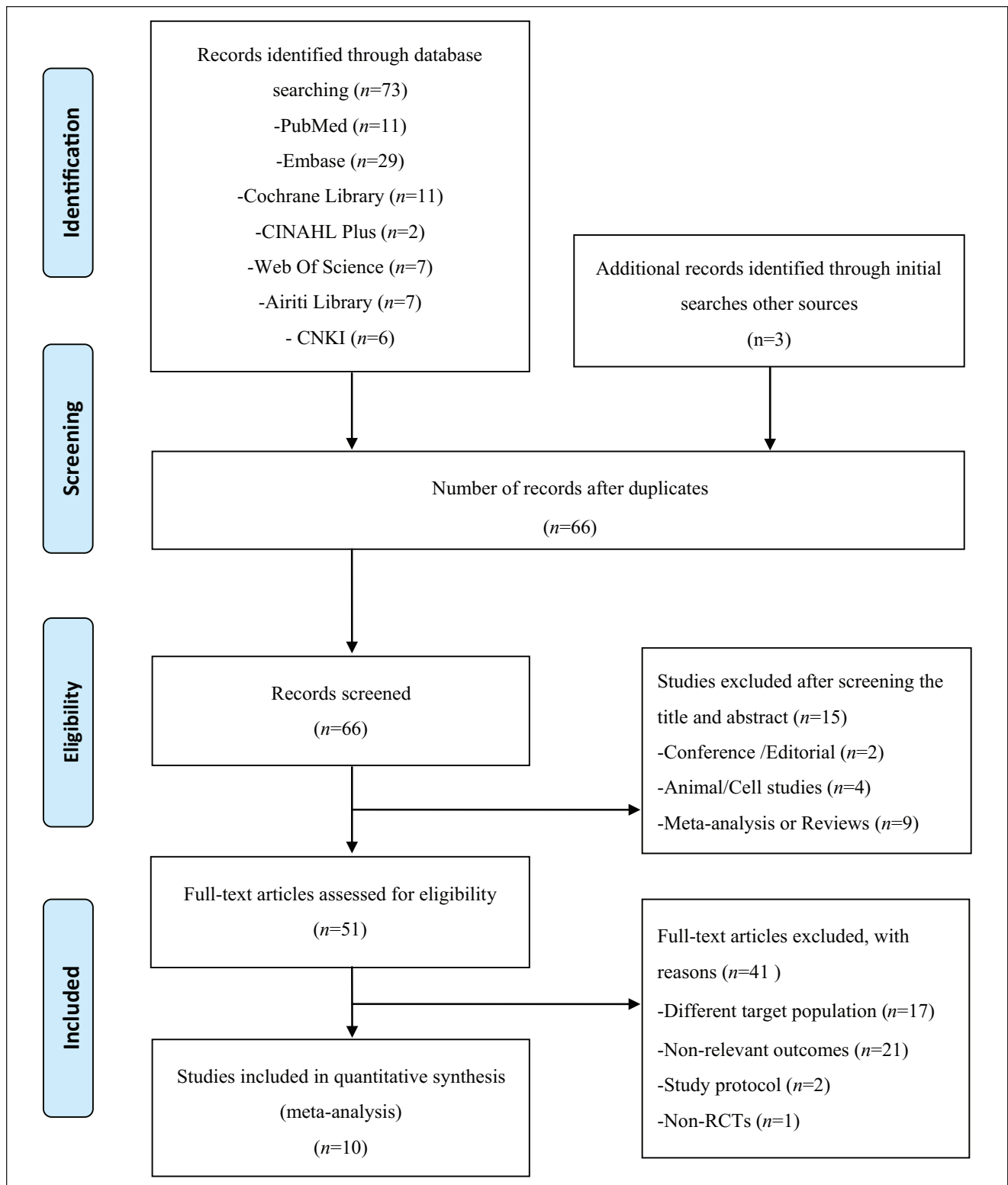
Figure 1. PRISMA flow diagram of the review process.

review, of which 41 studies were excluded due to the following reasons: different target population (n=17), study protocols (n=2), non-relevant outcomes (n=21), non-RCT study design (n=1). Finally, ten studies[29-38] were included for further qualitative and quantitative analyses. The PRISMA flow diagram of the review process is presented in Figure 1.

Table 2. Risk of Methodological Bias of the Included Studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
Beith et al[29]	L	L	L	L	L	L	H
Hu and Zhao[31]	L	H	H	U	L	H	H
Ji et al[38]	L	L	L	L	L	L	L
Li[36]	L	L	L	L	H	L	H
Lu et al[34]	L	L	H	U	L	L	H
Liu[35]	L	L	H	U	L	H	H
Meng and Lü[30]	L	L	H	U	L	L	H
Shi[37]	L	L	H	H	H	L	L
Xie et al[33]	L	H	H	L	L	H	H
Zhu et al[32]	L	H	H	U	L	L	H

Abbreviations: L, low risk; H, high risk; U, unclear risk of bias.

Characteristics of the Included Studies

All 10 of the included studies were conducted with a randomized control design, with a total of 650 participants (intervention, n = 328; control, n = 322). The populations among the included studies were all breast cancer with a wide variety of chemotherapeutic regimens. Papers were published between 2012 and 2019. Most were carried out in China[30-38]; only one took place in Australia.[29] The interventions used different types of acupuncture, including 2 trials with manual acupuncture, 2 trials with electroacupuncture, 2 with acupoint catgut embedding, and 4 moxibustion. Characteristics of the included studies are presented in Table 1.

Methodological Quality Assessment

The methodological quality of the selected studies is reported in Table 2. All included studies reported random sequence generation. Three studies[31-33] reported neither the procedure for allocation concealment nor blinding of participants and personnel in the research, so they presented a high risk of bias. For the item of blinding of the outcome assessment, four[29,33,36,38] were classified as having low risk, and one had high risk. In terms of how the studies addressed incomplete outcome data, 8 studies[29-35,38] were classified as having low risk with reported rates of follow-up and withdrawal, and the remaining 2 had high risk. Seven studies[29,30,32,34,36-38] had a low risk of selective reporting. And also, 2 studies[37,38] had low risk of bias with respect to other sources of bias.

The Effect of Acupuncture on Relieving Hematopoietic-Suppression Outcomes

The overall effect sizes of the ten studies were significant for acupuncture improving WBCs and neutrophils when patients were undergoing chemotherapy. The overall effect size was Hedges' *g* of 0.68, $P < .001$, and $I^2 = 34\%$ for increased WBCs by acupuncture (Figure 2). The overall effect size for increased neutrophils was Hedges' *g* of 0.80, $P < .001$, $I^2 = 0\%$ by acupuncture (Figure 3).

Subgroup Analyses

In this study, subgroup analyses were performed on different types of acupuncture. Mixed effects showed $Q = 2.99$, $P = .08$. This indicated that regardless of the various types of acupuncture, overall WBCs were increased. Data are shown in Figure 4.

Publication Bias

Publication bias did not exist for the WBC models. Egger's test showed that the *t* value was 1.78, $P = .11$. Egger's regression test results are shown in Figure 5.

Trial sequential analysis (TSA)

The TSA was used to determine whether the sample size was sufficient to detect a specific effect, which could only be calculated by 3 or more trials. We examined the effects of WBCs and acupuncture in 8 trials[30-33,35-38] to determine the sufficiency of the sample size. With an α value of 5% (two-sided) and β of 20%, a cumulative *z*-curve (blue) was constructed using a random-effects model. The required information size of WBC levels was calculated to be 456, the *z*-curve crossed both the conventional and trial sequential monitoring boundaries, and the required information size was achieved; thus, there was sufficient evidence to reach a conclusion with no need for additional trials (Figure 6). To our knowledge the TSA of acupuncture on chemotherapy-induced leukopenia was applied for the first time, strengthening the conclusions achieved.
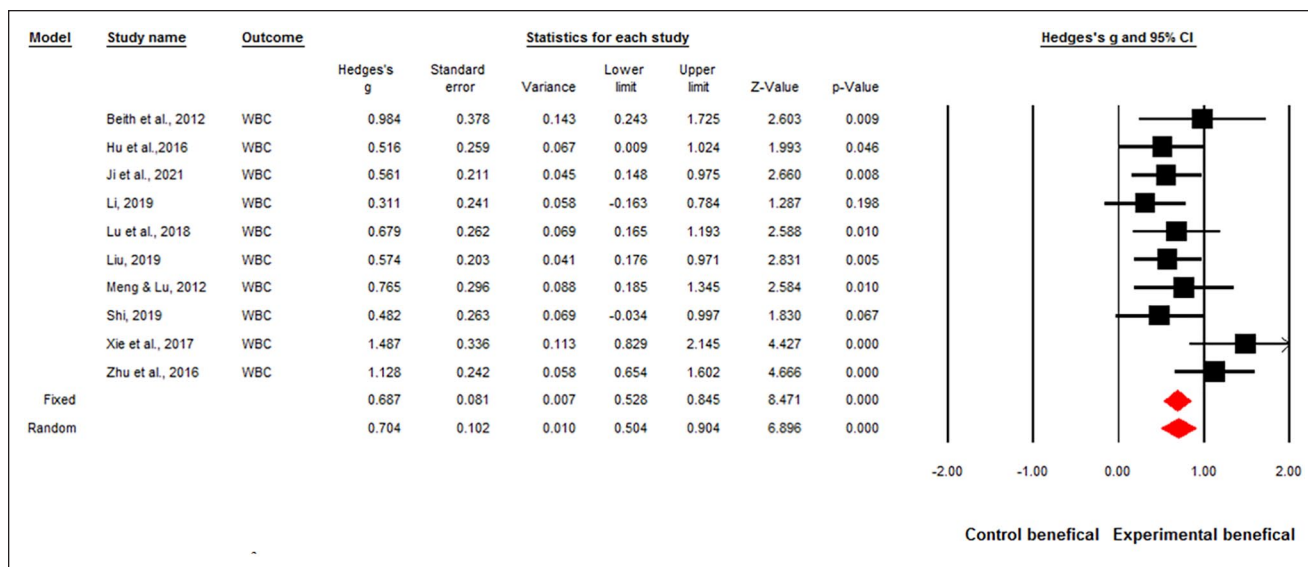
Figure 2. Forest plot of the overall effect sizes for studies measuring white blood cell (WBC) counts and acupuncture.
Q = 13.83, *P* = .12, *I²* = 34%. Fixed-effects Hedges' *g* = 0.68, *P* < .001. Random-effects Hedges' *g* = 0.70, *p* < .001.
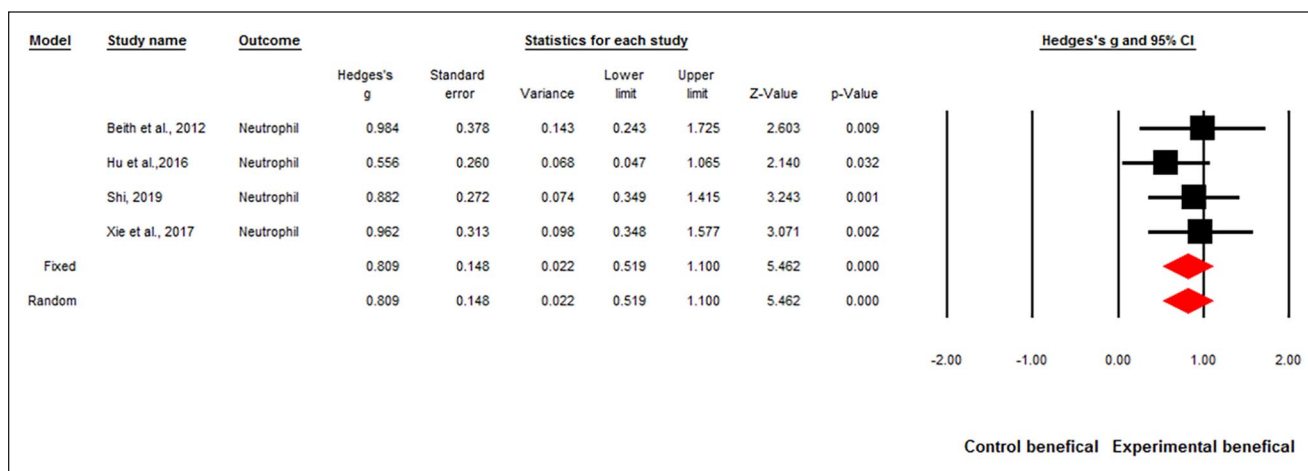

Figure 3. Forest plot of the overall effect sizes for studies measuring Neutrophil counts and acupuncture.
Q = 1.47, *P* = .68, *I²* = 0%. Fixed-effects Hedges' *g* = 0.80, *P* < .001. Random-effects Hedges' *g* = .80, *P* < .001.

Discussion

This meta-analysis of ten RCTs revealed a significant effect of acupuncture on the numbers of WBCs, which could ameliorate chemotherapy-induced hematopoietic suppression-related leukopenia in patients with breast cancer who were undergoing chemotherapy. In addition, regardless of the various types of acupuncture, overall WBCs increased.

Leukopenia often occurs in breast cancer patients who are treated with anthracyclines combined with taxane regimens, which is the primary regimen for breast cancer, thus the degree of leukopenia during chemotherapy is important because it is correlated with a reduction in resistance to

infections, particularly in breast cancer.[4,39] As the current meta-analysis revealed, the value of WBCs could be improved by acupuncture during chemotherapy in breast cancer patients. This result is consistent with a pilot RCT by Pais et al,[40] who investigated the effects of acupuncture on the immune system. All participants were randomized into acupuncture or control groups, and participants in the acupuncture group received 6 sessions of acupuncture point stimulation, twice a week, beginning a week prior to a cycle of chemotherapy and ending at the second cycle of chemotherapy. As their results indicated, the effects on WBCs, the ANC, and NK cells showed statistically significant increases overall compared to the non-acupuncture group (*P* = .036,
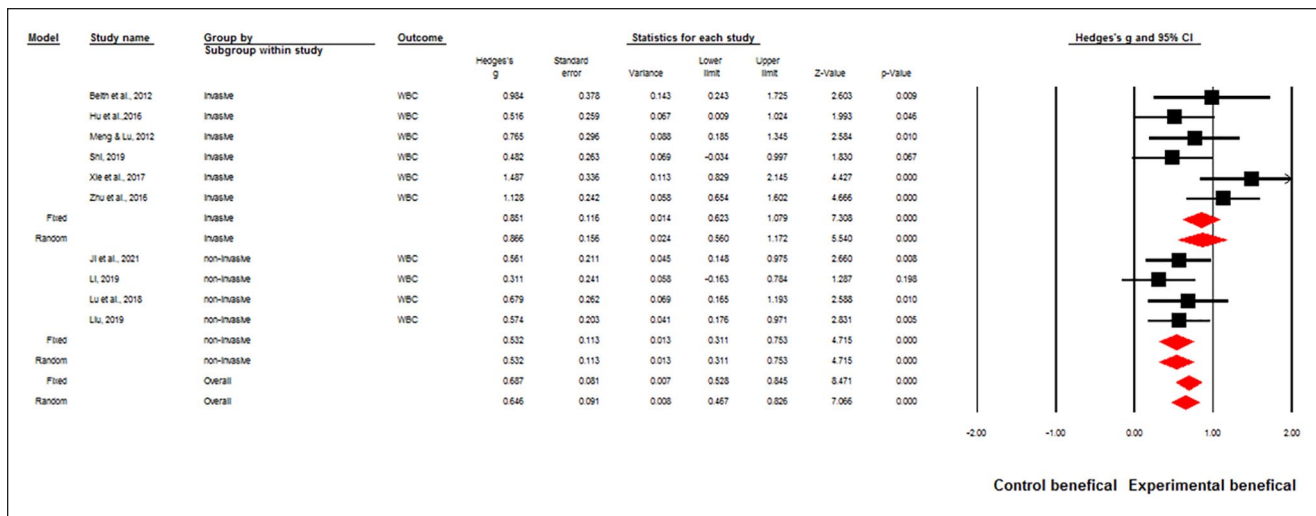
Model	Study name	Group by Subgroup within study	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Beith et al., 2012	Invasive	WBC	0.984	0.378	0.143	0.243	1.725	2.603	0.009
	Hu et al.,2016	Invasive	WBC	0.516	0.259	0.067	0.009	1.024	1.993	0.046
	Meng & Lu, 2012	Invasive	WBC	0.765	0.296	0.088	0.185	1.345	2.584	0.010
	Shi, 2019	Invasive	WBC	0.482	0.263	0.069	-0.034	0.997	1.830	0.067
	Xie et al., 2017	Invasive	WBC	1.487	0.336	0.113	0.829	2.145	4.427	0.000
	Zhu et al., 2016	Invasive	WBC	1.128	0.242	0.058	0.654	1.602	4.666	0.000
Fixed		Invasive		0.851	0.116	0.014	0.623	1.079	7.308	0.000
Random		Invasive		0.866	0.156	0.024	0.560	1.172	5.540	0.000
	Ji et al., 2021	non-invasive	WBC	0.561	0.211	0.045	0.148	0.975	2.660	0.008
	Li, 2019	non-invasive	WBC	0.311	0.241	0.058	-0.163	0.784	1.287	0.198
	Lu et al., 2018	non-invasive	WBC	0.679	0.262	0.069	0.165	1.193	2.588	0.010
	Liu, 2019	non-invasive	WBC	0.574	0.203	0.041	0.176	0.971	2.831	0.005
Fixed		non-invasive		0.532	0.113	0.013	0.311	0.753	4.715	0.000
Random		non-invasive		0.532	0.113	0.013	0.311	0.753	4.715	0.000
Fixed		Overall		0.687	0.081	0.007	0.528	0.845	8.471	0.000
Random		Overall		0.646	0.091	0.008	0.467	0.826	7.066	0.000

Control benefical   Experimental benefical

Figure 4. Mixed-effects model for different types of acupuncture.
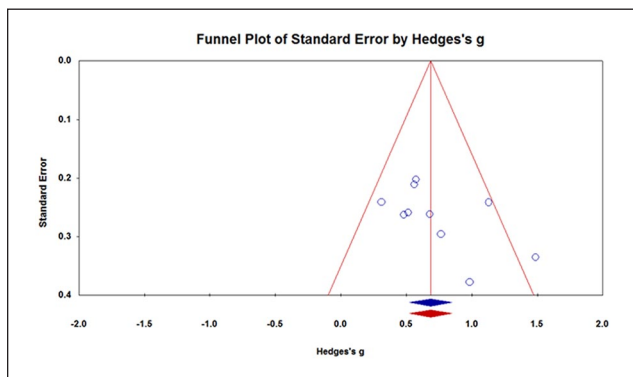Mixed-effect: $Q=2.99$, $P=.08$.

Figure 5. Funnel plot for assessing publication bias.
Egger's test showed that the t value was 1.78, $P=.11$.

$P=.046$, and $P<.0001$, respectively).[40] Additionally, our result was similar to a pilot RCT conducted by Lu et al,[20] in which 21 gynecologic malignancy patients undergoing chemotherapy were randomly assigned to an acupuncture or sham acupuncture group (sham needle sites were inserted away from standard TCM acupuncture points). The outcome measures on WBC values were significantly higher ($P=.04$) than the sham group after 6 interventions.[20]

Neutrophils are a type of white blood cell that is very important to defense and against infection. In breast cancer chemotherapy regimens, a drop in neutrophil blood levels typically occurs when the body uses immune cells faster than it produces them, or when the bone marrow is suppressed after chemotherapy treatment.[5] As our results indicated, the levels of neutrophil were increased by acupuncture significantly during chemotherapy. This finding was consistent with a systematic literature review that evaluated 67 relevant papers, claiming that total leukocytes were increased 43% by acupuncture with a population of leukopenic patients after chemotherapy.[41] In this review articles, the most measured outcome representative were used total leukocytes, followed by lymphocytes and neutrophils; in addition, 2 relevant papers showed neutrophils were enhanced after the intervention of acupuncture or electroacupuncture.[42,43] Another RCT conducted by Beith et al[29] also supported our results, in which 32 breast cancer patients were randomly assigned to true electroacupuncture or sham electroacupuncture while they receiving chemotherapy. There was a statistically significant increase in neutrophil counts compare to the sham electroacupuncture group at week 6 (median 3.55×10^9/L vs. 1.90×10^9/L, $P=.01$).

Our subgroup analysis was conducted with different types of acupuncture and the rise in WBC levels, which showed that regardless of the mode of application of acupuncture, overall leukocytes increased (mixed-effects model: $Q=2.99$, $P=.08$). In our study, the type of acupuncture included invasive, such as, acupuncture, electroacupuncture, catgut; and non-invasive such as moxibustion. Traditional Chinese acupuncture methods include a variety modalities. The principle of acupuncture (invasive/non-invasive) is through acupoint stimulation-increased cytokines and neurochemicals released.[8,21] In addition, acupoint stimulation enhances the antitumor efficacy on breast cancer by regulating the microvascular system and immunosuppression.[36] The clinical effects of acupoint stimulation may be attributable to enhancing immunity, relieving bone marrow suppression, and producing an antioxidant effect.[21] Moxibustion could attenuate inflammatory impairment and have an anti-inflammatory effect.[36] Moreover, there is an effect of acupuncture-moxibustion on preventing bone
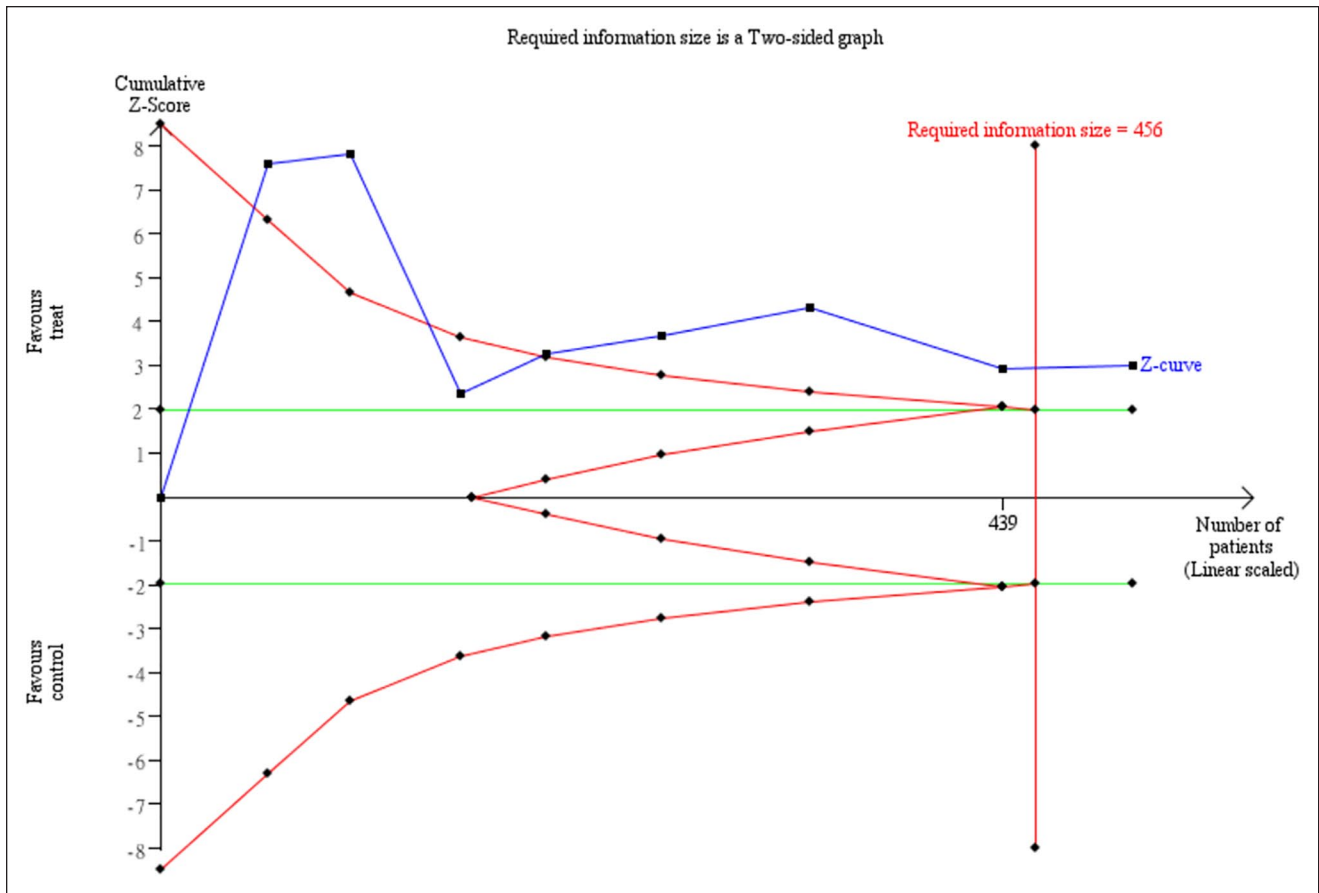
Figure 6. Trial sequential analysis of the effects of white blood cell (WBC) counts and acupuncture.

marrow suppression and recovering the leukocyte count after chemotherapy.[38] These effects have been proposed as potential mechanisms by which acupoint stimulation appears to improve leukopenia.[36,38,44] Another RCT also confirmed the previous statement. Shih et al[8] found that there was a significant interactive effect between acupoint stimulation and time to increasing blood levels of stem cell factor (SCF). The SCF is a mediating cytokine, which can stimulate growth and differentiation of prognostic cells, viz., the common myeloid progenitor and common lymphoid progenitor, and then produce mature blood cell components of granulocytes, lymphocytes, megakaryocytes, and erythrocytes.[8] This possibly implies acupoints stimulate efficacy of activity of cytokines-SCF and following the stimulation of blood cells produce, for example, neutrophils and WBCs.

The subgroup analyses were performed on different types of acupuncture, resulting in significant effects: regardless of the various modes of acupuncture, WBCs were increased overall. Our result was similar to a previous meta-analysis conducted by Chen et al[13] which pooled 31 studies and showed that various modes of acupuncture (acupoint needle insertion, acupoint injection, plaster application, and moxibustion) could ameliorate chemotherapy-induced bone marrow suppression (preventing reductions in Hb, platelets, and WBCs) through immunomodulation of cancer patients undergoing chemotherapy. A comprehensive systematic review by Chao et al[21] also scrutinized 26 studies to confirm that acupoint stimulation by any modality could manage adverse events related to treating breast cancer patients, which also showed that chemotherapy-induced leukopenia could be relieved through any type of stimulation of acupoints.

Limitations and Recommendations

Previous studies presented cytokines indicators for hematopoiesis, such as SCF, GM-CSF, and G-CSF.[8,20] Some scholarly research indicated that possible mechanism for acupuncture relieving chemotherapy-induced leukopenia include that acupuncture might enhance SCF and G-CSF, which would have the potential to relieve chemotherapy-induced myelosuppression.[3,8] However, these hematopoietic cytokines mentioned above could not be demonstrated in this study to further clarify the relationship between regulation of hematopoietic cytokines and acupuncture due to

the limited number of studies included. Additionally, the included studies mostly were all carried out in China, with only one taking place in Australia. There were high percentages of included studies with high risk for blinding of participants, and unclear descriptions of the blinding of outcome assessments, which were considered risks of performance bias and detection bias. However, in treatment trials, the blinding of participants is hard to implement.

Given the unclear methodological quality of the included studies, our results should be replicated in additional high quality research. More-rigorous trials should pay attention to quality issues noted in the quality assessment, in particular blinding of outcome assessments.

Conclusions

This is the first systematic review and meta-analysis to evaluate the effect of acupuncture on chemotherapy-induced hematopoietic suppression in patients with breast cancer. To our knowledge, the TSA of acupuncture on chemotherapy-induced leukopenia was applied for the first time to strengthen the conclusions achieved. The current meta-analysis with updated evidences supports acupuncture possibly ameliorating chemotherapy-induced leukopenia, since WBC and neutrophil values significantly increased after acupuncture in breast cancer patients undergoing chemotherapy. Additionally, regardless of the type of acupuncture used, values of WBCs increased. These novel findings are actionable and support both the clinical use of acupuncture to relieve chemotherapy-induced leukopenia and further research regarding the use of acupuncture in patients experiencing immunosuppression when undergoing chemotherapy.

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Author Contributions

Conceptualization: Y.W.S. and H.T.T.; methodology (screened papers for eligibility, appraised the quality of the studies, extracted the data, and sought additional information): Y.W.S., J.Y.S., and H.T.T.; software validation: Y.W.S., Y.S.K., Y.H.L., D.T.T.A., and E.S.R.; formal analysis: Y.W.S.; writing original draft preparation: Y.W.S.; writing-review and editing: Y.W.S., Y.H.L., and H.T.T; supervision: H.T.T. All authors read and agreed to the published version of the manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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