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Systematic Review and Meta-analysis on the Effectiveness of Acupuncture for Cancer Patients Alleviating Pain, Fatigue, Insomnia, and Anorexia

by

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Systematic Review and Meta-analysis on the Effectiveness of Acupuncture for Cancer Patients Alleviating Pain, Fatigue, Insomnia, and Anorexia

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ABSTRACT

Pain, fatigue, insomnia, and anorexia are the major symptoms experienced by cancer patients during and after cancer treatment. This research aimed to assess the evidence of acupuncture treatment for cancer patients alleviating these symptoms. After searching randomized controlled trials (RCTs) on acupuncture treatment for the symptoms and with all necessary measures reported for this continuous meta-analysis, 29 RCT studies with 2177 patients in English and Chinese were collected from several databases such as Google Scholar, EBSCO, and Wanfang. There was a strong support for heterogeneity among the 29 RCTs with statistical evidence [χ^2_{28} = 156.41 (p < 0.001), I^2 = 82%], and qualitative heterogeneity among them was also obvious, so random effects model was plausible in this meta-analysis. Pooled estimates for summary effect resulted in 1.04 points improvement [95% CI (-1.30; -0.80)] by standardized mean difference (SMD) score for the acupuncture intervention group compared against the control group in the random effects model. Qualitative heterogeneity in RCTs, such as different trial setting for control group and different intervention methods, was a hindering factor for getting decisive statistical evidence for the efficacy of acupuncture from the meta-analysis. However, all the subgroup

analyses and most of the RCTs in this field strongly supported the positive effect of acupuncture for cancer-related symptoms as well as this summary effect of meta-analysis did.

There were several factors that impede the definitive clinical evidence on the efficacy of acupuncture treatment for cancer symptoms through RCT. Diverse results depending on the mode of clinical setting for the control group, and unclear mechanism of effectuation from the acupuncture application, and the risks of bias during the RCT process and its output report were the intrinsic factors that weakened the statistical evidence for supporting the efficacy of the acupuncture treatment. Moreover, the Traditional Chinese Medicine (TCM)'s impossibility to make a one-size-fits-all diagnosis on a symptom of "pain" for all the patients also made it difficult to have an ideal set of acupoints under a clinical study, and this weakened the evidence. These were the critical issues that all the researchers and/or practitioners should have in mind during their planning a clinical trial setting and/or practicing an oncology acupuncture.

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ACKNOWLEDGMENTS

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Thank you, all!

I would also like to quote a famous Chinese adage as old as The Yellow Emperor's Internal Classic (黃帝內經) itself, from Confucius Analects (論語), Wei Zheng 15 (為政 15): The Master said, "Learning without thought is labor lost; thought without learning is perilous." (子曰 學而不思 則罔 思而不學 則殆)

I. INTRODUCTION

Acupuncture, a therapy originating from the Traditional Chinese Medicine (TCM), has been in use as a mode of treating diseases for at least 3000 years. In the United States, it is reported that about 3.5 million adults or 1.5% of the population receive acupuncture in the year of 2012 at the National Health Interview Survey (NHIS).[1] It had been increasing steadily from 1.1% of population at 2002 NHIS to 1.4% at 2007 NHIS those who received acupuncture treatment.[2]

Cancer is an agonizing disease that cause huge difficulty not only to the patient himself/herself but also to his/her families and friends. Cancer patients experience from cancer and/or treatment-related side effects such as nausea and vomiting, post-operative pain, cancer related pain, chemotherapy-induced leukopenia, post chemotherapy fatigue, xerostomia, and possibly insomnia, anxiety and lower quality of life.[3,4] Multidimensional factors contribute to these various symptoms in cancer patients, including tumor invasion or metastasis, anemia, polypharmacy, treatment side effects, hypogonadism in male patients, autonomic dysfunction, and release of inflammatory cytokines.[5]

The use of acupuncture for these patients has been recommended by the American Cancer Society (ACS) for the treatment of side effects associated with conventional cancer therapy and cancer-related ailments.[6] Therefore, acupuncture is increasingly offered as a treatment option for managing cancer-related symptoms, and it is becoming a part of evidence-based oncology. A study reported that the published studies on acupuncture therapy about the cancer had also been increasing over the past 2 decades, from 18 articles in 2000 to 182 articles in 2019.[7] Approximately one in 10 cancer survivors in the United

States have used acupuncture, with the rate of use noted to be higher among those with cancer as compared with those without.[8] In Australia, it is estimated that around 17% to 87% of the cancer patients have used one form of complementary therapy during their cancer treatment.[9]

On the other hand, practitioners in the related health care fields want more evidence to insure the efficacy of acupuncture treatment for cancer patients. Even though there exists a host of published RCTs and meta-analyses on this topic, the efficacy of acupuncture for the cancer patients is neither fully accepted to other health care workers nor to general public yet. Therefore, scrutinizing the clinical settings and processes of RCT on the field of acupuncture is required to find out the probable causes of hindrance to get a full acceptance. In this study, firstly, meta-analyses on the effectiveness of acupuncture for alleviating symptoms on cancer patients was conducted. After the report on the result of meta-analysis, the difficulties for setting proper RCT environment under the characteristics of acupuncture were to be reviewed. Then, combining these two would bring in the conclusion.

OBJECTIVES

1. Based on of the RCTs on the acupuncture treatment, overviewing current oncology acupuncture for cancer patients, and validity of statistical evidence in the clinical trials.
2. Conducting a meta-analysis for the effectiveness of acupuncture treatment for cancer-related symptoms to report the summary effect, and other separate subgroup meta-analyses.
3. Reviewing the methodological issues in an RCT model setting for acupuncture trial such as choice of sham acupuncture mode, acupoints selection process, and different intervention methods.

LITERATURE REVIEW

To be integrated into the conventional medical practice, acupuncture needs evidence-based knowledge accumulation through rigorous clinical research. Many studies have suggested that acupuncture is a recommended mode of treatment for cancer patients as a palliative care.[11] The research publications on the acupuncture therapy for cancer have steadily increased over the last 20 years.[7] Many clinical researches on the acupuncture have supported cancer patients for improving their symptoms.[12] Therefore, it is expected that the proliferation of future clinical studies on acupuncture for cancer-related symptoms will provide more and more evidence for its effectiveness.

Pain was reported in 25% for those patients newly diagnosed with cancer, 33% for those undergoing active treatment, and greater than 75% for those with advanced disease.[13] In He et al.(2019)'s study, acupuncture and/or acu-pressure were significantly associated with reduced cancer pain and decreased use of analgesics, although the evidence level was moderate.[14] The efficacy and safety of acupuncture for chronic cancer-related pain may depend on the different applying methods, and network meta-analysis is also in developing process to see the difference.[15] In another study, acupuncture alone was not found to be better than pharmacotherapy for cancer-related pain, but acupuncture plus drug therapy resulted in increased pain remission rate, shorter onset time of pain relief, longer pain-free duration, and better quality of life without serious adverse effects.[16]

Fatigue is the most prevalent symptoms of cancer patients. As much as 90% of patients treated with radiation therapy, and 80% of those who undergo chemotherapy were experiencing cancer related fatigue.[17] Most of the RCTs have used Brief Fatigue Index

(BFI) for measuring improvement. Jang et al. (2020) reported that the true acupuncture group's BFI scores were 0.93 points better than sham acupuncture [95% CI (-1.65; -0.20)], and true acupuncture had improved BFI score by 2.12 points than usual care groups [95% CI (-3.21; -1.04)] in their meta-analysis.[18]

Concerning insomnia, cancer survivors showed that 52% reported sleeping difficulties and 58% reported cancer-aggravated sleeping problem.[19] There are some studies comparing acupuncture treatment with other conventional therapy. Choi et al. (2017)'s study supported some evidence that RCTs on acupuncture treatment for insomnia resulted in similar effects on response rate to those of conventional drug treatment in their meta-analysis.[19] Feng et al. (2011) also reported acupuncture was better than hormone therapy in the number of hours slept each night and number of times woken up each night.[54] Romero et al. (2020) reported that acupuncture treatment also alleviated co-morbid conditions contributing to insomnia such as anxiety, and it has durable therapeutic effects.[20] However, Garland et al. (2019) reported their RCT result that cognitive behavior therapy was more effective than acupuncture for cancer-related insomnia.[21]

Anorexia is defined as loss of appetite with or without weight loss, which occurs in half of newly diagnosed cancer patients and 26.8% ~ 57.9% of patients with advanced cancer.[22] Weight loss can be a side effect of cancer treatments, such as chemotherapy. However, weight loss is also associated with cancer-caused anorexia, because cancers can secrete substances that change the body's metabolism. Yoon et al. (2015) reported that patients' appetite showed improvement after acupuncture treatment, with an average score of 3.04 on the Visual Analog Scale (VAS) and 4.14 on Simplified Nutritional Appetite Questionnaire (SNAQ) compared to the preintervention scores.[23] Improving appetite of cancer patients is a basic need for maintaining the quality of life.

Many of these studies for the effectiveness of acupuncture are based on the randomized controlled trials. A researcher using RCT for acupuncture needs to be aware that setting a control group environment of the clinical trial may produce different result, depending on the choice of managing control group such as waitlist or sham acupuncture.[24] There are other problems in clinical acupuncture research such as the diverse forms of intervention, needing individualized treatments, blinding process, choosing a credible control model, selecting diagnosis in TCM.

Kaptchuk et al. (2010) surveyed on how the acupuncture practitioners in Europe and America thought about the RCT reports on chronic low back pain, and the result can be summarized:[25]

> 1) methodological weaknesses; 2) inappropriateness of placebo controls; 3) questions as to whether acupuncture placebo controls are "inert;" 4) rejection of evidence-based medicine epistemology; 5) discrepancy between acupuncture performed in RCTs with real world acupuncture; 6) enhanced placebo effects of acupuncture; and 7) needs to re-evaluate acupuncture theory. (from the abstract)

This study revealed what the acupuncturists in Europe and America were thinking about RCT, and they thought RCT was not an adequate clinical setting. Moreover, as Ho et al. (2020) described, there were also several non-specific effects of acupuncture that originate from patient characteristics, acupuncturist skill, the patient-practitioner relationship, and the clinical environment which cannot be incorporate into a RCT model.[26] These factors make it more difficult to build a suitable RCT model for acupuncture treatment study.

II. MATERIALS AND METHODS

2.1 Materials

This study aimed to systematically appraise the evidence for the use of acupuncture for symptom management in cancer and supportive care for cancer patients. For the meta-analysis, RCT studies were searched in databases on the acupuncture treatment to alleviate symptoms such as (a) pain, (b) anorexia, (c) insomnia, and (d) fatigue. Electronic databases of Google scholar, EBSCO, and Wanfang were utilized. The accessing period was between January and February in 2021. The searched terms were “acupuncture,” “cancer,” “pain,” “fatigue,” “insomnia,” “anorexia,” and their related terms such as “tiredness,” “sleeping disorder” or “eating disorder.” There were 3712 studies for acupuncture treatment for cancer patients as shown in Figure 1. After screening the 3712 studies through titles and abstracts, 181 studies were selected for full-text article review. Eventually 35 studies for qualitative synthesis, and 29 RCT studies were chosen for the meta-analysis.

Inclusion criteria

Including the studies for meta-analysis were decided by the following criteria:

① RCTs comparing acupuncture and/or related therapies with a valid comparison that allows evaluation of intervention effect.

② Patients who are diagnosed with any type of cancer.

③ Any form of acupuncture or related techniques are considered for intervention group, including needle-based acupuncture, electroacupuncture, auricular acupuncture and intradermal acupuncture.

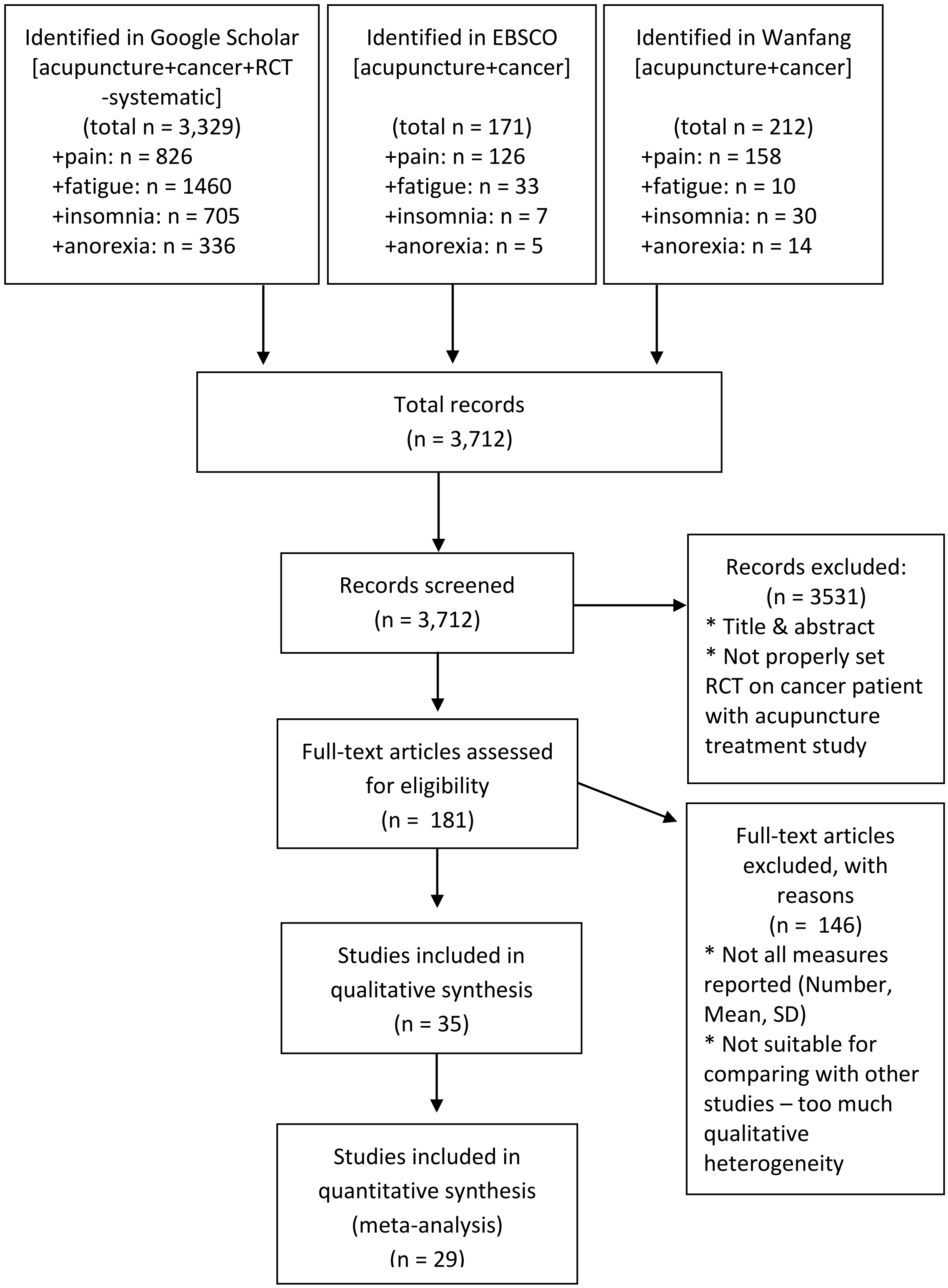

Figure 1. RCT Data-selection flow diagram

④ Control groups may have used some type of treatment that may also or may not apply to intervention group. These include sham acupuncture, waitlist, conventional drug treatment, behavioral therapies, and so on.

Exclusion criteria

Even if all inclusion criteria required above had been satisfied, studies without report on clear data for continuous meta-analysis were excluded. The requirements were clearly reported data on both base and resulting measurement index scores with average and standard deviations. Report on the number of patients for both intervention and control groups were also required.

2.2 Methods

In most studies on the effect of acupuncture treatment, the effect is reported as a mean difference between two groups. These two groups are intervention (or experimental) group and control group. More generally expressed, the mean difference or "difference in means" is a statistical data that measures the numerical difference between the mean values in two groups from a clinical trial. This estimates the amount of difference that the intervention has resulted in some effect on the intervention group compared with the control group.

The mean difference, D, can be expressed

$$D = \bar{X}_1 - \bar{X}_2$$

Where $\bar{X}_1$ and $\bar{X}_2$ be the sample means of the two independent groups, intervention group and control group. The D is a raw value of effect difference between these two groups, and often called "raw mean difference" that is not standardized yet.

Estimation of the effect size for meta-analysis

For meta-analysis, standardized mean difference will be calculated from the data published in each study. Sample size, mean difference and sample standard deviations of the two groups in each study should be provided in each published RCT. Let S_1 and S_2 are the sample standard deviations with sample sizes n_1 and n_2 in each study. Assuming the same standard deviation of the population, standardized mean difference (SMD) is calculated within group standard deviation, S_{within}. Let estimated SMD be d, then[27]

$$d = \frac{\overline{X_1} - \overline{X_2}}{S_{within}}$$

where

$$S_{within} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

This SMD in a study is essential information needed for the meta-analysis, and it is obtained from the reported data in an included study. Using this SMD, one can assess the treatment effect across studies consistently, even if the measuring indexes are different each other in their clinical trials. The variance of d is given by

$$V_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)}$$

This variance of the estimated standard mean difference (d) is an approximation used in most meta-analysis.[27] Then, the standard error of d (SE_d) is a parameter determined by taking square root of the variance V_d, as obtained above.

$$SE_d = \sqrt{V_d}$$

To correct the bias come from small sample size, researchers often adopt Hedge's *g* as an unbiased estimator for the *d,* and variance of it in a study with small sample size.

Weighting method for the mean and its confidence interval

There are two models for calculating the summary effect statistics, the fixed effect model or the random effects model. The fixed effect model assumes that every study has acquired its sample from the same population and has applied homogenous treatment method. So, the true effect sizes for all studies are the same. Then, the weight depends only on the variance of each study. In the random effects model, however, the true effects are different, and add the τ^2 (which is the variance among SMDs) to the individual study variance (V_{Y_i}, same as V_d for study *i*) for estimating weighted summary effect.

The assigned wight for fixed effect model for each study is

$$W_i = \frac{1}{V_{Y_i}}$$

where V_{Y_i} is the variance of the SMD for study *i.*

Weighted mean, *M*, is

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i}$$

where Y_i is the effect size of study *i*, and $W_i Y_i$ is the product of effect size multiplied by weight of that study.

The variance of summary effect, V_M, is the inverse of the sum of weight, that is

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i}$$

The standard error of weighted mean in the summary effect, SE_M, is

$$SE_M = \sqrt{V_M}$$

Using these parameters, 95% confidence interval of the weighted mean of the summary effect will be estimated by

$$M + 1.96 \times SE_M$$

for upper limit, and

$$M - 1.96 \times SE_M$$

for lower limit.

These are the basic ideas explaining how the meta-analysis in fixed effect model manages available data from the collected RCTs.

Why meta-analysis and which model?

Meta-analysis is a quantitative and formal process of data manipulation to assess a body of research to get a more consolidated outcome. For getting the consolidated outcome, each of these included studies should provide a point estimate of effect size that the study had pursued, and it should also provide the measure of precision of the estimate often expressed in standard deviation. Then, the outcomes from a meta-analysis can present more precise statistical score than an individual study, because they have pooled the data from several related studies of interest. However, variability of clinical setting and/or heterogeneity of intervention methods among the included studies are the critical problems that researchers have to understand.

The fixed effect model and the random effects model are two major statistical models for meta-analysis, depending on the assumption about the data.[28] Under the fixed effect model, it is assumed that there is one true effect size that underlies all the studies included in the meta-analysis. In other words, all the studies are assumed to be qualitatively homogenous in fixed effect model. Under the random effects model, however, the true effect sizes are different from one study to the other due to its heterogeneity in clinical setting. The existence of heterogeneity among included studies is the benchmark for choosing the suitable model for a meta-analysis. Choosing one of these two models, a researcher should consider both quantitative and qualitative heterogeneity.

Funnel plot and p-curve to detect publication bias

Publication bias is a crucial concern for the researchers doing meta-analysis, since it will distort the result of summary effect. The output of a meta-analyses is based on the available data from the publication (or sometimes with added unpublished data) of interested studies, so the resulting evidence depends completely on the goodness (or truthfulness) of the included studies. There is widespread evidence that a study is more likely to be published if its findings are statistically significant, or conform to the desired hypothesis. If a clinical trial were not published, the study should stay in researcher's file drawer. So, the publication bias is sometimes called the "file drawer" problem. One can check the publication bias through a funnel plot. A funnel plot is a scatter plot of the studies' observed effect sizes on the x-axis against a measure of their standard error on the y-axis. If the scatter plot shows roughly symmetrical in an inverted funnel shape, it is likely to have less publication bias problem.[29]

If the funnel plot is asymmetrical, we can calculate a bias-corrected estimate of the true effect size. It is called a "trim and fill funnel plot." The trim-and-fill method is done by three stages. Firstly, one removes (trims) studies from the original funnel plot until it becomes symmetric. Secondly, one adds (fills) mirror images of missing studies (i.e., presumably unpublished studies) to the original funnel plot. Thirdly, one calculates the adjusted effect estimate based on original and added studies.[30] The trim and fill funnel plot helps seeing the presumed missing studies, and correcting the summary effect.

Another method for checking publication bias is a *p*-curve plot. Simonsohn et al. (2014) have contrived *p*-curve for a test of publication bias.[31] This *p*-curve is a distribution of statistically significant *p* values for the set of studies. If *p* value of a study in the set is greater than 0.05, it will be excluded from the *p*-curve plot. The right skewed *p*-curves represents the study set contains evidential value that it is less likely to be biased due to "*p*-hacking." The *p*-hacking is a manipulation of the clinical output until the threshold of the statistical significance level ($p < 0.05$) has reached. There are several ways of doing *p*-hacking. They could adjust the hypothesis after clinical results were known to meet the significance level, or can tweak the number of observations to increase the precision through smaller standard error, and so on. Both of publication bias and *p*-hacking can cause the overestimation of the summary effect size calculated from the set of chosen clinical trials.

In this study, 29 RCT studies were gathered applying the inclusion and exclusion criteria stipulated above. After arranging the gathered RCT data in MS Excel form, R version 4.0.4 statistical software with the "meta" package was run for the result of meta-analysis.[32] Subgroup analyses were done separately. R language's "dmetar" package for *p*-curve plot, and "robvis" package for risk of bias plot were also utilized.

III. RESULTS

Figure 2 presents the statistical results of the meta-analysis. 29 RCTs (with 2177 patients) were included in the study to get the summary effect for the acupuncture treatment group against control group. Detailed description about these 29 RCT studies will be reported in the tables at subgroups section below. For the statistical heterogeneity test, calculated chi-squire test score from the 29 studies was 156.41 [χ^2_{28} = 156.41 (p < 0.001), I^2 = 82%], and the probability of these RCTs were homogenous was less than 0.1 %. There were also obvious heterogenous clinical trial settings among 29 RCTs. Therefore, random effects model was adopted in this meta-analysis to report the summary effect.[28,32] Compared with the control group, the result of acupuncture intervention group improved 1.05 in SMD score with 95% CI (-1.30; -0.80) in random effects model. As for the significance level of each study, 9 studies failed to be effective in their SMDs for acupuncture treatment within 95% confidence interval as shown in Figure 2. Input data for each study are the number of patients, mean difference with standard deviation for both invention and control group, and they are reported in APPENDIX - A.

The SMD was used for representing the effect size in each RCT study, and effect size was the outcome difference between the acupuncture intervention group and the control group. The use of SMD as a measure of effect size was inevitable, because many studies used different indexes for the measurement of treatment effects. Another parameter on these SMDs (the inverse score of each SMD's variance) were used to get the weighted average into a summary effect in a process of meta-analysis. By increasing the number of observations in the study of interest, the precision of estimated effect size shall increase by

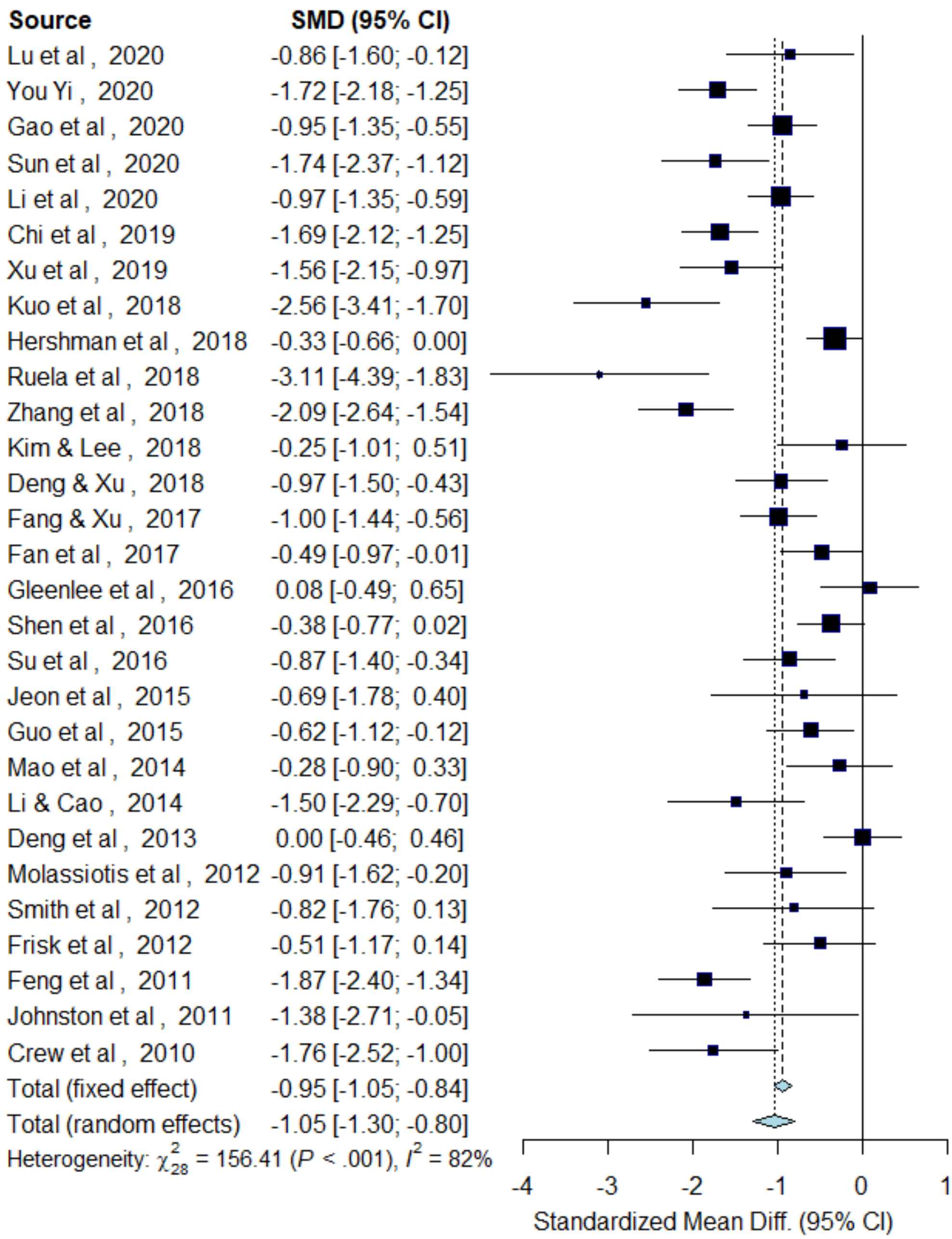

Figure 2. Forest plot with summary effect of meta-analysis

decreasing standard deviation (SD) of the summary effect. Therefore, the summary effect from the meta-analysis usually reveals stronger statistical precision (as a smaller SD) than an individual RCT. This higher precision help increase the evidence for the effectiveness of acupuncture treatment for cancer patients by decreasing confidence interval for 95% CI, and eventually increasing significant level (with lower *p* value). However, the huge variety in clinical settings among these 29 RCTs was an impeding factor not to reach a definitive conclusion for the efficacy of acupuncture treatment.

Heterogeneity of the RCTs

It is a well-accepted fact that the efficacy of acupuncture treatment is affected by the selection of acupoints, needling depth, manipulation techniques, treatment frequency and total number of treatment sessions. The 29 RCTs included in this study contained a lot of qualitative heterogeneity. They covered 10 for pain, 8 for fatigue, 6 for insomnia, and 5 for anorexia. These were the four subgroups designed to have separate analyses: pain, anorexia, insomnia and fatigue. Countries included in these RCTs were 16 China, 6 USA, 2 S. Korea, 1 UK, 1 Sweden, 1 Australia, 1 Taiwan, and 1 Brazil. So, the population from which each study had chosen its sample were diverse.

There were significant differences among modes of acupuncture intervention in these RCTs. The acupuncture style, index used, number of sessions and duration of intervention were varied among the RCTs included in this study. Most of the trials used manual acupuncture based on TCM theory, but some studies adopted Ashi points too. Out of 29 RCTs, thirteen studies intervened with acupuncture (many studies with other methods). Four studies adopted Chinese herbal medicines with acupuncture.[35,47,48,58] Four studies used electro-acupuncture,[43,54,60,61] three studies used ear acupuncture,[41,62,69] and three studies used ear acupuncture and acupuncture together.[40,50,59] Two studies used intradermal acupuncture.[42,68] Ernst & Lee (2008) pointed out that a trial design should generate only positive results if the design features were set to compare A + B (acupuncture + e.g., usual care) against B (e.g., usual care).[33] 8 out of 29 studies were designed in this clinical setting.[37,39,40.41,49,51,59,69]

For acupoint selection, most of the trials used a predetermined set of acupoints based on the theory of TCM. Some studies combined a set of Back-shu points corresponding to the anatomical Zang-Fu organs with other distal points for the symptoms. Three studies used Ashi points in addition to traditional acupoints.[42,57,67] Three study adopted the acupoints to be at the patients most painful joint areas of each patient, even though the detailed acupoints of choice were a little different each other.[36,40,54] In five studies, acupuncture therapies were compared with conventional drug therapy alone.[35,58,59,61,66] One study used trigger points around the joint with the most pain for electro-acupuncture.[54] Proper needling depth was depending on the point where a needle was applied, and manipulation techniques were also depending on the expertise of the participating acupuncturist. The number of sessions administered was ranged from 5 to 40 with different frequencies throughout the RCT studies, and this would make the heterogeneity among the studies worse in the meta-analysis.

These were the discrepancies among the included RCTs, and they demonstrated the existence of severe qualitative heterogeneity. Eventually, the existence of this qualitative heterogeneity was a strong support for the random effects model in this meta-analysis.

Funnel plot

Publication bias in the meta-analysis arises mainly from the possible missing reports due to their insignificant research outcomes. A funnel plot is designed to check out the

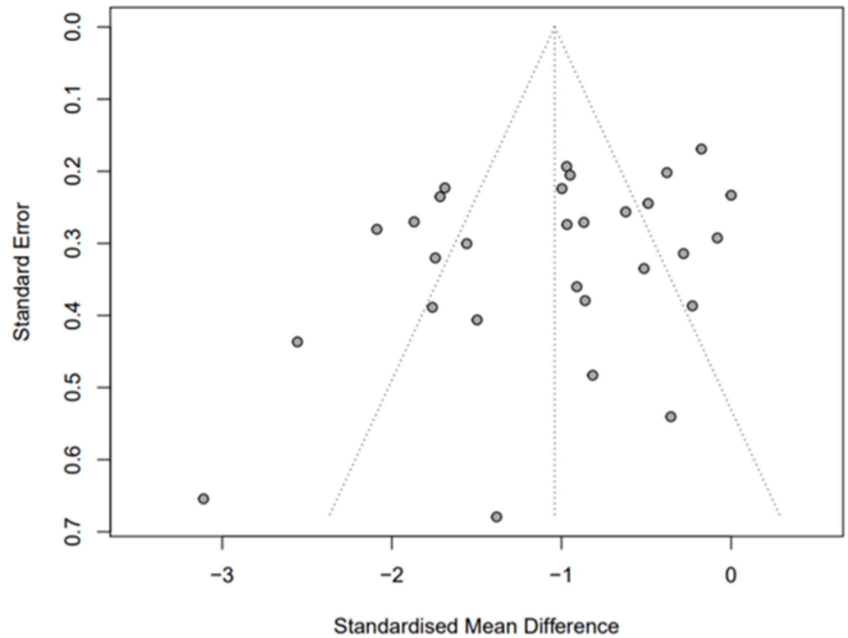

Figure 3. Funnel plot of the included RCTs

existence of the publication bias in the study set. Visual asymmetricity indicates the existence of publication bias in a scattered plot known as funnel plot.[29] Therefore, the asymmetric shape of the funnel plot in Figure 3 that came from the 29 RCT studies might indicate the existence of publication bias. Publication bias, however, is one of several possible reasons for asymmetrical funnel plot. The quantitative heterogeneity among studies, as shown in this one [χ^2_{28} = 156.41 (p < 0.001)], can cause the asymmetry in the funnel plot. There was also another kind of heterogeneity that caused the asymmetry, and this qualitative heterogeneity came from the different study settings among RCTs, different types of participants, and/or different intervening methods. This qualitative heterogeneity could be a major cause of the asymmetricity. If there was publication bias in the selected set of studies, it might have distorted the estimation of summary effect size.

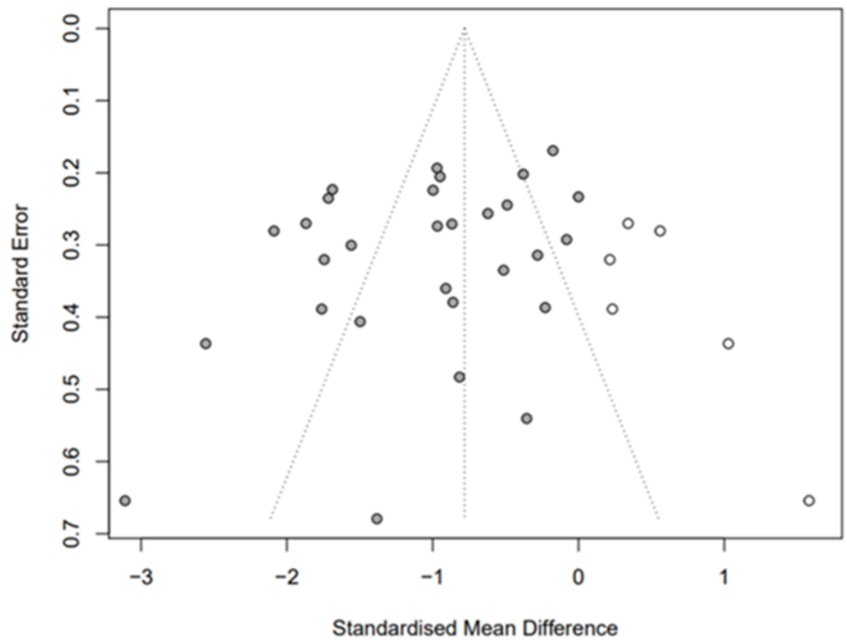

Figure 4. Funnel plot with trim and fill

Funnel plot with trim and fill

If one assumes that the asymmetry of funnel plot is a sign of publication bias due to missing studies because of their insignificant level in the statistical score. Then, one can also deduce these missing studies based on the current information by "trimming" and "filling." Trimming the studies that caused the asymmetry, one can find probable missing studies as the opposite positions of the studies causing asymmetricity. By adding these presumptive missing studies, one can get a new result and funnel plot. It is called a "trim and fill funnel plot." The funnel plot drawn in Figure 4 included these presumptive missing studies, and the hollow dots located at the right lower quadrant are the assumed missing studies.[30] This result implied that the statistically poor outcomes could not published, and stayed in the researcher's "file drawer." This "file drawer" problem will eventually lead to an over-valuation of the estimated summary effect size.

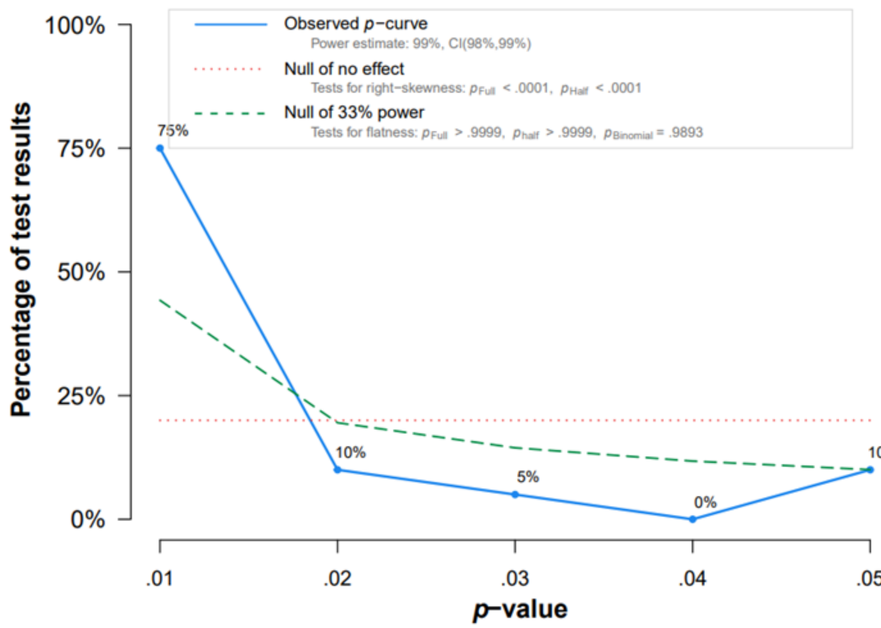

Figure 5. *p*-curve of the included RCTs

p-curve plot

Figure 5 is the *p*-curve plotted from the 29 RCT studies included in the meta-analysis. The plot is designed to check the existence of "*p*-hacking." The right skewed *p*-curve indicates containing more studies with low *p* values ($p < 0.01$) than high *p* values ($0.04 < p < 0.05$). Thus, it is less likely to exist "*p*-hacking" that describes the conscious or subconscious manipulation of data to get a desirable *p*-value.[31] In the Figure 5, studies where *p* values are greater than 0.05 were excluded in this *p*-curve diagram. 9 out of 29 studies were excluded in this study, and these excluded 9 studies had touched zero horizontal line by their 95% confidence interval in the forest plot of Figure 2. The *p*-curve shown in Figure 5 was strongly right-skewed, so it can be accepted that the publication bias in terms of "*p*-hacking" was not a serious problem in this meta-analysis.

IV. DISCUSSION

Acupuncturists in the oncology setting may encounter patients with a wide range of comorbidities resulting from either cancer treatment and/or from the disease itself. Using information identified from the published articles and supplementary materials, researchers should prove the validity of acupuncture therapy for alleviating cancer-related symptoms in meta-analysis. However, the qualitative differences in the clinical interventions among studies are serious barriers to get the objective validation for efficacy using meta-analysis from RCTs in the field. The well-known causes of qualitative difference are different study setting, different types of participants, and/or different intervention methods among RCTs. Subgroup analysis can help understanding the diversity of summary effect among the included clinical studies in different categories. Following are the meta-analyses of subgroups and sub-categories to get the more detailed characteristics of 29 RCTs.

Pain-subgroup meta-analysis

The subgroup of treatment for cancer-related pain includes 10 RCTs with 656 patients. Intervention methods are acupuncture (n=7),[34,35,36,37,38,39,40] auricular acupuncture (n=1),[41] intradermal acupuncture (n=1),[42] and electro-acupuncture (n=1).[43] Summary statistics for this subgroup meta-analysis is 0.92 improvement in SMD with 95% confidence interval (-1.36; -0.48) in the random effects model. Implementing style for acupuncture in the RCTs have heterogenous settings such as applying with Chinese herbal medicine (Xu, 2019),[35] nerve block surgery (Li & Cao, 2014).[39] The quantitative heterogeneity statistics is also strongly supported by this subgroup meta-analysis [$\chi^2_9 = 47.76$ ($p < 0.001$), $I^2 = 81\%$] as

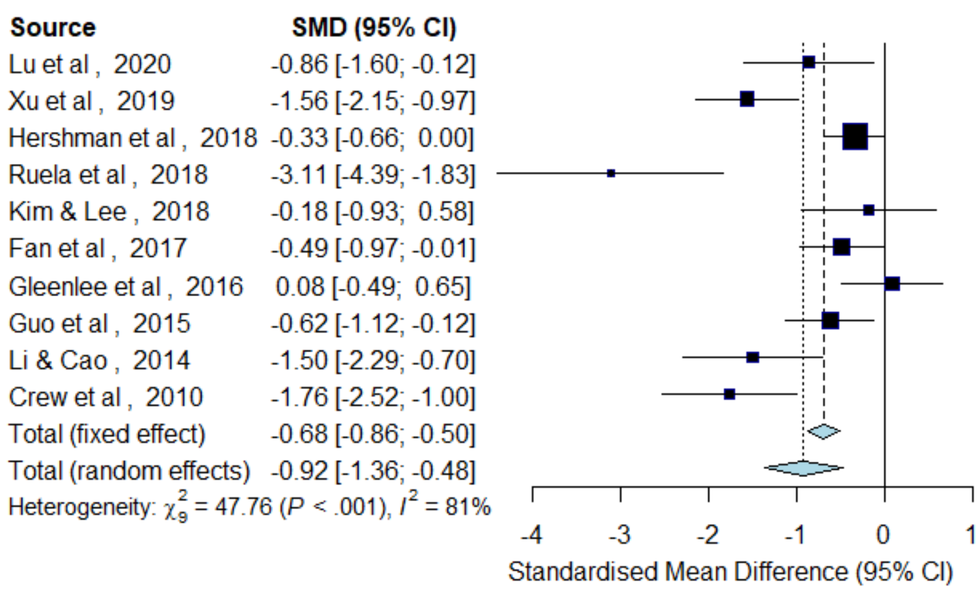

Figure 6. Forest plot of pain subgroup

seen in Figure 6. The size of square in the forest plot in Figure 6 represents the relative weight of each study for total summary effect calculation.

The cancer-related pain is one of the most common excruciating symptoms caused by the cancer itself and/or by its treatment such as surgery, chemotherapy and radiotherapy. World Health Organization (WHO) suggested administering a sequential 3-step analgesic ladder from nonopioids to weak opioids, eventually to strong opioids according to pain intensity. Two of studies applied WHO three-ladder standard scheme for both intervention and control groups (Fan et al., 2017 and Guo et al., 2015).[37,38] They did not apply sham acupuncture for control group, so the outcome did not include placebo effect but the effectiveness of acupuncture only.

In 3 arms trial setting, the acupuncture against waitlist control group was found to be more effective than that of sham control group in several previous studies.[36,52,54] Sham acupuncture control trial showed less effectiveness of treatment comparing with waitlist

Table 1. Pain subgroup: characteristics of RCTs

Study	Experiment Group	Control Group	Acupuncture Points	Sessions; Index	Cancer; Country
Lu et al.,[34]	Acupuncture; + electro-acupuncture	Waitlist control;	TE 5, Baxie(八邪) and/or SP 6 and LR 3 bilaterally	8 weeks (2X/week); BPI-SF*	Breast cancer; USA
Xu et al.,[35] 2019	Acupuncture + Longxing Zhitong(龙星止痛膏) ointment external application	Only oxycodone hydrochloride tablets	PC 6, LI 4, LU 6, LU 7, LU 1, ST 36	2 weeks (1X/day); VAS**	Various; China
Hersh-man et al.,[36] 2018	Acupuncture; Gleenlee(2015) with STRICTA† method	Three arms setting: Sham acupuncture (no acu pts + shallow needle insertion) or waitlist	Acu pts at 3 of the patient's most painful joint areas	6 weeks (2X/week); BPI-SF	Breast cancer; USA
Ruela et al.,[41] 2018	Auricular Acupuncture (AA); (0.20 mm x 1.5 mm)	AA but sham points (Eye point and Trachea)	(AA): Shenmen, Kidney, Sympathetic etc.	8 weeks (1X/week); NPS***	Various; Brazil
Kim & Lee,[42] 2018	Intradermal acupuncture (needle was kept attached on the skin for 48 to 72 hours)	Sham intradermal acupuncture (no-penetration)	CV 12, bilateral ST 25, LI 4, LR 3, PC 6, and Ashi points	3 weeks (3X/week); NRS††	Various; S. Korea
Fan et al.,[37] 2017	Acupuncture + WHO three-ladder standard therapeutic scheme	WHO three-ladder standard therapeutic scheme	PC 6, LI 4、ST 36、SP 9, SP 6	20 days (1X/day); NRS	Lung cancer; China
Gleen-lee et al.,[43] 2016	Electro-acupuncture + taxane	Sham electro-acupuncture (lateral side of original pts) + taxane	GB 34, ST 36, LI 4, LI 10, Bafeng(八风), Huatuojiaji (華陀夾脊)	6 weeks (2X/week); BPI-SF	Breast cancer; USA
Guo et al.,[38] 2015	Acupuncture + WHO pain management ladder guidance	WHO pain management ladder guidance	Bilaterally ST 36, SP 6, LI 4, PC 6	8 weeks (5X/week); NRS	Stomach cancer; China
Li & Cao,[39] 2014	Acupuncture + thoracic-lumbar paravertebral block or Thoracic-lumbar sympathetic block	Thoracic-lumbar paravertebral block or Thoracic-lumbar sympathetic block	Chest Pain: LU 5, SP 9, BL 13, Abdomen pain: ST 36, SP9, BL 60	2 weeks (2X/day); VAS	Various; China
Crew et al.,[40] 2010	Acupuncture; body and one point for auricular acupuncture	Sham acupuncture; superficial needle used	Varied; acu points near 3 most painful joint areas + ear	6 weeks (2X/week); BPI	Breast Cancer; USA

* BPI-SF: Brief Pain Inventory - Short Form, ** VAS: Visual Analogue Scale, *** NPS: Numeric Pain Scale, † STRITCA: Standards for Reporting of Controlled Trials in Acupuncture, †† NRS: Numeric Rating Scale

control group. Hershman et al. (2018) applied acupuncture for aromatase inhibitors induced breast cancer patients pain management with three arms clinical setting: acupuncture, sham acupuncture, and waitlist group.[36] 30 ~ 45 minute sessions were administered over a period of six weeks. Chosen acupoints are joint-specific points of most painful joint areas. The sham needles were applied minimally at non-acupoints. There were two sets of mean difference in the study, "true acupuncture *vs* sham acupuncture" and "true acupuncture *vs* waitlist." The fitted differences of average pain in two settings are -0.60 [95% CI (-1.17; -0.03)] against sham acupuncture and -0.71[95% CI (-1.28; -0.15)] against waitlist. In their RCT, one can see the effect size of true acupuncture against waitlist group was larger than that against sham acupuncture control group.

The RCT research in cancer pain is limited with major methodological shortcomings such as risk of bias and erroneous model setting. To implement the shortcomings, STRICTA (Standard for Reporting Intervention in Clinical Trial of Acupuncture) has been recommended. The acupuncture rationale, the details of needling, the treatment regimen, other components of treatment, the practitioner background, and the control or comparator interventions are important parts of checklist in STRICTA, and Hershman et al. (2018) have tried to adopt this method in their study.

Fatigue-subgroup analysis

In cancer-related fatigue (CRF) subgroup, there were 8 RCTs with 680 patients. Intervention methods were acupuncture (n=7)[47,48,49,50,51,52,53] and electro-acupuncture (n=1).[54] The meta-analysis resulted in 1.0 improvement measured by SMD with [95% CI (-1.57; -0.42)] in the random effects model. Not only quantitative heterogeneity [χ^2_7 =

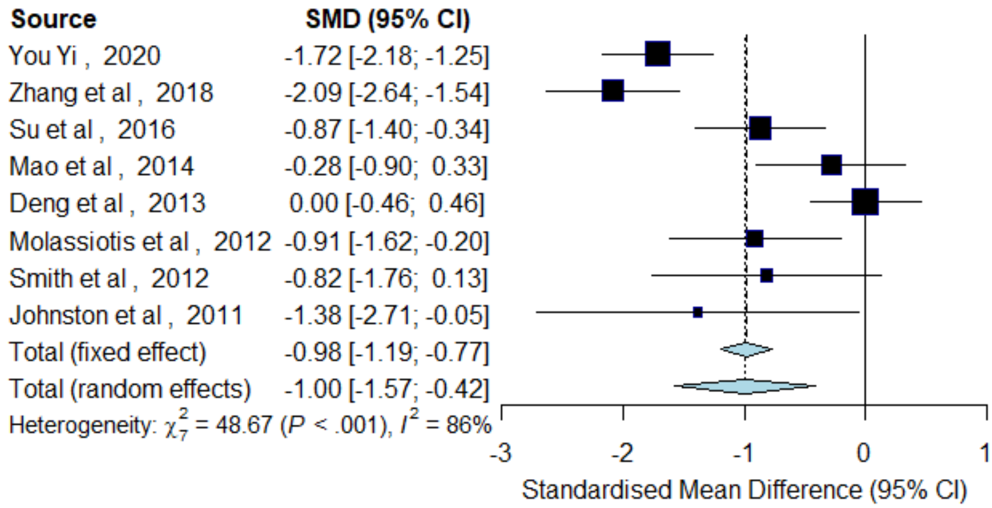

Figure 7. Forest plot of fatigue subgroup

48.67 ($p < 0.001$)] but also qualitative heterogeneity was supported as seen in Table 2. The difference between normal fatigue and CRF is disproportionate to exertion level and is not relieved by rest or sleep. A study reported that 40% of individuals with cancer experience CRF at diagnosis, as do 90% of those treated with radiation and 80% of those who undergo chemotherapy.[17] RCT studies for acupuncture combined with Chinese herbal medicine was more effective than other studies with only acupuncture treatment or usual cancer care, and it improved quality of life (You 2020, Jhang 2018).[47,48]

Deng et al. (2013)'s study showed zero efficacy on acupuncture treatment, even though they used TCM acupoints and used nonpenetrating sham needles for control group.[50] This study needs more scrutiny for its bias in the clinical trial and intervention method. They used sham needle without insertion, and the sham points were slightly away from the predefined ones (CV 6, CV 4, KD 3, SP 6, ST 36, LI 11, HT 6), and those were for the acupuncture group. Needle sensation (or Deqi), manual stimulation, 20 min retention were also applied. The changes of Brief Fatigue Inventory (BFI) were same for both intervention

Table 2. Fatigue subgroup: characteristics of RCTs

Study	Experiment Group	Control Group	Acupuncture Points	Sessions; Index	Cancer; Country
You Yi,[47] 2020	Acupuncture + Fuzheng Jiedu decoction(扶正解毒方) + best supportive treatment	Best supportive treatment; pain management, nutritional support, aerobic exercise, psychological and sleet therapy	CV 4、CV 6、and bilaterally ST 25, and ST 36	6 weeks (5X/week); PFS*	Colorec-tal cancer; China
Zhang et al.,[48] 2018	Acupuncture + Xiaoyan decoction (消岩汤) + moxibustion	Normal support for chemo-therapy	CV 17, CV 12, CV 6, SP 10, PC 6, SP 6, ST 36	3 weeks (1X/day); CFS	Various; China
Su et al.,[49] 2016	Acupuncture + nutritional support and symptomatic management	Nutritional support and symptomatic management	CV 6, CV 4, ST 36, SP 10	2 weeks (1X/day); PFS	Various; China
Mao et al.,[54] 2014	Electro-acupuncture	Sham acupuncture; non-penetrating needles at least 5cm away from the pain area	Trigger pts: points around the joint with the most pain areas	8 weeks (2X/week); BFI**	Gyneco-logical tumor; China
Deng et al.,[50] 2013	Acupuncture + ear acu	Sham acupuncture; w/ sham needles & points off the meridians	CV 6, CV 4, KD 3, SP 6, ST 36, LI 11, HT 6 + ear acu (nervous subcortex)	6 weeks (1X/week); BFI	Various; USA
Molassi-otis et al.,[51] 2012	Acupuncture	Enhanced usual care according to Macmillan/Cancer Backup	ST 36, SP 6, and LI 4, alternative points are GB 34 and SP 9	6 weeks (1X/week); MFI***	Breast Cancer; United Kingdom
Smith et al.,[52] 2012	Acupuncture	Sham acupuncture; (non-invasive) on no acu pts	Bilateral KI 3, KI 27, ST 36, SP 6 and unilateral CV 4 and CV 6	3 weeks (2X/week); BFI	Breast cancer; Australia
Johnston et al.,[53] 2011	Acupuncture + self-massage, exercise, nutrition, and stress management + usual care	Usual care on National Comprehensive Cancer Network (NCCN) clinical practice guidelines	LI 4, SP 6, ST 36, KI 3 for all + (gastrointestinal) PC 6, SP 4 (emotional) LU 7, KI 4, LV 3, Yintang, GV 20 (sleep) HT 7, KI 4, and UB 62	8 weeks (1X/week); BFI	Post-breast cancer; USA

* PFS: Piper Fatigue Scale, CFS: Cancer Fatigue Scale, ** BFI: Brief Fatigue Inventory, *** MFI: Multi-dimensional Fatigue Index

group and control group. Did this imply that the placebo effect of sham acupuncture was exactly as good as real acupuncture? When Moffet (2009) asserted that sham acupuncture might be as efficacious as true acupuncture, he meant the sham acupuncture with needle

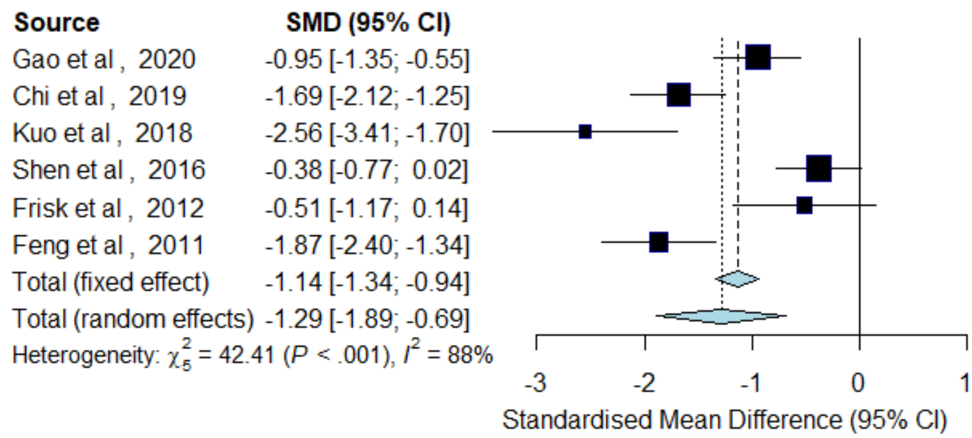

Figure 8. Forest plot of insomnia subgroup

insertion but on non-points (locations that are not known acupoints) or on wrong points (points not indicated for the condition).[45] Therefore, the (no effect) result of Deng et al. (2013)'s study was not expected as long as they used sham acupuncture without needle insertion, so it was highly possible that there were other deviations from the clinical setting during their experimental intervention.

Insomnia-subgroup analysis

In insomnia subgroup, 6 RCTs were included, with a total of 488 patients. Intervention methods are acupuncture (n=3),[57,58,59] electro-acupuncture (n=2),[60,61] and auricular acupuncture (n=1).[62] For measurement, 5 RCT studies used Pittsburgh Sleep Quality Index (PSQI) for sleep quality index, and one used simple "hours of sleep" as an index. Acupuncture treatment group improved by 1.29 measured in SMD with [95% CI (-1.89; -0.69)]. Sleep problems (inadequate sleep duration, poor sleep quality, poor sleep timing, sleep disorders) are the easily encountering symptoms for cancer patients. It often coexists with pain, fatigue, depression, and anxiety in cancer patients. This co-existence makes a

Table 3. Insomnia subgroup: characteristics of RCTs

Study	**Experiment Group**	**Control Group**	**Acupuncture Points**	**Sessions; Index**	**Cancer; Country**
Gao et al.,[57] 2020	Acupuncture + standardized three－ladder acesodyne regimen; External application of Chinese medicine	Standardized three－ladder acesodyne regimen; external application of Chinese medicine at pain points	Main points: PC 6, LI 4, SP 6, ST 36, Optional points: BL 13, LU 6, Ashi pts	2 weeks (1X/day); PSQI*	Lung cancer; China
Chi et al.,[58] 2019	Acupuncture combined with Tianwang Buxin Dan(天王补心丹)	Oral Estazolam Tablets;	KD 3, SP 6, BL62, KD 6, Optional points: Heart and Kidney meridian pts	2 weeks (1X/day); PSQI	Lung cancer; China
Kuo et al.,[62] 2018	Auricular acupuncture; Vaccaria seed was kept at one ear lobe for 3 days.	Verbal and written advice on sleep hygiene practices	Shenmen (TF4), Xin (Heart; CO15), Pizhixia (Subcortex; AT4), and Neifenmi (Endocrine; CO18) points.	6 weeks (2X/week); PSQI	Ovarian cancer; Taiwan
Shen et al.,[60] 2016	Electro-acupuncture	Three ladder analgesic therapy + Zolpidem	KD 6, BL 62, HT 7, Yintang(印堂), Sishengcong(四神聪)	4 weeks (1X/day); PSQI	Lung-cancer; China
Frisk et al.,[61] 2012	Electro-acupuncture	Hormone therapy; estrogen/ progestogen therapy	Unspecified	12 weeks (?/week); hours of sleep	Breast cancer; Sweden
Feng et al.,[59] 2011	Acupuncture + ear acupuncture	Fluoxetine Hydrochloride Capsule (Prozac)	ST 40, SP 9, SP 10, SP 6, Yintang (EX-HN3), DU 20, Sishencong (EX-HN1), PC 6 Shenmen, TF 4.	30 days (1X/day); PSQI	Various; China

* PSQI: Pittsburgh Sleep Quality Index

positive feedback loop where all symptoms are amplified and overall burden is increased.

Chi et al. (2019) used both acupuncture and Chinese herbal medicine (Tianwang Buxin Dan) for intervention group comparing against oral Estazolam tablets for control group.[58] This study produced strong evidence for the acupuncture and herbal medicine, but one could not discern the level of contribution in each therapy. However, Feng et al. (2011) had strong support for acupuncture against pharmacological treatment (Prozac) in control

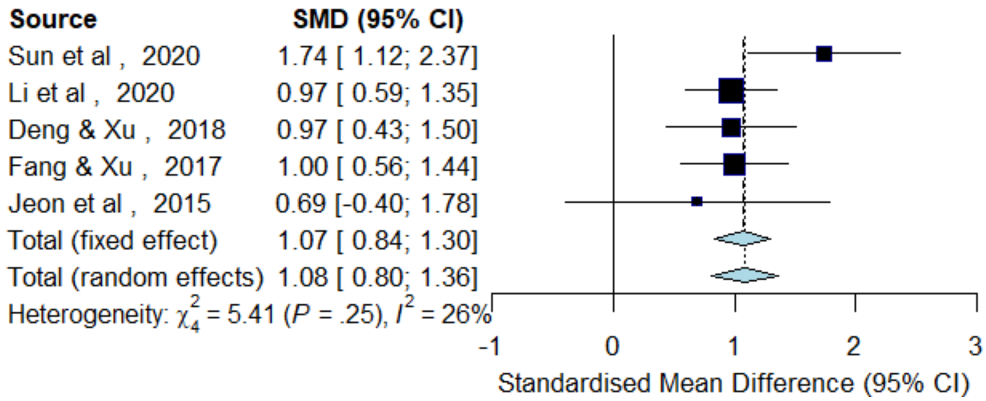

Figure 9. Forest plot of anorexia subgroup

group, and resulted higher SMD improvement than Chi et al.'s study.[59] The etiology of insomnia is also an important factor for the effective therapy. If the insomnia was caused more by psychological factors, other therapy could be more effective. As an example, Garland et al. (2019) reported in their RCT result that the cognitive behavior therapy had been more effective than acupuncture for cancer-related insomnia.[21] Patients' perception on the treatment's evidence, experience with the treatment, and patient-practitioner relationship are also significant factors for realizing effective results in a therapy.

Anorexia-subgroup analysis

In anorexia subgroup, 5 RCTs with 353 patients were included in the meta-analysis. Acupuncture (n=4)[65,66,67,68] and an auricular acupuncture (n=1)[69] are the types of intervention. For the consistency of effect size, the positive sign of effect size as SMDs in Figure 9 was changed to a negative sign in the total meta-analysis at Figure 2. For the measurement index score for anorexia, such as Simplified Nutritional Appetite Questionnaire (SNAQ), higher score represents better condition, but the pain index such as

Table 4. Anorexia subgroup: characteristics of RCTs

Study	Experiment Group	Control Group	Acupuncture Points	Sessions; Index	Cancer; Country
Sun et al.,[69] 2020	Auricular acupuncture + usual nutritional supportive care; taped intradermal needles for 2 or 3 days	Only usual nutritional supportive care	Shenmen, stomach, spleen and subcortex, sympathetic, liver, small intestine and Sanjiao	4 weeks (3X/week); SNAQ*	Various; China
Li et al.,[65] 2020	Acupuncture; stimulated manually every 10 min; electro-acupuncture (ST36)	Same as true acupuncture, but stimulation points are not traditional Chinese meridians; no manipulation	RN 12, LR 13, bilaterally, RN 6, ST 25, bilaterally, PC 6, bilaterally, ST 36, bilaterally	5 days (1X/day); SNAQ	Various; China
Deng & Xu,[66] 2018	Acupuncture;	Western medicine; Sertraline Hydrochloride tablet (Zoloft)	PC 6, LV 3, SP 9 + others	4weeks; QLQ-C30**	Various; China
Fang & Xu,[67] 2017	Acupuncture + relaxation training	Relaxation training	Mainly Ashi points with various meridian points	3 weeks (5X/week); CPQOL†	Various; China
Jeon et al.,[68] 2015	Intradermal acupuncture	Sham intradermal acupuncture; (No-penetration)	LI 4, LR 3, ST 36, SP 6, KI 2	2 weeks (3X/week); ASC††	Thyroid Cancer; S. Korea

* SNAQ: Simplified Nutritional Appetite Questionnaire, ** QLQ-C30: Quality of Life Questionnaire - Core 30, † CPQOL: Cancer Pain and Quality of Life(中国癌症患者的疼痛与生活质量问卷), †† ASC: Anorexia/ Cachexia Subscale in the FAACT(Functional Assessment of Anorexia/ Cachexia Therapy)

BPI represents contrarily. Hence, the summary effect of meta-analysis and SMDs in Figure 9 presented as the positive values.

The quantitative heterogeneity test for this subgroup revealed that the probability of being homogenous is relatively high [χ^2_4 = 5.41 (p = 0.25), I^2 = 26%], so it can not reject the homogeneity hypothesis with 95% confidence interval. Therefore, both fixed effect model and random effects model should be considered. In the fixed effect model, it is assumed that there is a single true underlying effect size (here, SMD), and the model ignores adding the τ^2 (which is the variance among SMDs) for the weighting with inverse of variance score. More importantly, all the RCTs should have homogenous trial setting to have the same true effect size for them in the fixed effect model. Due to this intrinsic connotation, the qualitative heterogeneity among the studies should prevail the quantitative heterogeneity (i.e., chi-square test result) for choosing a model in meta-analysis. Table 4 also explained obvious qualitative heterogeneity. Therefore, random effects model should be adopted in this anorexia subgroup meta-analysis. The random effects model presented 1.06 improvement in SMD with its 95% CI (0.75; 1.37).

One can compare the three studies in the anorexia subgroup to see the quantitative and qualitative heterogeneity, even though they have resulted in similar SMD scores shown in the forest plot of figure 9. In the RCT studies, Deng & Xu (2018) treated control group with Sertraline Hydrochloride tablet (Zoloft) to compare the SMD of acupuncture treatment (SMD = 0.97),[66] and the result was similar to the SMD in Fang & Xu (2017)'s RCT where control group received relaxation training as well as intervention group (SMD = 1.00).[67] Similar effect size of Li et al. (2020)'s study with only acupuncture was reported (SMD = 0.97). These three studies resulted in similar SMD, and this led to low χ_4^2 score. Even though the statistical test supported homogeneity in this subgroup, the quantitative conformity is neither a sufficient nor a necessary condition of homogeneity for choosing between fixed and random effects model. This is the reason why qualitative heterogeneity always prevails quantitative heterogeneity in choosing a model in meta-analysis.

Issues on the validity of the effect for acupuncture treatment in a RCT setting

Outcomes from the four subgroup meta-analyses were briefly reviewed above, and all of them supported strongly in statistical terms for the effectiveness of acupuncture treatment for cancer care. In reality, however, this strong support for effectiveness of an acupuncture treatment is not accepted as much as the statistical summary effect terms claim.

MacPherson and Hammerschlag (2012) mentioned about differentiating the concept of effectiveness from the concept of efficacy:[70]

> … *Effectiveness* is a measure of the *overall impact* of an intervention on outcome, as would be expected to occur in routine care, with an emphasis on *generalisability*. *Efficacy* is a measure of the impact of an intervention on outcome in as *ideal conditions* as possible, with an emphasis on controlling for *placebo effects*, thereby limiting the effects of bias. When evaluating *effectiveness*, a comparative design is commonly used, in which acupuncture is compared to another active treatment. (*italic* added)

For ensuring the efficacy, the authors implied that patients in the control group should believe they were treated with real acupuncture to activate full placebo effect even with a sham acupuncture treatment. Therefore, the research-designer should provide an ideal condition sufficing this to demonstrate the efficacy as a difference between the controlled placebo group and real acupuncture group. Practicing acupuncture has intrinsic difficulty to make this ideal condition for an RCT. Different effect size depending on mode of sham acupuncture, unclear mechanism of the needle work, divergent diagnosis systems are the main causes of the difficulty. So, followings are discussion about these issues on the RCT setting in the clinical investigation for the validity of acupuncture treatment.

Different modes of Control Group

In the RCTs for acupuncture, the clinical mode of control group plays important role in an experimental setting to get an effect size. For example, the different choice of sham acupuncture mode will lead to a different effect size. There are three different applying modes for sham acupuncture. They are; ① The sham needles were blunt-tipped needles that move up inside their handle when pressed against the skin. ② Insertion with needle wrong points that not indicated for the condition in acupuncture theory. ③ Insertion on the non-points locations that were not known acupoints. In modes of ② and ③, the sham acupuncture can be as efficacious as true acupuncture.[45,71] In this setting, the RCTs can be the validity of traditional acupuncture theory about specific point locations and their therapeutic indications. Xiang et al. (2017) reported that true acupuncture against nonpenetrating sham acupuncture showed statistically more effective [SMD = -0.70, 95% CI (-1.21; -0.20)] than true acupuncture against pooled penetrating and nonpenetrating sham control trials [SMD = -0.46, 95% CI (-1.11; 0.18)] for pain relief, and the latter was not as statistically significant as nonpenetrating studies only.[72]

When the nontreatment (waitlist) control group was included, the 3 arms of clinical setting (nontreatment or waitlist, nonpenetrating or penetrating sham, and true needle-insertion) had shown different tendency for the effects of RCTs. Chen et al. (2016) reported on the proportion of positive conclusions in different control designs. The nontreatment controls had the highest tendency to yield a positive conclusion (84.3%), compared with no needle-insertion (using sham needle) controls (53.3%), and trials with needle-insertion (penetrating sham acupoints) controls had the lowest tendency of positive conclusions (37.8%).[73] These results implied that the scientific rationales for acupuncture trials were needed to define valid controls, and the theoretical basis for traditional acupuncture practice needed to be re-evaluated in its application to RCTs.

Out of 29 RCTs in this study, 9 RCTs adopted sham acupuncture in their control group. Three of them applied penetrated sham acupuncture and six of them applied nonpenetrating

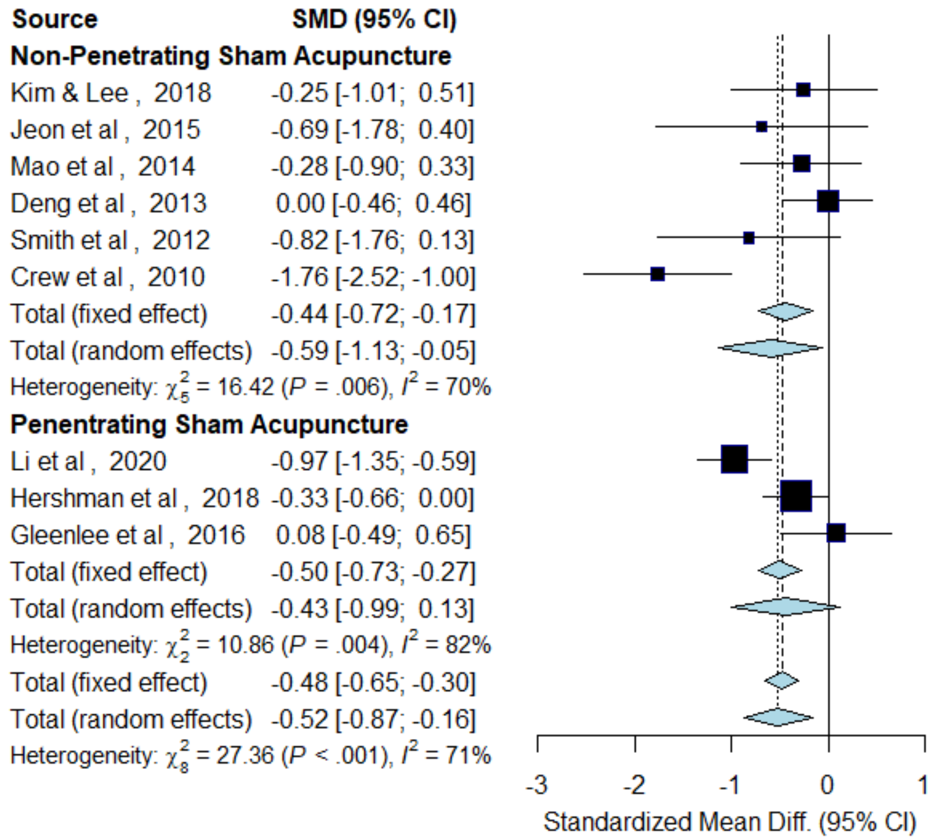

Figure 10. Penetrating vs nonpenetrating sham acupuncture

sham acupuncture. Figure 10 is the result of comparing pooled studies between these two different modes of sham acupuncture. The heterogeneity in both quantity and quality of the studies was obvious as seen above. For penetrating group, the quantitative heterogeneity was tested to be $\chi^2_2 = 10.86$ ($p < 0.004$), and $\chi^2_5 = 18.15$ ($p < 0.003$) for non-penetrating group. Qualitive heterogeneity strong as it had been examined above, especially in Table 1, 2, and 4. Therefore, the comparison was based on random effects model. In the random effects model, the group applied nonpenetrating sham acupuncture revealed a little higher effect size [SMD = - 0.59, 95% CI (-1.13; -0.05)] than the penetrating group [SMD = - 0.43, 95% CI (-0.99; 0.13)], but the summary effect sizes of fixed model showed contrary

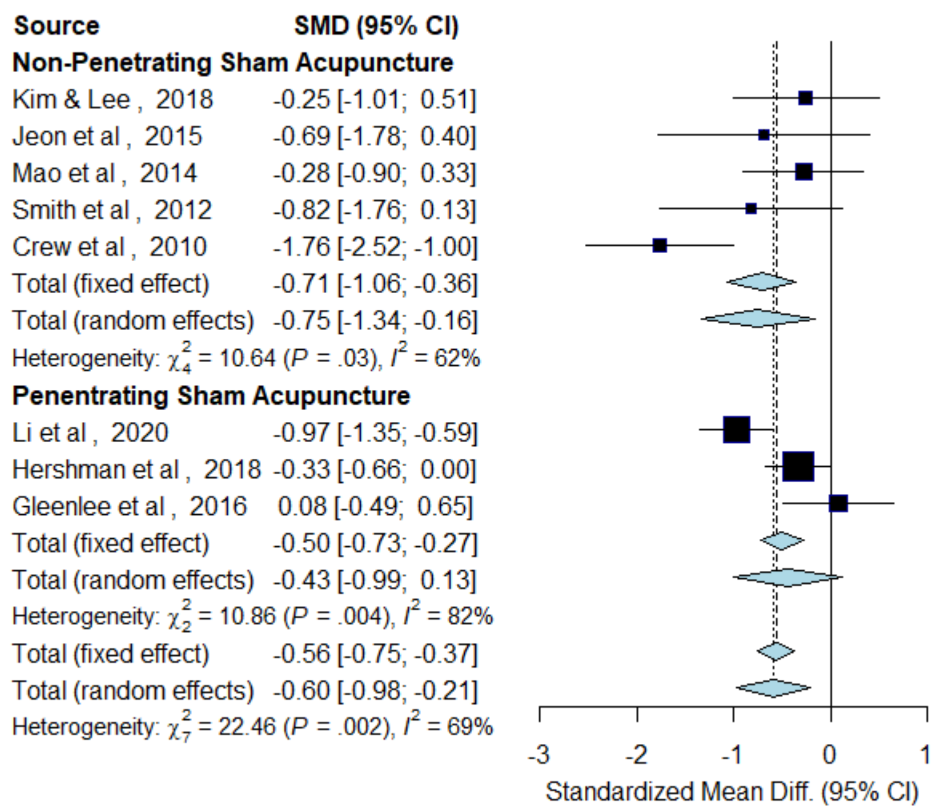

Figure 11. Penetrating vs nonpenetrating sham acupuncture except Deng et al.

result. These results could not fully support that the nonpenetrating group showed higher effect size than the needle-penetrating group. Therefore, more studies were needed to resolve their suggestion about the effects of different sham acupuncture.

If the study of Deng et al. (2013) was removed from the nonpenetrating group for a sensitivity analysis, the summary effect provided more conformity to the Xiang et al. (2017) as seen in Figure 11. As mentioned earlier in *Fatigue-subgroup analysis*, Deng et al. (2013)'s study seemed to have strong bias during their clinical trial, because it was unusual to get a result of zero SMD in non-penetrating sham controlled acupuncture. In Figure 11, the summary effect size of pooled modified nonpenetrating sham acupuncture group [SMD = - 0.75, 95% CI (-1.34; -0.16)] showed higher summary effect than that of the penetrating

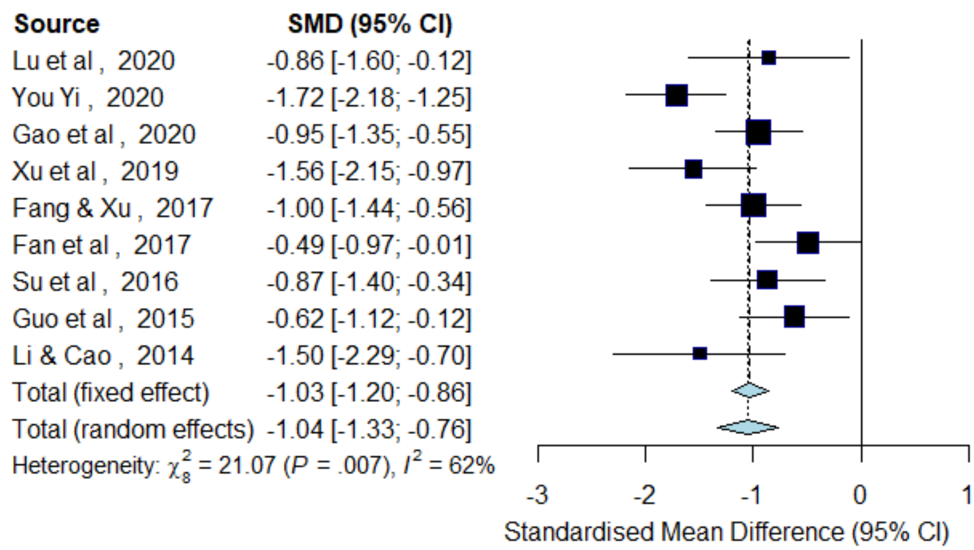

Figure 12. Forest plot of RCTs with waitlist control trial

sham acupuncture group (SMD = - 0.43) in random effects model.

Figure 12 is a forest plot of the pooled studies that were based on the clinical setting of a "waitlist" trial. Only one study (Lu et al. 2020) had pure waitlist control group setting,[36] the others were set in trial for comparing A + B (acupuncture + e.g., usual care) against B (e.g., usual care) as Ernst & Lee (2008) mentioned.[33] The result showed higher effect size of pooled waitlist group (SMD = -1.04) than the sham acupuncture groups as shown in Figure 10, 11 (SMD = -0.53, -0.60). Therefore, the results from this study conformed to the study done by Chen et al. (2016).[73] The pooled waitlist studies clearly showed higher summary effect size than that of the pooled sham acupuncture. These results revealed a tendency that the effect sizes were affected by the choice of control group setting.

Mechanism of the acupuncture application

In traditional acupuncture theory, the effect from choice of acupoints may depend on the specific symptom being treated, type of needle stimulation, and accuracy of point location. Except the *qi* flow and meridian theory, however, no plausible explanation how a needle works presented in the TCM. The mechanism of acupuncture is not well understood in a modern anatomical and physiological concept. This makes it difficult to set a RCT to investigate the effect of acupuncture treatment. In some RCT setting, the study could be a test whether a set of acupoints were effective for a specific symptom. Hence, the results of RCTs and systematic reviews about the effective of acupuncture have remained controversial, and the unclear mechanism of acupuncture is one of the reasons.

Several researches have raised some alternative explanations about this acupuncture mechanism in modern scientific perspective.[74,75,76] For example, Cheng (2014) explained the mechanism of acupuncture with 3 layers of its effects. They are; ① Local effects that work for the treatment of musculoskeletal conditions in nerve function and blood circulation along with cytokines. ② Somato-autonomic reflex on homeostasis by the autonomic reflex that involves the sympathetic and parasympathetic nervous system. ③ Distal systemic effect through neurotransmitters in the brain such as stimulating the secretion of endorphin is also considered an effect of acupuncture treatment.[74]

Acupuncture treatment could effectuate on human body through multi-dimensional channel. Moreover, real therapeutic effects are also affected by other contributing factors such as needle sensation (or Deqi), needle manipulation, and needle duration.[77,78] It is desirable to have more research and experiments on this subject, and incorporating the modern scientific theory into the mechanism of acupuncture. Then there will be improvement in setting an ideal clinical trial, and eventually acupuncture therapy will have stronger evidence for the mainstream health care providers.

Risk of bias in the RCTs

Risk of bias (ROB) is one of big issues in RCTs for any meta-analysis, and it is also a frequently encountered problem in RCTs for testing efficacy of acupuncture. Checking the ROB of a study is to assess the internal validity of the studies through the risk that they may over-estimate or under-estimate the true intervention effect. The ROB includes the process of random allocation generation, allocation concealment, and report of incomplete data, fair agreement for blinding of participants and personnel, blinding of outcome assessment, and selective reporting.[79,80] This ROB can be recapitulated as the ineffective blinding of research participants and selective report in on the resulting data from the RCTs. It is also essential to randomize distribution of patients between intervention and control group according to age, sex, and race, so that they can evenly represent the demography of population in both experimental and control groups.

Blinding participants is essential especially for realizing the placebo effects in a clinical experimental design. Blinding patients between intervention and control groups, however, may be a different hypothesis test, depending on its clinical design. For example, sham acupuncture with real needle insertion may be a testing hypothesis not for the efficacy of acupuncture itself but for the validity of a specific acupuncture theory on which the study's intervention points have been selected. Therefore, nonpenetrating sham acupuncture should be applied for the control group to measure the placebo effects from the study, and blinding the participants is a crucial requirement. It is meaningful to investigate the risk of bias in the nonpenetrating sham controlled trials.

Six studies from 29 RCTs were chosen for ROB assessment, because they had settings with nonpenetrating sham acupuncture mode for their control groups. These six studies

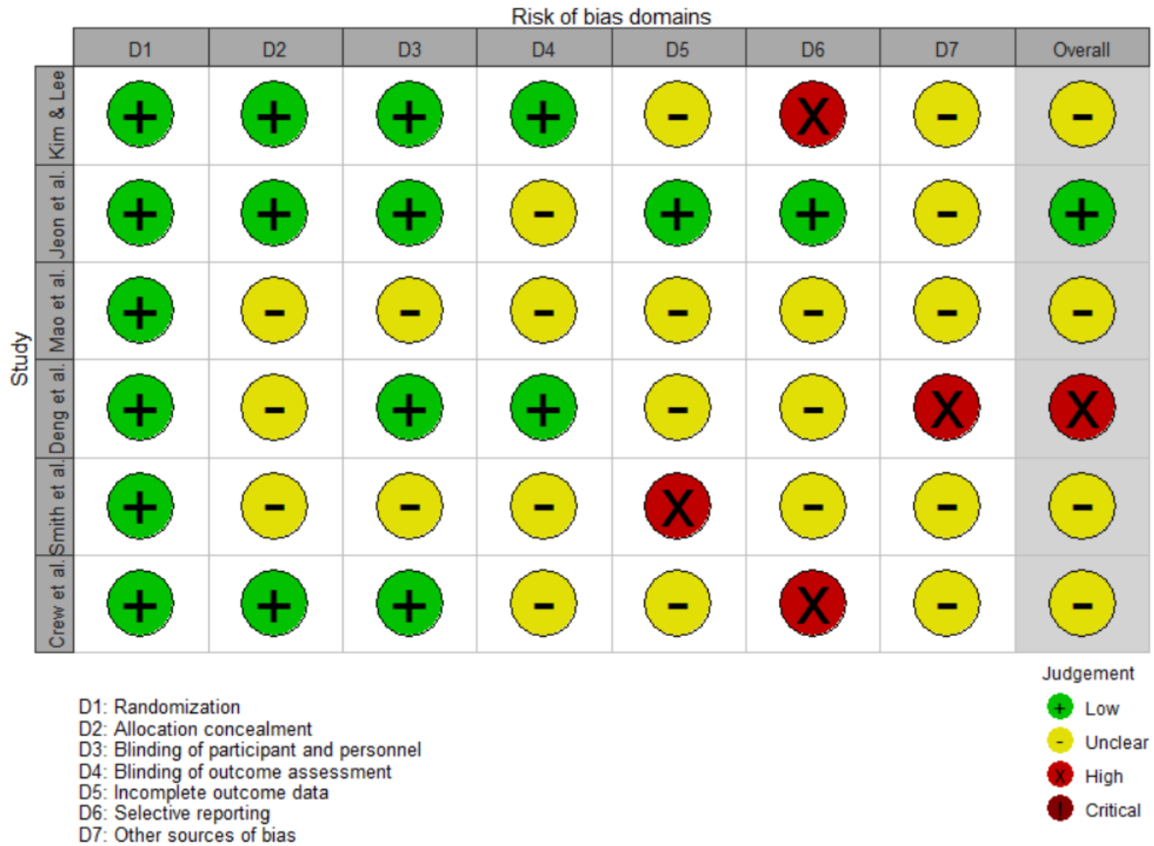

Figure 13. Bias plot for nonpenetrating sham control studies

were Kim & Lee (2018),[44] Jeon et al. (2015),[70] Mao et al. (2014),[56] Deng et al. (2013),[52] Smith et al. (2012),[54] and Crew et al. (2010).[42] For assessment of ROB, 7 major domains are defined, D1: Randomization, D2: Allocation concealment, D3: Blinding of participants and personnel, D4: Blinding of outcome assessment, D5: Incomplete outcome data, D6: Selective reporting, D7: Other source of bias. Figure 13 is the assessment outcome from selected RCTs, and Figure 14 is the plot for summary bias of these studies. More detailed contents about these 6 studies for assessing the ROB are described in APPENDIX - B.

Deng et al. (2013) reported unusually high incidents of 11 serious adverse events such as nausea (n=1), vomiting (n=2), renal failure (n=2), dyspnea (n=1), back pain (n=1), and

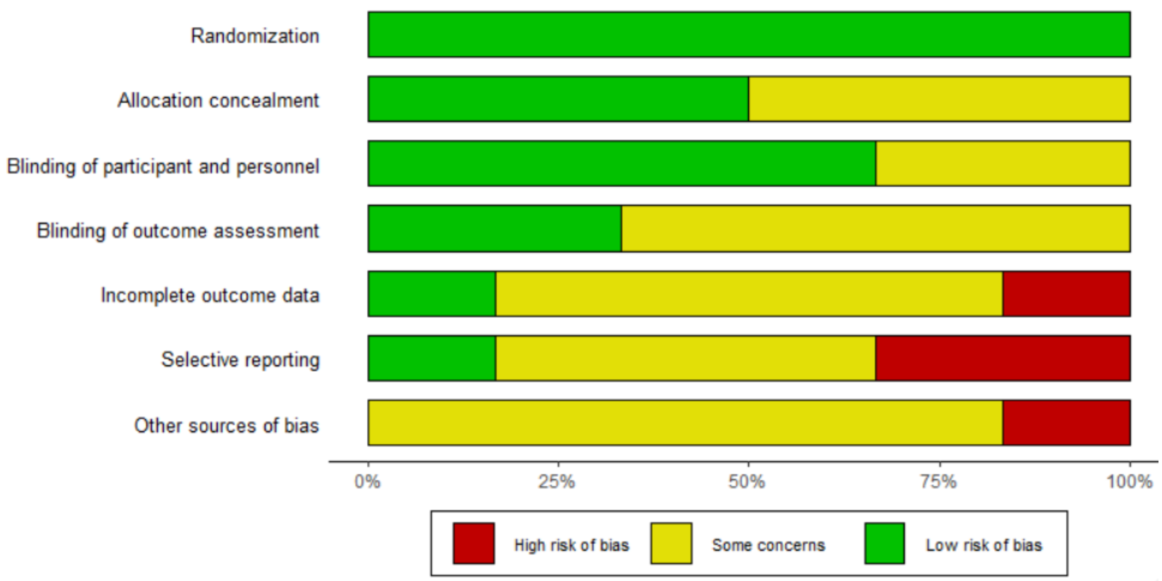

Figure 14. Summary bias for nonpenetrating sham control studies

so on, but the authors believed that these adverse events were not directly related to the acupuncture treatment with no acceptable explanation. Therefore, we could decide that there might be other sources of bias in their study. Crew et al (2010) claimed that "22% of subjects who received SA (sham acupuncture) reported a 2 point decrease in the BPI" without their data supported, they also reported that 57% of patients in the sham group believed they were receiving true acupuncture. It was needed to conduct more realistic sham acupuncture treatment for their study. Two of the six studies, Mao et al. (2014) and Smith et al. (2012), set up 3 arms clinical setting. Generally, real acupuncture group showed larger effect size than sham acupuncture group, and sham acupuncture group showed better effect than waitlist control group. The measure of the outcome difference of sham acupuncture group from waitlist control group was an important standard for measuring placebo effects in the 3 arms setting. Hence, the results of their studies showed roughly this tendency.

Reporting complete outcome data was an important domain for assessing the risk of bias in a study. The acupuncture rationale, details of acupuncture process, the treatment regimen, other components of treatment, the practitioner background, and other sham acupuncture interventions were to be reported. Reporting on clear outcome right after the intervention period and follow-up measure were also assessed. Assessing the blinding process usually depended on the authors' description. Kim & Lee (2018) and Deng et al. (2013) reported that the outcome evaluators were blinded. Jeon et al. (2015) set up the clinical environment to blind the acupuncturist. It was notable that the clinical study for acupuncture treatment for cancer patients was susceptible to outside influence/bias during the trials, because cancer patients were usually treated with other conventional care such as pharmacological treatment while getting the intervention.

Diagnosis in the Traditional Chinese Medicine

Another issue on clinical study for acupuncture is the problem of difficulty in using a standardized regimen (especially acupoints selection) for specific clinical trial setting. It is well known that the effect of acupuncture therapy is affected by the selection of acupoints with their therapeutic indications. In some study settings, the diagnoses for acupoints selection were based on the TCM diagnostic system such as "Zang-Fu diagnosis" and "Eight Principles diagnosis: yin/yang, hot/cold, internal/external, excess/deficiency," if they provided a diagnosis.[81] If two of these TCM diagnostic systems ('Zang-fu' and 'Eight Principle') are combined, numerous combinations are possible candidates of diagnosis for a disease. For example, diagnosis of a pain can has several categorical classes depending on its etymology framed by a specific theory in the diagnostic system. Therefore, it is almost impossible for setting acupoints that can cover all the diagnoses for pain-patients in a clinical setting.

This might be the reason why Greenlee et al. (2015) suggested standardized acupoints protocol for breast cancer patients depending on joints selection for applying patient's specific acupoints,[82] and some RCTs also adopted this way of acupoints selection to be patient-specific approach in the current meta-analysis.[36,40,54] Chen et al. (2021) provided meaningful protocol for points selection covering symptom with several differentiations such as excess/deficiency, Zang-Fu diagnosis, and Qi/Blood/Phlegm diagnoses.[83] Even though this kind of intervention methods become more complicated to a trial acupuncturist, the selected acupoints suit well for the test of acupuncture effectiveness. First of all, diagnosis for a symptom, mechanism of acupuncture, and etiology of a disease should go together for the ideal clinical setting, and the researchers should keep this matter in mind to have better standardized protocol for their studies.

Adverse effect & Prospective of the study

Acupuncture for cancer care may accompany minor adverse effects such as bruising, spot bleeding, local discomfort, nausea and dizziness. However, no serious adverse reactions that were directly related to the acupuncture treatment were reported in the RCTs. There are also other cancer-related symptoms acupuncture treatment can help. Hot flashes, hiccups, xerostomia, dyspnea, lymphedema, and psychological well-being from depression are the other possible accompanying symptoms from cancer itself and/or cancer therapy. The efficacy of acupuncture on these symptoms was not definite but assumptive based on the available RCTs studies.[84] As the more researches for acupuncture treatment on these symptoms are accumulated, we can have the more evidence for the efficacy of acupuncture on them.

Several methodological issues about the RCTs on acupuncture therapy were briefly reviewed. Considering some of these issues, Luo et al. (2015) suggested a new research model in which a typical RCT mode and the "real world research" model were combined to test the effectiveness of acupuncture.[85] Most of all, realizing these methodological shortcomings in clinical trials for the efficacy of acupuncture will help practitioners understanding current trend of acupuncture application for cancer care, and it will also help researchers developing better environment and more plausible clinical setting for future research. Despite all these problems and difficulties, many published RCTs and meta-analyses on acupuncture for cancer care have contributed to the provision of more evidence for its clinical appropriateness. They also help becoming acupuncture an important part of integrative health care services in the modern society.

V. CONCLUSION

Acupuncture has been a capable modality for alleviating many adverse symptoms from cancer itself and/or cancer treatment. The outcomes from this meta-analysis presented that acupuncture treatment was highly effective for cancer-related symptoms such as pain, fatigue, insomnia, and anorexia. However, the heterogeneity of the clinical settings and intrinsic difficulties of RCT for acupuncture trials made it difficult to get the definitive proof for the efficacy of these clinical outcomes. Different clinical result depending on the selected mode in the control group, unclear mechanism how acupuncture works, and the risk of bias in RCT have been hindering factors not to reach a definitive conclusion for the study. The TCM has its own several diagnosis systems such as "Zang-Fu diagnosis" and "Eight Principles diagnosis," and this also makes it difficult to have consistent acupoints for the specific symptom in a clinical study setting.

Even if the included RCTs in this meta-analysis had some limitations to be in an ideal experimental setting, study combining these RCTs would have contributed to the evidence of effectiveness for oncology acupuncture in theory and for practice.

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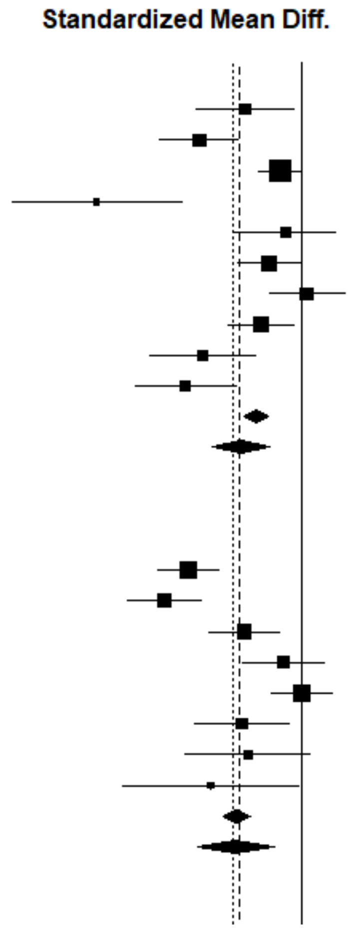
APPENDIX - A

Summary Report with Input Data and Subgroup Meta-Analysis

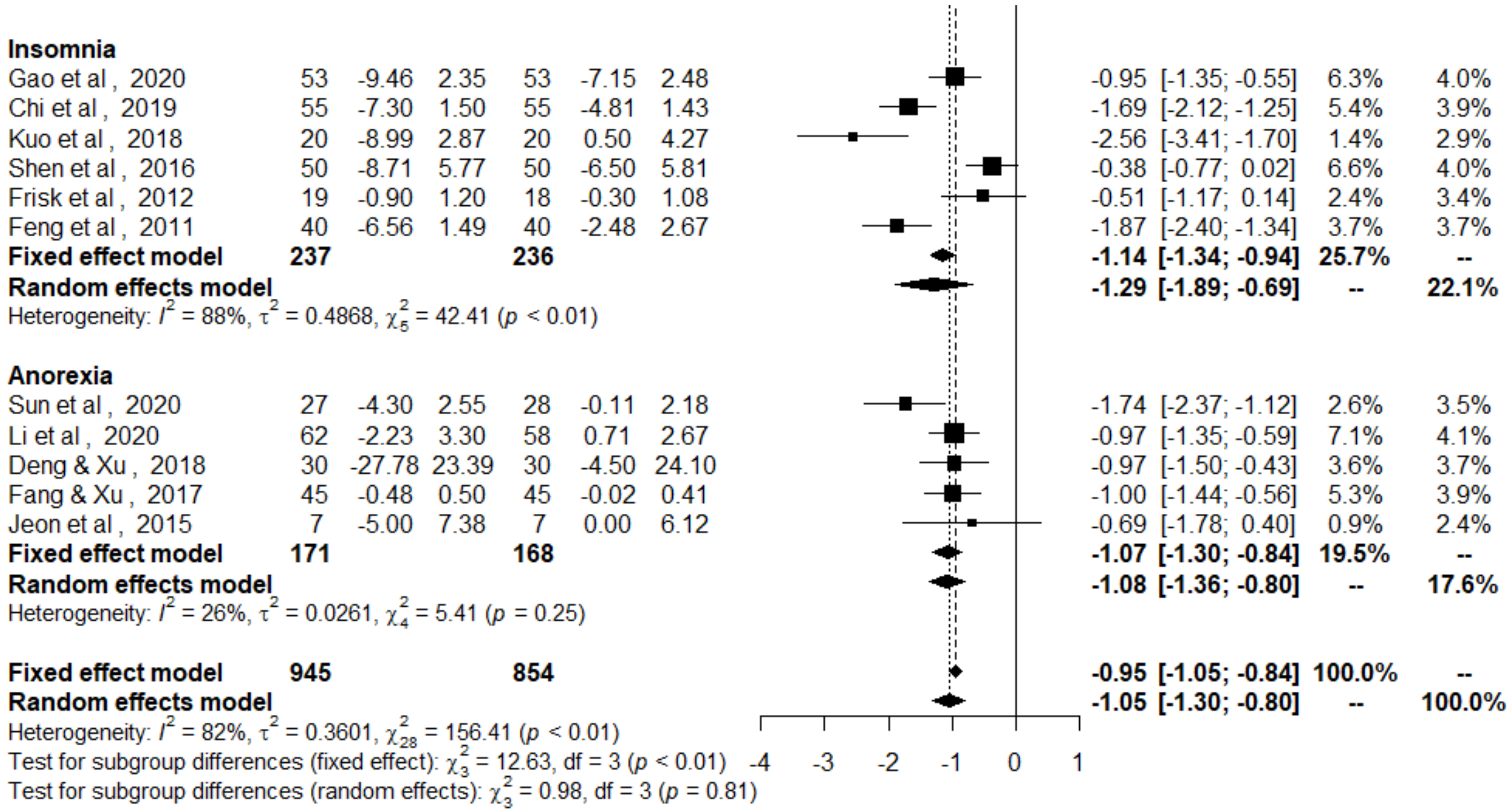
Following figure presents the detailed input-data for the meta-analysis, and results of subgroup analyses. The homogeneity hypothesis in the RCTs was rejected in the study, because the RCTs revealed both quantitative and qualitative heterogeneity. Quantitative heterogeneity was tested with χ^2_{28} score determining the variance between the studies that is 156.41 *(p* < 0.001). Qualitative heterogeneity was obvious, since there were so many different trial settings such as methods of experimental intervention, different interventions for control group, different modes of sham acupuncture, and so on.

In the fixed effect model, it is assumed that there is a single true underlying effect (here, SMD). So, it is expected that all the RCTs are homogenous. In DISCUSSION section, Figure 9 showed that the anorexia subgroup's chi-square test was $\chi^2_4 = 5.41$ ($p = 0.25$). This quantitative heterogeneity might support the fixed effect model. However, the qualitative heterogeneity, as shown in Table 4, was strong enough to support for the random effects model. One could believe that the true underling effects were different each other among the studies. In this case, a researcher should choose the random effects model in the anorexia subgroup meta-analysis, even though the quantitative heterogeneity seemed to support the fixed effect model.

Author(s), Year	Intervention Num	Intervention Mean	Intervention SD	Control Num	Control Mean	Control SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Pain										
Lu et al , 2020	14	-1.50	1.94	17	0.20	1.91	-0.86	[-1.60; -0.12]	1.9%	3.2%
Xu et al , 2019	35	-3.90	0.74	25	-2.80	0.63	-1.56	[-2.15; -0.97]	3.0%	3.6%
Hershman et al , 2018	100	-1.45	1.79	54	-0.76	2.55	-0.33	[-0.66; 0.00]	9.3%	4.2%
Ruela et al , 2018	11	-5.27	1.60	12	0.33	1.85	-3.11	[-4.39; -1.83]	0.6%	2.0%
Kim & Lee , 2018	14	-1.54	1.45	13	-1.15	1.57	-0.25	[-1.01; 0.51]	1.8%	3.2%
Fan et al , 2017	35	-1.45	1.38	34	-0.75	1.45	-0.49	[-0.97; -0.01]	4.5%	3.8%
Gleenlee et al , 2016	25	0.30	2.60	22	0.10	2.20	0.08	[-0.49; 0.65]	3.1%	3.6%
Guo et al , 2015	32	-3.64	1.21	32	-2.86	1.27	-0.62	[-1.12; -0.12]	4.1%	3.8%
Li & Cao , 2014	16	-5.08	1.11	16	-3.19	1.34	-1.50	[-2.29; -0.70]	1.6%	3.1%
Crew et al , 2010	20	-3.34	1.78	18	0.10	2.05	-1.76	[-2.52; -1.00]	1.8%	3.2%
Fixed effect model	**302**			**243**			**-0.69**	**[-0.87; -0.51]**	**31.5%**	**--**
Random effects model							**-0.93**	**[-1.37; -0.49]**	**--**	**33.6%**
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.3838$, $\chi^2_9 = 47.29$ ($p < 0.01$)										
Fatigue										
You Yi , 2020	50	-59.37	7.87	50	-45.47	8.21	-1.72	[-2.18; -1.25]	4.8%	3.9%
Zhang et al , 2018	40	-1.55	5.65	40	9.76	5.06	-2.09	[-2.64; -1.54]	3.4%	3.7%
Su et al , 2016	30	-1.08	0.99	30	-0.30	0.77	-0.87	[-1.40; -0.34]	3.6%	3.7%
Mao et al , 2014	21	-1.40	3.04	20	-0.60	2.51	-0.28	[-0.90; 0.33]	2.7%	3.5%
Deng et al , 2013	34	-1.20	1.62	40	-1.20	1.79	0.00	[-0.46; 0.46]	4.9%	3.9%
Molassiotis et al , 2012	46	-3.72	2.98	10	-0.62	4.83	-0.91	[-1.62; -0.20]	2.1%	3.3%
Smith et al , 2012	9	-3.10	2.06	10	-1.50	1.69	-0.82	[-1.76; 0.13]	1.1%	2.7%
Johnston et al , 2011	5	-4.20	1.31	7	-1.62	1.95	-1.38	[-2.71; -0.05]	0.6%	2.0%
Fixed effect model	**235**			**207**			**-0.98**	**[-1.19; -0.77]**	**23.3%**	**--**
Random effects model							**-1.00**	**[-1.57; -0.42]**	**--**	**26.7%**
Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.5681$, $\chi^2_7 = 48.67$ ($p < 0.01$)										



Forest plot continues …



Output of summary effects with each study input data & subgroup analyses

APPENDIX – B

Detailed information for the assessing the risk of bias: non-penetrating sham acupuncture trials for control group

Table 1. Risk of Bias, Summary Characteristics of Randomized Clinical Trials

Study	Sample Size / Age Randomization	Intervention	Control	Treatment; Outcomes	Summary of Result	Adverse Events
Kim & Lee,[42] 2018	30 various cancer patients/ 56 (42 – 73) Patient-assessor-blinded (Computerized random number generator)	<A> Intradermal acupuncture: needle was kept attached on the skin for 48 to 72 hours (n = 15, 1 withdrawal)	<B> Sham intradermal acupuncture, no-penetration (n = 15, 2 withdrawal)	3 weeks (3X/week); NRS, QOL, Change in analgesics	NRS: <A> MD, −1.57 ± 2.06, <B> MD, −1.54 ± 1.20 EORTC QLQ-C30: <A> MD, −7.29 ± 10.58, <B> MD, −8.77 ± 11.14	fatigue
Jeon et al.,[68] 2015	14 throid cancer patients Age: True- 42.3, Sham- 46.3 Computer generated randomization; blinding both acupuncturist and patient	<A> Intradermal acupuncture (n=7)	<B> Sham intradermal acupuncture(n=7)	2 weeks (3X/week); ASC, VAS, FAACT	ASC: <A> MD, 5±7.38 <B> MD, 0±6.12	No adverse event
Mao et al,[54] 2014	76 breast cancer patients/ 59.7 (41-76) Computer-generated numbers sealed in opaque envelopes	<A> Electro-acupuncture (30 min, n=22)	<B> Sham acupuncture; non-penetrating needles at least 5cm away from the pain area (n=22) <C> Waitlist (n=23)	8 weeks (2X/week) - 2weeks; (1X/week) – 6weeks BFI, PSQI, HADS	<A> vs <B>: MD, -0.6 (-2.53;1.33) → not significant <A> vs <C>: MD, -0.5 (-2.69, 1.69) → not significant	Not reported
Deng et al,[50] 2013	98 various cancer patients/ True Acu 54(46-58) Sham 53(45-59)	<A> Acupuncture (n = 47, 13 withdrawal)	<B> Sham acupuncture; w/ sham needles & points a	6 weeks (1X/week);	BFI: <A> : MD, -1.2 (1.47 ←SD) <B> : MD, -1.2 (1.79)	11 serious adverse

	Fax to a central randomization service; Patients and evaluators blinding		few mm off the meridians (n = 51, 11 withdrawal)	BFI, HADS, FACT-G	FACT-G overall: <A> : MD, 3.9 (11.39) <B> : MD, 4.5 (14.45)	events: nausea, vomiting, …
Smith et al,[52] 2012	30 breast cancer patients/ <A> 55(8.8), <B> (12.5) <C> 58(7.5) Computer generated randomization	<A> Acupuncture	<B> Sham acupuncture; (non-invasive) on no acu pts <C> Waitlist	3 weeks (2X/week); BFI	BFI after 4 weeks; <A> vs <B> : MD, -1.8(1.875 ←SD) → not significant <A> vs <C> : MD, -2.4(1.95)	Not reported
Crew et al,[40] 2010	43 breast cancer patients/ <A> 58 (44-77) <B> 57 (37-77) Blinding all participants except acupuncturists	True acupuncture (TA); + auricular acupuncture (n = 23, 3 withdrawal)	Sham acupuncture (SA); superficial needle used, no true acu points (n = 20, 2 withdrawal)	6 weeks (2X/week); BPI	BPI for <A> vs <B>: Worst pain: MD, -3.59 (0.94) Pain severity: MD, -3.44 (0.81) Pain-related inference: MD, -1.97 (1.14)	Not reported

BFI: Brief Fatigue Inventory, BPI: Brief Pain Inventory, SD: Standard Deviation, PSQI: Pittsburgh Sleep Quality Index, ASC: Anorexia/Cachexia Subscale in FAACT, MD: Mean Difference

Table 2. Risk of Bias, Details of Acupuncture Procedure

Study	Theory & Rationale	Points Used	Depths of Insertion	Responses elicited	Needle Stimulation	Needle Retention time	Needle type	Treatment Regimen	Practitioner background
Kim & Lee,[42] 2018	TCM theory	CV 12, bilateral ST 25, LI 4, LR 3, PC 6, and 0~3 Ashi points	1.5 mm	Not specified (intra-dermal acu)	Patient press twice a day	attached on the skin for 48 to 72 hours	stainless steel IA needles (0.18x1.3x 1.5 mm) Dong-Bang	3 weeks	Doctors of Korean medicine, Experience > 3 year

Jeon et al.,[68] 2015	TCM theory	(bilaterally) LI 4, LR 3, ST 36, SP 6, KI 2	1.5 mm	Not specified (intra-dermal acu)	No stimulation	30 min	Stainless steel IA (0.2x 1.5x2 mm), Dong-Bang	2 weeks (6 sessions)	Not reported
Mao et al,[54] 2014	TCM theory	Trigger pts: at least 4 local points around the joint with the most pain. EX) Shoulder: LI 15 (bilateral), SI 9 (bilateral) Knee: ST34 (bilateral), ST35 (bilateral), SP9 (bilateral), etc	Not reported	Deqi	Manual stimulation (beginning and ending), Electro-acupuncture	30 min	Stainless steel (0.25x30, 0.25x40mm) Seirin-America	8 weeks (10 sessions)	Two: 8 years and 20 years of experience
Deng et al,[50] 2013	TCM theory	Unilateral: CV 6, CV 4, Bilateral: KD 3, SP 6, ST 36, LI 11, HT 6, ear acupuncture, A sham needle manufactured by AsiaMed	0.5–1″ deep	Deqi	Manual stimulation	20 min	Stainless steel 1/2″ to 3″ long and 32–38 G in width, Seirin or Tai Chi	6 weeks (6 sessions)	Licensed acupuncturist by the New York State, Experience > 3 year
Smith et al,[52] 2012	TCM theory	Bilateral KI 3, KI 27, ST 36, SP 6 and unilateral CV 4 and CV 6	Not reported	Deqi	Not reported	20 min	Stainless steel (0.25×40 mm and 0.22×25 mm), Vinco	3 weeks (6 sessions)	Licensed by Australian Acupuncture and Chinese Medicine Association
Crew et al,[40] 2010	TCM theory	Varied; acu points near 3 most painful joint areas + ear acupuncture	Not reported	Deqi	Manual stimulation	20~25 min	(25 mm or 40 mm and 34-gauge), Cloud & Dragon Medical Device	6 weeks (12 sessions)	Not reported

Table 3. Risk of Bias, Assessment

Study	Randomization	Allocation concealment	Blinding of partipant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Kim & Lee, 2018	low	low	low	low	moderate	high	moderate	moderate
Jeon et al., 2015	low	low	low	moderate	low	low	moderate	low
Mao et al., 2014	low	moderate	moderate	moderate	moderate	moderate	moderate	moderate
Deng et al., 2013	low	moderate	low	low	moderate	moderate	high	high
Smith et al., 2012	low	moderate	moderate	moderate	high	moderate	moderate	moderate
Crew et al., 2010	low	low	low	moderate	moderate	high	moderate	moderate