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Effectiveness of acupuncture as an adjunctive therapy for lung cancer: A systematic review and meta-analysis

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Abstract

Objectives : Lung cancer is one of the most common cancer and the leading cause of cancer deaths worldwide. This study aimed to evaluate the role of acupuncture as an adjunctive therapy for lung cancer.

Methods : We conducted a systematic review and meta-analysis on the role of acupuncture therapy in lung cancer treatment by electronic and manual searching in ninedatabases, including PubMed, Cochrane library, Embase, Korean databases, and Chinese medical databases.

Results : A total of 21 trials were included in the meta-analysis. The study results showed that acupuncture therapy had significant efficacy in immuneregulation, including CD3 andCD4. Further analysis revealed that acupuncture therapy significant improvements in quality of life, including Karnofsky performance status(KPS)score, functional assessment of cancer therapy-lung cancer subscale (FACT-L) and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). In addition, the pooled studies also showed that acupuncture therapy reduced cancer pain and chemotherapy-induced nausea and vomiting.

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Conclusions : Our study provides moderate evidence of the efficacy of the acupuncture therapy in the treatment of lung cancer.

Keywords : Acupuncture, lung cancer, Systematic review, Meta-analysis

Introduction

Lung cancer is one of the most common cancer and the leading cause of cancer deaths worldwide. In 2018, over 2 million people were new diagnosed with lung cancer, accounting for 11.6% of the world's total cancer incidence. In mortality, lung cancer caused over 1.7 million cancer deaths, more than breast, prostate, and colon cancer combined[1]. Early lung cancer patients are usually asymtomatic and early signs like cough are often ignored, delaying the diagnosis and leading to high mortality[2]. However, advances in diagnostic and therapeutic techniques including widespread use of spiral low-dose computed tomography(LDCT) have improved survival rate of lung cancer in recent[3]. 5-year survival rate of lung cancer in Republic of Korea was 30.2% in 2019, 16% higher than 20 years ago[4]. Therefore, interest in quality of life of patients with lung cancer is increasing worldwide.

Multiple surgical techniques are now available but are generally limited to the early-stage lung cancer[5]. Since only 20–25% of lung cancer patients are operable, most patients are treated with chemotherapy or radiotherapy[6]. These treatments have specific toxicities and usually accompany adverse events, including hematologic, gastrointestinal or neurological toxicity[7]. Current drugs or other approaches to counteract chemotherapy-induced adverse effects are often incompletely effective, or may even induce other side-effects which only add to patients discomfort[8].

Acupuncture has been used in cancer treatment for a long time because of its efficacy and safety. Clinical practice guidelines, on the evidence-based use of integrative therapies during and following breast cancer, recommended acupressure and acupuncture for reducing chemotherapy-induced nausea and vomiting[9]. Also, a meta-analysis reported that a significant combined effect was observed for quality of life (QOL) change in patients with terminal cancer in favor of acupuncture and Tuina[10]. However, there is no recent review on the benefit of acupuncture therapy for lung cancer. This study aimed to observe the effect of acupuncture on QOL and reduction of side effects, especially nausea and vomiting in patients with lung cancer.

Methods

Data Sources and Search Strategy

The search was conducted in the following nineelectronic databases up to May 2020: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Journal integration platform (VIP), Korean Medical Database(Kmbase), National Discovery for Science Leaders (NDSL), and Oriental Medicine Advanced Searching Integrated System (OASIS). We also searched the references of all included studies by hand, grey literature, dissertations, letters, government documents, research reports, conference proceedings, and abstracts to avoid publication bias.

The search terms were as follows: ("Lung

Neoplasms"[Mesh] OR Pulmonary Neoplasms OR Neoplasms, Lung OR Lung Neoplasm OR Neoplasm, Lung OR Neoplasms, Pulmonary OR Neoplasm, Pulmonary OR Pulmonary Neoplasm OR Lung Cancer OR Cancer, Lung OR Cancers, Lung OR Lung Cancers OR Pulmonary Cancer OR Cancer, Pulmonary OR Cancers, Pulmonary OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung) AND ("Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture Treatment OR Acupuncture treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Electroacupuncture OR Acupuncture Points OR Meridians OR Acupoint). We adjusted similar search strategies for each of the databases. Chinese language database was retrieved with similarsearch strategy in Chinese.No restrictions were imposed on language, publication type or date.

Eligibility Criteria and Study Selection

Two reviewers evaluated the inclusion criteria independently. If two reviewers had disagreements, they were resolved by discussion.

Types of studies. Only randomized controlled trials (RCTs) up to May 2020 were considered eligible. Other study designs such as in vivo, in vitro, case reports, case series, conference papers, editorials, abstracts, retrospective studies, and cross-over designs were excluded.In addition, non-randomized and quasi-randomized trials were excluded.

Types of participants. Participants were patients with lung cancer confirmed by pathological diagnosis. No restrictions were placed on age, sex, ethnicity, stage of cancer, and sample size.

Types of interventions. The intervention that we were concerned with in this review was acupuncture therapy. However, the interventions combined with herbal medicine were excluded. Also, acupoint injection, acupressure and ear acupuncture were excluded. The comparisons in this review included sham acupuncture, chemotherapy, chemoradiotherapy, and analgesic drugs.

Types of outcome measures. The primary outcomes that were selected consisted of the immunoregulation data (CD3+, CD4+, and CD8+T cell level), Karnofsky Performance Status (KPS) score, Functional Assessment of Cancer Therapy – Lung (FACT-L), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Secondary outcomes consisted of the numerical rating scale (NRS) related to the cancer pain, and the incidence of chemotherapy-induced nausea and vomiting.

Assessment of Risk of Bias

Two independent reviewers assessed methodological quality using the Cochrane risk of bias tool (RoB). Disagreements between the two reviewers were resolved by discussion witha third reviewer. The following items were used to assess the methodological quality of RCTs: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Data Extraction and Synthesis of Results

Two reviewers independently screened the articles according to the inclusion and exclusion criteria and extracted the data based on a standardized data collection form. Disagreements between the two reviewers were resolved by consensus or by inviting a third reviewer.

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Collaboration was used for data analysis. For dichotomous data, the risk ratio (RR) and 95% confidence interval (CI) were reported. For continuous variables, standardized mean difference (SMD) with 95% CI wasreported. We used a random effects model to estimatetreatment effects. Heterogeneity was assessed using the I2 statistic, and I2> 50% was assumed to have high heterogeneity.P value < .05 was considered statistically significant.

Results

Characteristics of the included studies

A total of 1243 studies were identified by searching PubMed (n=65), CENTRAL(n=101), Embase (n=256), CNKI (n=166), Wanfang database (n=321), VIP (n=103), Kmbase (n=187), NDSL (n=39), and OASIS (n=5). Among them, 244 studies were excluded because they were duplicates. After reviewing based on titles and abstracts, 922 studies were excluded because they were case reports, nonclinical trials, or not related to the study. The full-texts of 77 studies were reviewed, and 22[11)-32)]studies were included in the qualitative synthesis and 20[11), 12), 14)-17), 19)-32)] studies were included in the quantitative synthesis. The study selection process details were described in Figure 1.

The characteristics of the included trials are listed in Table 1. All of the studies were

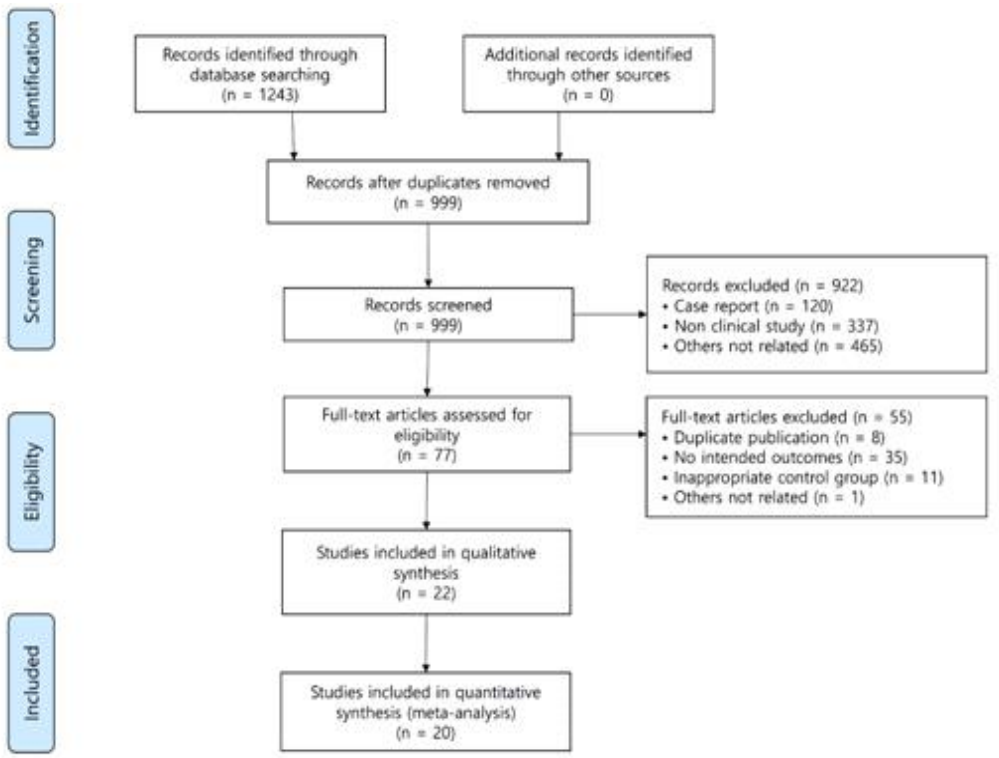


Figure 1. Flow chart of the study selection.

published from 2003 to 2020. A total of 22 studies with 1423 patients were analyzed, whereas 713 patients were from intervention group, and the other 710 patients were from control group. Acupuncture intervention included acupuncture, electroacupuncture, warming acupuncture, fire needle therapy. The most commonly used acupuncture points were ST36 (eleven studies), BL17 (seven studies), and SP6, PC6, BL19 (six studies).

Risk of bias in the included studies

The risk of bias of included 22 studies was shown in Figure 2. Sixteen RCTs[11),12), 14), 15), 17)-19), 23), 24), 26)--32)] reported using a "random number tables", while the five RCTs[13), 16), 21), 22), 25)] referred only to "randomization" without providing further details. One study[20)] neither mentioned "randomization" nor reported any detail randomization methods.Allocation concealment was reported in five of the included RCTs[11), 17)-19), 27)] and were not reported in the remaining seventeen[12)-16), 20)-26), 28-32)] RCTs. In one study[12)], sham acupuncture was used as a control group, and had a low risk of bias in blinding of participants and personnel.One study[32)] had a high risk of bias in terms of blinding of participants and personnel because it stated that it did not use double blinding in the study.In the remaining twenty studies evaluated as unclear in blinding of participants and personnel.All studies were unclear on blinding of outcome assessment and selective reporting outcome.One study[18)] were unclear on attrition bias because it is impossible to confirm whether the reported data were correct. Other biases were also evaluated as unclear in all studies due to insufficient information.

Meta-analysis

Immunoregulation

Immunoregulation was evaluated by CD3+, CD4+, and CD8+T cell level. We observed an improvement in the CD3+ T cell level (SMD = 0.65, 95% CI: 0.27 to 1.04, P = 0.0009, I2 = 66%, six studies, 340 patients) (Figure 3A)[15), 20)-22), 25), 26)]. Subgroup analysis showed that fire needle therapy (SMD = 0.59, 95% CI: 0.07 to 1.11, P = 0.03, one study) and warming

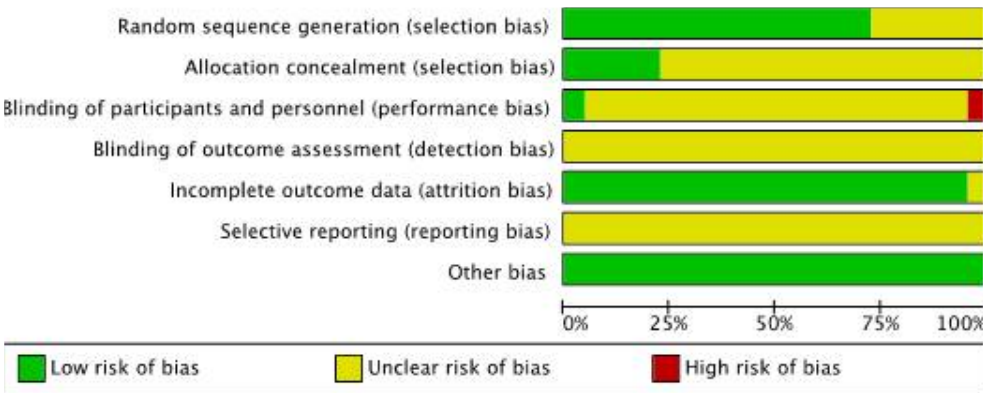


Figure 2. Risk of bias assessment among included studies.

Table 1. Characteristics of included studies.

First author, year	Cancer stage	Sample size (A/C)[a]	Acupuncture group		Control group	Assessment of outcomes	Duration
			Acupoints	Intervention			
Chen 201611)	Lung cancer (stage: n.r.)	60 (30/30)	ST36, ST25, PC6 (bilateral), RN12	(A) AT + tropisetron hydrochloride injection + EP	(B) Tropisetron hydrochloride injection + EP	KPS	3 days
Cheng et al. 201712)	NSCLC (stage: I-IV)	28 (14/14)	LI4, Ren6, ST36, KI3, SP6	(A) AT + CT or RT	(B) Sham AT + CT or RT	FACT-L	4 weeks, follow up-2 weeks
Guo 201713)	NSCLC (stage: n.r.)	45 (22/23)	Wrist ankle acupuncture	(A) AT + cisplatin based CT	(B) Gsplatin based CT	KPS	5 days
Li et al. 201414)	NSCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + TP/GP	(B) TP/G P	KPS	21 days
Li et al. 202015)	NSCLC (stage: III-IV)	64 (32/32)	ST36, RN6	(A) WAT + PC	(B) PC	CD3, CD4, CD8	21 days * 4courses
Lin et al. 201016)	Lung cancer (stage: III-IV)	83 (41/42)	BL17	(A) EAT + (NSCLC, NP or SCLC, EP)	(B) NSCLC, NP or SCLC, EP	1. FACT-L 2. KPS	10 days
Lin et al. 201617)	NSCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + TP/GP	(B) TP/GP	KPS	1 week
Lin et al. 201918)	NSCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + TP/GP	(B) TP/GP	KPS	1 week
Pei 201619)	NSCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + TP/GP/DP/NP	(B) TP/GP/DP/NP	1. KPS 2. FACT-L	21 days
Shi et al. 200320)	Lung cancer (stage: n.r.)	32 (18/14)	BL23, BL20, ST36, RN6, RN4 (bilateral)	(A) EAT + general anesthesia	(B) General anesthesia	CD3, CD4	Not reported
Wang 201521)	NSCLC (stage: III-IV)	60 (30/30)	Not reported	(A) EAT + TP/GP	(B) TP/GP	1. CD3, CD4, CD8 2. FACT-L 3. KPS	10 days
Wang et al. 201622)	NSCLC (stage: n.r.)	140 (70/70)	ST36, SP6 (bilateral)	(A) EAT +GP	(B) GP	1. CD3, CD4, CD8 2. KPS 3. QOL (QLQ-C30)	3 weeks
Wang et al. 201823)	Lung cancer (stage: n.r.)	60 (30/30)	AT based on syndrome differentiation	(A) EAT + oxycontin	(B) Oxycontin	1. QOL (QLQ-C30) 2. nausea and vomiting	14 days
Wang et al. 201924)	Lung cancer (stage: n.r.)	150 (50/50/50)	ST36, RN12, PC6	(A) AT before CT + tropisetron hydrochloride (B) AT after CT + tropisetron hydrochloride	(C) CT + tropisetron hydrochloride	KPS	3 days
Xu 201225)	NSCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + TP/GP	(B) TP/GP	1. CD3, CD4, CD8 2. FACT-L 3. KPS 4. nausea and vomiting	1 week
Yan 201826)	Lung cancer (stage: III-IV)	44 (22/22)	ST36, SP6, PC6, SP10 (bilateral), RN4, RM6	(A) AT + CRT	(B) CRT	CD3, CD4, CD8	2 weeks
Zhang 201427)	NSCLC, SCLC (stage: III-IV)	60 (30/30)	BL17, BL19 (bilateral)	(A) Fire needle therapy + cisplatin based CT	(B) Gsplatin based CT	1. KPS 2. FACT-L 3. nausea and vomiting	1week
Fan et al. 2017 (1)28)	Lung cancer (stage: n.r.)	116 (39/39/38)	PC6, LI4, ST36, GB34, SP6 (bilateral)	(A) AT + three ladder analgesic therapy (B) Psychological intervention + AT + three ladder analgesic therapy	(C) Three ladder analgesic therapy	NRS	10 days
Fan et al. 2017(2)29)	Advanced lung cancer (stage: n.r.)	69 (35/34)	PC6, LI4, ST36, GB34, SP6 (bilateral)	(A) AT + three ladder analgesic therapy	(B) Three ladder analgesic therapy	NRS	10 days * 2 courses
Shen et al. 201630)	Lung cancer (stage: III-IV)	100 (50/50)	AT based on syndrome differentiation	(A) EAT + three ladder analgesic therapy and combined with zolpidem	(B) Three ladder analgesic therapy and combined with zolpidem	NRS	4 weeks
Wang 201631)	Advanced NSCLC (stage: n.r.)	60 (30/30)	LI4, PC6, ST36, SP6	(A) EAT + oxycontin	(B) Oxycontin	1. NRS 2. QOL (QLQ-C30)	14 days
Wang 201932)	Bone metastasis of lung cancer	60 (20/20/20)	RN4, RN6, ST36, a shi points	(A) WAT + three ladder analgesic therapy (B) AT + three ladder analgesic therapy	(C) Three ladder analgesic therapy	1. NRS 2. QOL (QLQ-C30) 3. KPS	4 weeks

a: A/C, data of acupuncture group/ data of control group(s);
n.r., not reported; AT, acupuncture; EP, etoposide + cisplatin; TP, paclitaxcel + cisplatin; GP, gemcitabine + cisplatin; PC, Pemetrexed combined with Cisplatin; NP, vinorelbine + cisplatin; DP, docetaxel + cisplatin; AP, pemetrexed + cisplatin; KPS, Karnofsky performance status CT, chemotherapy, RT, radiotherapy; FACT-L, functional assessment of cancer therapy-lung cancer subscale; NRS, numeric rating scales; WAT, warm acupuncture; EAT, Electroacupuncture; QLQ-C30, EORTC core quality of life questionnaire; CRT, chemoradiotherapy.

A. CD3+ T cells

B. CD4+ T cells

C. CD8+ T cells

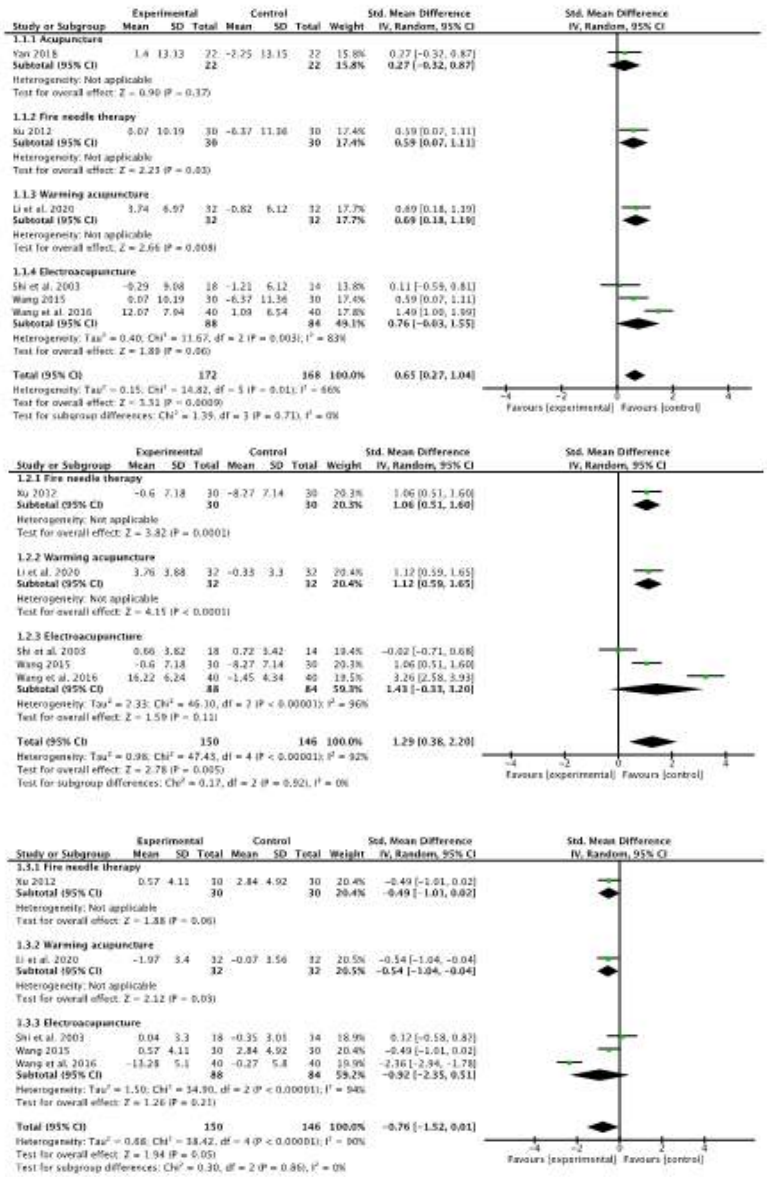
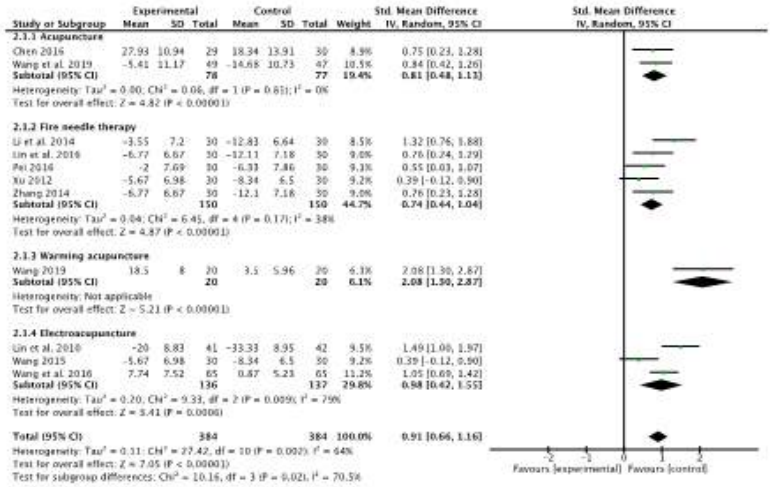


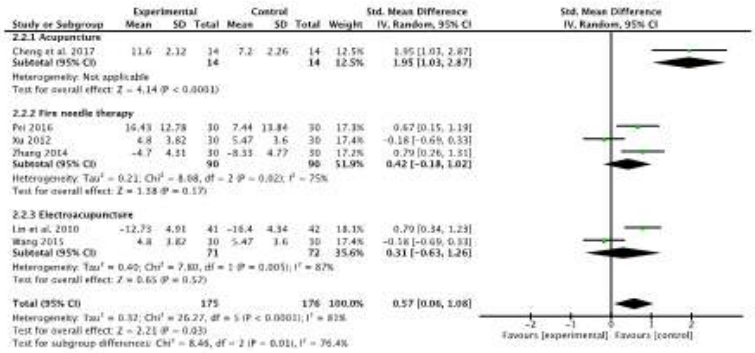
Figure 3. Immunoregulation of acupuncture in lung cancer patients. A, CD3+ T cells; B, CD4+ T cells; C, CD8+ T cells.

acupuncture (SMD = 0.69, 95% CI: 0.18 to 1.19, P = 0.008, one study) had advantage in CD3+ improvement, while acupuncture (SMD = 0.27, 95% CI: -0.32 to 0.87, P = 0.37, one

A. KPS score



B. FACT-L



C. QLQ-C30 total score

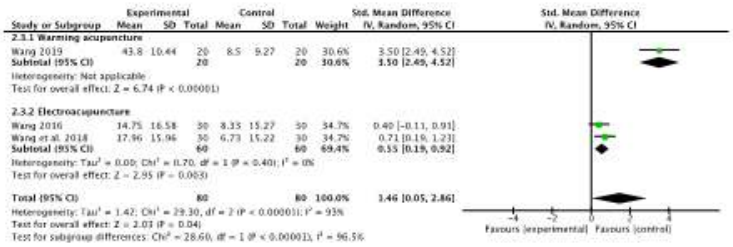


Figure 4. The assessments of the Quality of life. A, KPS score; B, FACT-L score; C, QLQ-C30 total score. KPS, karnofsky performance status FACT-L, functional assessment of cancer therapy lung cancer subscale; QLQ-30, EORTC core quality of life questionnaire.

study) and electroacupuncture (SMD = 0.76, 95% CI: -0.03 to 1.55, P = 0.06, three study) had no significant advantage in CD3+ improvement.

NRS

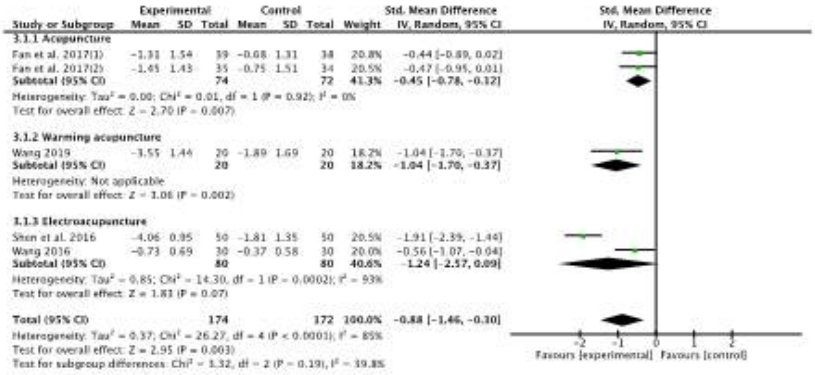


Figure 5. The efficacy of the acupuncture for the treatment of cancer pain. NRS, numeric rating scales.

Vomiting and Nausea

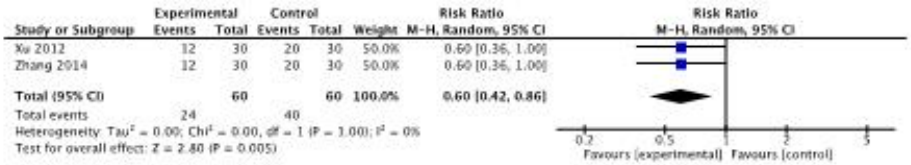


Figure 6. The efficacy of the fire needle therapy for reduction of number of patients with nausea and vomiting caused by chemotherapy.

Meta-analysis indicated that the CD4+ T cell level was significantly increased in the intervention group when compared to the control group (SMD = 1.29, 95% CI: 0.38 to 2.20, P = 0.005, I2 = 92%,five studies, 296 patients) (Figure 3B)[15), 20)-22), 25)]. Subgroup analysis showed that fire needle therapy (SMD = 1.06, 95% CI: 0.51 to 1.60, P = 0.0001, one study) and warming acupuncture (SMD = 1.12, 95% CI: 0.59 to 1.65, P< 0.0001, one study) had advantage in CD4+ improvement, while electroacupuncture (SMD = 1.43, 95% CI: -0.33 to 3.20, P = 0.11, three study) had no significant advantage in CD4+ improvement.

The CD8+ T cell level in the intervention group has shownno significant difference compared with the control group (SMD = -0.76, 95% CI: -1.52 to 0.01, P = 0.05, I2 =90%, five studies, 296 patients) (Figure 3C)[15), 20)-22), 25)]. Subgroup analysis showed that CD8+ was significantly different between warming acupuncture group (SMD = -0.54, 95% CI: -1.04 to -0.04, P = 0.03) when compared to the control group, while fire needle therapy group (SMD = -0.49, 95% CI: -1.01 to 0.02, P = 0.06) and electroacupuncture group (SMD

= -0.92, 95% CI: -2.35 to 0.51, P = 0.21) has shown no significant difference compared to the control group.

Quality of life

Quality of life was evaluated by KPS score, FACT-L, and EORTC QLQ-C30. Meta-analysis showed that the KPS scores were significantly increased in the intervention group when compared to the control group (SMD = 0.91, 95% CI: 0.66 to 1.16, P< 0.00001, I2 =64%, eleven studies, 768 patients)(Figure 4A)[11), 14), 16), 17), 19), 21), 22), 24), 25), 27), 32)]. Subgroup analysis showed that acupuncture (SMD = 0.81, 95% CI: 0.48 to 1.13, P< 0.00001), fire needle therapy (SMD = 0.74, 95% CI: 0.44 to 1.04, P< 0.00001), warming acupuncture (SMD = 2.08, 95% CI: 1.30 to 2.87, P< 0.00001), and electroacupuncture (SMD = 0.98, 95% CI: 0.42 to 1.55, P= 0.0006) had significant advantage in KPS score.

The results of meta-analysis showed a significant increase of FACT-L in the intervention group compared to the control group (SMD = 0.57, 95% CI: 0.06 to 1.08, P = 0.03, I2 = 81%, six studies, 351 patients)(Figure 4B)[12), 16), 19), 21), 25), 27)]. Subgroup analysis showed that acupuncture significantly improved the FACT-L (SMD = 1.95, 95% CI: 1.03 to 2.87, *P* 0.0001), while fire needle therapy (SMD = 0.42, 95% CI: -0.18 to 1.02, *P* 0.17) and electroacupuncture (SMD = 0.31, 95% CI: -0.63 to 1.26, *P*= 0.52) found no significant differences.

EORTC QLQ-C30also showed a total favorable score in the intervention group compared to the control group (SMD = 1.46, 95% CI: 0.05 to 2.86, *P*= 0.04, I2 = 93%, three studies, 160 patients)(Figure 4C)[23), 31), 32)]. Subgroup analysis showed that warming acupuncture (SMD = 3.50, 95% CI: 2.49 to 4.52, *P* 0.00001) and electroacupuncture (SMD = 0.55, 95% CI: 0.19 to 0.92, *P*= 0.003) had significant advantage in EORTC QLQ-C30.

Cancer pain

Cancer pain wasevaluated by NRS. The NRS had a significant improvement in the intervention group compared to the control group (SMD = -0.88, 95% CI: -1.46 to -0.30, *P*= 0.003, I2 = 85%, five studies, 346 patients)(Figure 5) [28)-32)]. Subgroup analysis showed that acupuncture (SMD = -0.45, 95% CI: -0.78 to -0.12, *P*= 0.007) and warming acupuncture (SMD = -1.04, 95% CI: -1.70 to -0.37, *P* 0.002) had advantage in NRS improvement, while electroacupuncture (SMD = -1.24, 95% CI: -2.57 to 0.09, *P*= 0.07) had no significant advantage in NRS improvement.

Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting was recorded in two studies[25), 27)]. Meta-analysis showed that the incidence of chemotherapy-induced nausea and vomiting was significantly lower in fire needle therapy group when compared to the control group (SMD = 0.60, 95% CI: 0.42 to 0.86, *P*= 0.005, I2 = 0%, two studies, 120 patients)(Figure 6).

Discussion

In this study, we reviewed the role of acupuncture therapy in lung cancer treatment.

This meta-analysis showed that acupuncture therapy (including acupuncture, electroacupuncture, warming acupuncture, and fire needle therapy) significantly improved immunologic function, and quality of life for lung cancer patients. Further analysis also showed that acupuncture therapy decreased the chemotherapy-induced nausea and vomiting, and reduced cancer related pain.

Acupuncture is a well-known medical treatment, and the application is extensive and profound. Electroacupuncture, warming acupuncture and fire needle therapy are commonly used in clinical treatment. Electroacupuncture is the application of electrical stimulation to acupuncture needles. Warming acupuncture involves stimulating acupoints by needle penetration followed by burning of a piece of moxa attached to the needle[33]. Fire needle therapy involves heating needles over alcohol lamps until they were red-hot, then quickly inserting the needle into the acupoints and removed as quickly as possible. In recent years, with the deepening of research on the underlying mechanism of the acupuncture efficacy, multiple theories have been proposed to explain the mechanism of acupuncture. By acupuncture application, an increase of immune-regulating neurotransmitters has been observed, such as β -endorphin, met-encephalin, leu-encephalin, serotonin. These effects are generally accepted to be a keystone pathway to the immune system after the acupuncture application[34]. Roger et al.[35] also reported that acupuncture activates the defense systems and increase cellular immune function of patients with malignant tumors. Also, the electroacupuncture at Zusanli (ST36) alleviates postoperative immunosuppression and promote the recovery of immune function in rats[36]. In this study, we evaluated the levels of CD3, CD4, and CD8 T cells in patients with lung cancer to assess immune function. It is encouraging to see that acupuncture treatment significantly increased the levels of CD3 andCD4 in patients compared to the control group, suggesting that acupuncture has a positive effects on immune regulation in lung cancer patients.

Pain is extremely common in cancer patients and may be directly related to the cancer or to certain treatments the patient is undergoing.In our study, acupuncture significantly reduced cancer pain in lung cancer patients, which is in accordance with previous study findings[37]. Previous meta-analysis indicated that acupuncture is effective in relieving cancer-related pain, and can be adopted as part of a multimodal approach for reducing cancer-related pain[38]. Cancer-related pain affects their quality of life. KPS score, FACT-L and EORTC QLQ-C30were used in our study to evaluate the quality of life of lung cancer patients. The analysis showed that acupuncture treatment also has advantages in improvement of quality of life.

The side effects of chemotherapy, such as gastrointestinal reactions, marrow depression, neurotoxicity etc., affect the patient's compliance. Therefore, it is important not only to increase the effectiveness of treatment, but also to reduce side effects. Nausea and vomiting are two of the most common side effects of cancer chemotherapy. Animal studies have provided the evidence that vagal-dependent pathway is a primary mechanism by which most chemotherapeutic agents cause acute emesis[39]. Acupuncture at the Neiguan (P6) point has shown to lessen nausea and vomiting, increase

vagal modulation of the subjects[40]. These studies suggested that acupuncture reduces nausea and vomiting caused by chemotherapy, which is in line with our present findings.

Our systematic review and meta-analysis had several limitations. Firstly, although we conducted a comprehensive search in different languages and databases, all the included studies were conducted in China, so there was still a certain degree of uncertainty regarding the accuracy of the finding results.For this reason, ourresults might not apply to populations in other parts of the world. Secondly, there are variations among the studies in terms of interventions, acupuncture (including warming acupuncture, fire needle therapy, electroacupuncture) and acupoint, which may contribute to heterogeneity among the studies. Thirdly, the risk of bias of the included studies showed that the methodological quality of the included RCTs were generally not high. Sixteen RCTs reported using a "random number tables", while the five RCTs referred only to "randomization" without providing further details. Allocation concealment was reported in only five of the included RCTs and were not reported in the remaining seventeen four RCTs. A number of studies are unclear in blinding of participants and personnel, aswell as outcome assessments. Therefore their outcomes should be interpreted with great caution. Fourthly, only one RCT reported follow-up, while the remaining twenty-one RCTs did not report follow-up. Therefore, methodological flaws which might lead to potential biases. In addition, there are no CONSORT(Consolidated Standards of Reporting Trials) or STRICTA guideline[41] which might affect the reliability of findings.

In conclusion, this systematic review and meta-analysis provides moderate evidence of the efficacy of acupuncture therapy in the treatment of lung cancer. Our results indicated that acupuncture effective for improving immune function and quality of life, reducing cancer pain and chemotherapy induced AEs. However to provide stronger evidence for the use of acupuncture in lung cancer, high-quality rigorous and large-scale RCTs will be needed in the future.

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