

## RESEARCH ARTICLE

# Acupuncture and Moxibustion for Cancer-related Fatigue: a Systematic Review and Meta-analysis

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### Abstract

**Background:** Faced with highly prevalent and recalcitrant cancer-related fatigue (CRF), together with the absence of any official guidelines on management, numerous groups have been striving to seek and test alternative therapies including acupuncture and moxibustion. However, different patients have various feedbacks, and the many clinical trials have given rise to varied conclusions. In terms of the therapeutic effect of acupuncture and moxibustion, there exist vast inconsistencies. **Objective:** The aim of the study was to evaluate the auxiliary effectiveness of acupuncture and moxibustion in the treatment of CRF, and to provide more reliable evidence to guide clinical practice. **Methods:** Randomized controlled trials (RCTs) published before December 2012 were all aggregated, focusing on evaluation of acupuncture or moxibustion for CRF. The quality of the included studies was assessed basing on Cochrane handbook 5.1.0, and the available data were analyzed with RevMan software (version 5.2.0). Descriptive techniques were performed when no available data could be used. **Results:** A total of 7 studies involving 804 participants were eligible. With real acupuncture versus sham acupuncture, subjects receiving true acupuncture benefited more in the reduction of fatigue. With real acupuncture versus acupressure or sham acupressure, fatigue level appeared 36% improved in the acupuncture group, but 19% in the acupressure group and only 0.6% with sham acupressure. When real acupuncture plus enhanced routine care was compared with enhanced routine care, the combination group improved mean scores for general fatigue, together with physical and mental fatigue. With real acupuncture versus sham acupuncture or wait list controls, the real acupuncture group displayed significant advantages over the wait list controls at 2 weeks for fatigue improvement and better well-being effects at 6 weeks. When moxibustion plus routine care was compared with routine care alone, the meta-analyses demonstrated the combination had a relatively significant benefit in improving severe fatigue and QLQ-C30. **Conclusion:** Up to the search date, there exist few high quality RCTs to evaluate the effect of acupuncture and moxibustion, especially moxibustion in English. Yet acupuncture and moxibustion still appeared to be efficacious auxiliary therapeutic methods for CRF, in spite of several inherent defects of the included studies. Much more high-quality studies are urgently needed.

**Keywords:** Acupuncture - moxibustion - cancer - fatigue - systematic review - meta-analysis

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### Introduction

Even though 20% decline of cancer overall death rate compared with their peak in 1991 through a variety of relatively efficacious therapies, one in 4 deaths is due to cancer in the United States according to Siegel et al. (2013). Faced with persistent and heavy disease burden, as well as numerous side effects on account for chemo-radiotherapy etc, an increasing number of patients suffered from cancer has been trying Complementary and Alternative Medicine (CAM), such as acupuncture and moxibustion. CAM appears far more influential and popular than previously considered as an efficacious portion of cancer treatments in recent years, especially for

its unique advantages on managing side effects (Arthur et al., 2012; Huntley Valois et al., 2012; Ip et al., 2012).

Regarded as a highly prevalent and recalcitrant side effects, the National Comprehensive Cancer Network (NCCN) defines Cancer-Related Fatigue (CRF) as “a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Mock et al., 2000). It is acknowledged that, CRF has significantly led to the Quality Of Life (QOL) deterioration rapidly in patients with cancer or even who were disease free, together with willpower to conquer cancer devil and interpersonal relationships (including family and

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society) (Scott et al., 2011). Fortunately, with the notable improvement of biological–psychological–social medical model, extension of the overall survival time and much more confirmed pursuit towards higher QOL, CRF has aroused stronger concern among medical personnel, patients and corresponding relatives. Regretfully, faced with the absence of any official guidelines on how to manage CRF, it is essential to explore alternative therapies for CRF (Mitchell, 2010; Berger et al., 2012; Saibul et al., 2012).

As an indispensable portion of CAM in handling side effects, the acupuncture and moxibustion treatments which developed over hundreds and thousands of years of clinical experience plus exploration in China, has been receiving acknowledgements worldwide step by step in the treatment of CRF, taking the advantages of simplicity, convenient, efficacy, inexpensiveness, and lack of side effects (Wu, 2012; Lehmann, 2013). Patients suffered from cancer also often display great interests in them when conventional treatments are insufficient. Acupuncture refers to penetrating filiform needle into the skin at precise locations (acupuncture points) or other specific areas, then using twiddle and lifting technique to treat diseases; Acupressure is known as the non-invasive form of acupuncture. Moxibustion is stimulating skin thermally by the burning moxa, also at precise locations (moxibustion points) or other specific areas (Liu, 2009; Zhang and Wu, 2010; Jia et al., 2011). The possible rationale of acupuncture and moxibustion may be open the channels and network vessels, assist right qi, expel evil qi, regulate the body's physiological functions, thus achieving the goals of treating disease and cultivating health (Cheng, 2008).

To date, although several published reviews and clinical trials focusing on acupuncture and moxibustion for CRF were available, we urgently require highly persuasive evidence. Hence, we aim to performed comprehensive searches to identify all relevant RCTs to assess the effectiveness of acupuncture and moxibustion in treatment with CRF. And this study was critically based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) items (Moher, 2010).

## Materials and Methods

### *Protocol and registration*

No protocol has been registered in public, but considered draft with respect to the study already exists.

### *Search Strategy for identification of relevant studies*

Extensive electronic databases searches were carried out from their inception to December 2012 to identify all published and unpublished RCTs as possible as we could, comparing effects of acupuncture or moxibustion as complementary alternative therapy (arm A) with placebo or routine care only (arm B) for cancer-related fatigue. All languages were considered. The electronic databases, such as PubMed, EMBASE, the Cochrane Library, ISI Web of Knowledge, Chinese Biomedical Literature Database (CBM), Chinese Journal Full-text Database (CJFD), Chinese Scientific Journal Full-text Database (CSJD)

and Wanfang Data, were searched by two reviewers independently. Using searching terms which included “acupuncture”, “moxibustion”, “acupressure”, “cancer”, “carcinoma”, “neoplasm”, “fatigue”, which were all performed by the combination of medical subject headings (Mesh) terms (<http://scientific.thomson.com/support/fag/wok3new/medline/#Mesh>) and free terms. In addition, the published reference lists of these articles were also checked for further eligible publications.

### *Included studies*

**Types of studies:** We took into account the trials whose topics were the evaluation of acupuncture (or moxibustion) in treatment with CRF. We included RCTs only with no limitations in the follow-up duration and languages.

**Types of participants:** The study included participants complaining cancer-related fatigue (fatigue prior to cancer diagnosis), without the restriction of tumor types, gender, ethnicity or nationality. The inclusion criteria in details are as follows: (1) The objects included were all adult human beings (age>18 years) suffering from cancer; (2) Subjects without a history of known bleeding disorder, anticoagulant therapy, severe anemia, anticipated survival less than 6 months or so, or other diseases that would decrease the chances of obtaining reliable data to some extent (pacemaker for example); (3) Not scheduled to receive cancer mainstay treatment (such as chemotherapy, radiotherapy ect) during the study.

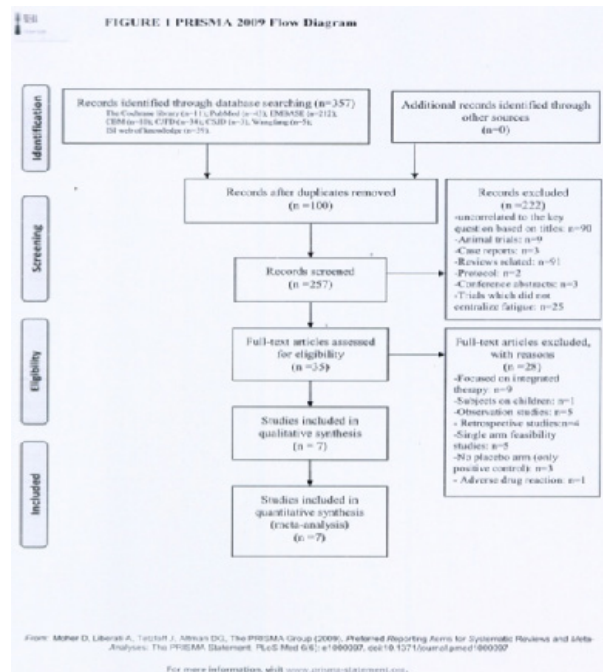
**Types of interventions:** The experiment group received targeted treatments (real acupuncture or moxibustion), which were all described according to the STRICTA recommendations (MacPherson et al., 2002) for reporting acupuncture trials, were also based on the Traditional Chinese Medicine style. Furthermore, the standardized acupuncture point location had been used in previous research suggesting a therapeutic effect, as well as consistent acknowledgements received by acupuncture experts. All acupuncturists had received formal education on acupuncture or moxibustion, with relatively abundant clinical experience. The control group received routine care or sham treatments. The true and sham needles (brand, diameter, length etc), along with other equipments used in trials were identical among groups.

**Document screening and Data extraction:** The results, combined with all titles, abstracts, or the full text when necessary, were screened independently by two authors, and the corresponding predefined methods had been described in detail above. When faced with disagreement, independent inspection by a third author was needed. Data extraction was carried out independently by the same reviewers using standard data extraction forms, including publication year, country, trials design, sample size, disease type, mean age, brand of needles, size of needles, location of points, treatment course and various outcomes (FACIT-F, SF-36, CRFDS, CESD, MFI, HADS, FACT-B, BFI, W-BQ12, MYCaW, QLQ-C30, PFS, KPS, immune function).

**Quality evaluation:** The study quality was conformed to the Cochrane Handbook for Systematic Reviews of interventions, which had obtained consistent

**Table 1. Detailed Interpretation on Points of Location**

Points of location	Detailed interpretation
SP6	Sanyinjiao, on the tibial aspect of the crus, 3 cun superior to the prominence of the medial malleolus, posterior to the medial border of the tibia.
LI4	Hegu, on the dorsum of the hand, between the first and the second metacarpal bones, on the radial side of the midpoint of the second metacarpal bone.
ST36	Zusanli, on the anterior aspect of crus, 3 cun inferior to Dubi, one fingerbreadth (middle finger) lateral to the anterior border of tibia.
Ren6/CV6	Qihai, on the lower abdomen, on the anterior midline, 1.5 cun inferior to the center of the umbilicus.
KI3	Taixi, on the medial aspect of the foot, at the posterior aspect of the medial malleolus, in the depression between the prominence of the medial malleolus and the calcaneal tendon.
LI12	Erjian, with a loose fist, in the distal depression of the radial side of the second metacarpophalangeal joint of the index finger.
GB33	Xiyangguan, on the lateral aspect of the knee, 3 cun superior to Yanglingquan, in the depression proximal to the lateral epicondyle of the femur.
BL62	Shenmai, on the lateral aspect of the foot, directly in the depression inferior to the lateral malleolus.
GB34	Yanglingquan, on the lateral aspect of the crus, in the depression anterior and distal to the head of the fibula.
SP9	Yinlingquan, on the tibial aspect of the crus, in the posteroinferior depression of the bulge of the medial end of quadriceps femoris.
KI27	Shufu, in the anterior thoracic region, just inferior to the clavicle, 2 cun lateral to the anterior midline
CV4	Guanyuan, on the lower abdomen, on the anterior midline, 3 cun inferior to the centre of the umbilicus.

**Figure 1. PRISMA 2009 Flow Diagram**

acknowledgement worldwide. The quality items assessed were as follows: Item 1: Random sequence generation (selection bias); Item 2: Allocation concealment (selection bias); Item 3: Blinding of participants and personnel (performance bias); Item 4: Blinding of outcome assessment (detection bias); Item 5: Incomplete outcome data (attrition bias); Item 6: Selective reporting (reporting bias); Item 7: Other bias. For individual studies each criterion was assigned a label of 'yes', 'unclear' or 'no' to estimate risk of bias, and each one was signed three quality grades including A (low risk of bias), B (moderate risk of bias) and C (high risk of bias), which depended on the possibility of bias from low to high. Two of us tested every criterion step by step, and checked outcomes together. In case of disagreement, discussions were carried out with a third one.

**Meta-analyses and descriptive techniques:** Meta analyses were performed by the Review Manager (version 5.2.0) software. The odds ratio (OR) was calculated along with its 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) was calculated for continuous outcomes. Statistical heterogeneity between studies was assessed by means of chi square and the extent of inconsistency was assessed by the  $I^2$  statistic. When  $I^2 < 40\%$ , heterogeneity was considered as questionably

important; 30%-60% was thought to possibly represent moderate heterogeneity; 50%-90% was regarded as possible substantial heterogeneity; and higher than 75% was deemed a considerable level. If there were no heterogeneity in treatment effect between studies, the fixed effects model was appropriate; otherwise the random-effect model would be more conservative. Descriptive techniques were used when clinical heterogeneity existed and also when no data could be used in Meta analyses. The stability of outcome was tested by sensitivity analysis when necessary.

## Results

### Literature search

357 studies were identified initially. Endnote X5 Software was used and 100 duplicates were removed. And 61 studies were excluded based on titles and 167 articles were included to receive evaluation in depth with abstracts or full texts. Through sifting layer upon layer strictly, 7 studies (Molassiotis et al., 2007; Balk et al., 2009; Chen et al., 2011; Molassiotis et al., 2012; Qin et al., 2012; Smith et al., 2012; Yang et al., 2012) were included ultimately. Figure 1 shows PRISMA statement of search flows in details.

### Description of Studies

**Participants:** 7 prospective randomized controlled trials involving 804 patients met the specified inclusion criteria, originated from America (Balk et al., 2009), Britain (Molassiotis et al., 2007; Molassiotis et al., 2012), Australia (Smith et al., 2012), and China. The participants included all suffered from cancer (in five trials, mean age was 55 or so; in two trials, mean age was 70 or so; but the gender not clear); 2 studies only concentrated on breast cancer, yet the specific subtypes varied widely in other studies.

**Acupuncture and moxibustion interventions and controls (study design):** Four trials (Molassiotis et al., 2007; Balk et al., 2009; Molassiotis et al., 2012; Smith et al., 2012) which based on the standards for Reporting Intervention in clinical trials of acupuncture recommendations, focused on the therapeutic effect of acupuncture for cancer-related fatigue in English language, while the other three (Chen et al., 2011; Qin et al., 2012; Yang et al., 2012) with a view on moxibustion in Chinese language. Of the seven studies included, 5 studies (Balk et al., 2009; Chen et al., 2011; Molassiotis



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Balk 2009	+	+	+	+	+	?	?
Chen 2011	+	?	?	?	+	?	?
Molassiotis 2007	+	+	+	+	+	?	?
Molassiotis 2012	+	+	?	+	+	?	?
Qin 2012	+	?	-	+	+	?	?
Smith 2012	+	+	+	+	+	?	?
Yang 2012	?	?	?	?	+	?	?

**Figure 2. Methodological Quality Assessments - Risk of bias Summary** (each risk of bias item for each included study)

et al., 2012; Qin et al., 2012; Yang et al., 2012) were two arm paralleled and the specific subtypes of control group varied widely in 2 studies (Molassiotis et al., 2007; Smith et al., 2012) (real acupuncture VS sham acupuncture in Balk et al., 2009; acupuncture plus enhanced routine care VS enhanced routine care in Molassiotis et al., 2012; moxibustion plus routine care VS routine care, 2 studies were three arm paralleled and the control group also varied widely (real acupuncture VS acupressure VS sham acupressure in Molassiotis et al., 2007; real acupuncture VS sham acupuncture VS wait list controls in Smith et al., 2012). Sham acupuncture, replicates acupuncture procedure except for telescoping blunt-edged needle or plus sham points. Acupressure refers to non-invasive form of acupuncture, yet sham acupressure group was taught to apply pressure in points that are not associated with “energy” in tradition Chinese Medicine. 4 reports (Molassiotis et al., 2007; Balk et al., 2009; Molassiotis et al., 2012; Smith et al., 2012) covered the relatively absolute and identical information on brands and size of needles except for three Chinese ones. In spite of not completely consistency, locations of points (Table 1) were partially coincided, or similar (close to corresponding points).

**Duration of treatment and informed consents:** With respect to treatment course, all of the studies gave detailed data, indicating relatively consistency. All these studies had been approved by the Institutional Review Board and written informed consents were obtained in all cases.

*Methodological Quality of Studies*

All of them are randomized controlled trials, six (Molassiotis et al., 2007; Balk et al., 2009; Chen et al., 2011; Molassiotis et al., 2012; Qin et al., 2012; Smith et

al., 2012) of them claimed the methods of randomization clearly, namely computer program (such as computer-generated randomization table etc), while one (Yang et al., 2012) could not legibly described how the random allocation sequences were generated. Allocated concealment was reported in 4 trials (Molassiotis et al., 2007; Balk et al., 2009; Molassiotis et al., 2012; Smith et al., 2012) (such as using opaque envelopes), the other three (Chen et al., 2011; Qin et al., 2012; Yang et al., 2012) had no specific statement. Blinding of participants and personnel was performed in 3 (Molassiotis et al., 2007; Balk et al., 2009; Smith et al., 2012) trials , not in 1 (Qin et al., 2012) trial, and unclear in three (Chen et al., 2011; Molassiotis et al., 2012; Yang et al., 2012) trials. In terms of blinding of outcome assessment, 5 (Molassiotis et al., 2007; Balk et al., 2009; Molassiotis et al., 2012; Qin et al., 2012; Smith et al., 2012) studies carried out it, yet 2 (Chen et al., 2011; Yang et al., 2012) unclear. All these trials had no incomplete outcome data. Moreover, whether others bias existed were also unclear. The qualities of these included trials were relatively high. The methodological quality of these included trials is shown comprehensively in Figure 2.

*Efficacy and safety of acupuncture and moxibustion for CRF*

**Real acupuncture versus sham acupuncture (placebo):** One RCT (Balk et al., 2009) compared the efficacy of real acupuncture with those of receiving sham acupuncture (placebo), and showed goodish effects of acupuncture on CRF. Sham one in the trial referred to the same acupuncture points as the true acupuncture protocol, using the telescoping blunt-edged needle.

Primary outcome variable FACIT-F for fatigue measurement showed that those randomized to true acupuncture had more severe fatigue, but differences were not statistically significant (*P* value not mentioned). On account of the baseline difference that true acupuncture groups suffered from severe fatigue, the changes from baseline were calculated. True acupuncture improved more than sham, but differences were not significant (treatment *P*=0.457; time (3, 6, 10 weeks) *P*=0.106).

CRF distress (mean CRFDS), both physical (mean SF-36 physical component summary) and mental (mean SF-36 mental component summary) quality of life scores improved but were not statistically significant between groups or within groups, whose *P* values display like “not mentioned, treatment *P*=0.972 and time (6, 10 weeks) *P*=0.370, treatment *P*=0.197 and time (6, 10 weeks) *P*=0.454”. Depression scores (mean CESD) improved and were significant within groups but not between groups (treatment *P*=0.294; time (10 weeks) *P*<0.009). ACIT-F and CESD scores were correlated at both baseline (*r*=-0.485, *p*=0.01) and 6 weeks (*r*=-0.623, *p*=0.003). According to sample size analyses for future studies, 75 participants per group would be essential to possess adequate power.

**Real acupuncture versus acupressure or sham acupressure:** The study (Molassiotis et al., 2007) by Molassiotis et al reported the comparison of real acupuncture versus acupressure or sham acupressure,

**Table 2. The Meta-analysis on the Improvement of FPS after Treatment**

Outcome	Number of included studies	Total sample		Heterogeneity		Analysis model	Effect Estimate	
		Arm A	Arm B	P	I <sup>2</sup>		OR(95%CI)	P
FPS (mild or none)	2	96	102	0.08	67%	Random	2.96 (1.00, 8.73)	0.05
FPS (moderate)	2	96	102	0.001	90%	Random	0.90 (0.12, 6.75)	0.92
FPS (severe)	2	96	102	0.92	0%	Fixed	0.16 (0.07, 0.37)	<0.0001

**Table 3. The Meta-analysis on the Improvement of QLQ-C30 after Treatment**

Outcome	Number of included studies	Total sample		Heterogeneity		Analysis model	Effect Estimate	
		Arm A	Arm B	P	I <sup>2</sup>		OR(95%CI)	P
Sloe function	2	138	140	0.52	0%	Fixed	0.06 (-0.18, 0.29)	0.62
Emotional function	2	138	140	0.73	0%	Fixed	0.97 (0.72, 1.22)	<0.00001
Cognitive function	2	138	140	0.01	83%	Random	0.28 (-0.38, 0.93)	0.04
Social function	2	138	140	0.003	89%	Random	0.13 (-0.66, 0.92)	0.74
Global health status	2	138	140	0.03	80%	Random	0.81 (0.20, 1.43)	0.01
Fatigue	1	102	98	-----	-----	Fixed/ Random	-1.01 (-1.31, -0.72)	<0.00001

via MFI scale which provided information in five areas (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue). Real acupuncture equals as strong stimulation at acupoints, acupressure refers to mild stimulation at acupoints, and sham acupressure namely mild stimulation which not located at acupoints. Fatigue score significantly improved in the acupuncture and acupressure groups, with respect to four of the five MFI subscales, namely General fatigue ( $P<0.001$ ), Physical fatigue ( $P=0.016$ ), Activity ( $P=0.004$ ), and Motivation ( $P=0.024$ ); Mental fatigue displayed  $P=0.99$ . As the largest improvement, general fatigue appeared highest in the acupuncture group immediately post-treatment sessions (36%), followed by acupressure (19%), while the sham acupressure group did not improve at all. By means of regression analyses (ANCOVA), acupuncture and acupressure significantly improved General fatigue at the end of treatment, compared to sham acupressure ( $F=5.69$ ; d.f.=1,33;  $P=0.023$ ). Acupuncture indicated more significant effectiveness than acupressure or sham acupressure ( $F=7.37$ ; d.f.=1,33;  $P=0.01$ ).

Real acupuncture plus enhanced routine care versus enhanced routine care: Molassiotis et al published another relevant article (Molassiotis et al., 2012), to compare the therapeutic effect of real acupuncture plus enhanced routine care versus enhanced routine care alone. Enhanced routine care means providing all patients with a detailed information booklet on dealing with CRF.

Mean General Fatigue score at 6 weeks (measured by MFI) was primary outcome, the difference between the combination group and enhanced routine care group was -3.11 (95%CI: -3.97, -2.25,  $P<0.001$ ). The intervention also improved all other fatigue aspects measured by MFI, including Physical and Mental Fatigue (acupuncture effect, -2.36 and -1.94, respectively; both at  $P<0.001$ ), anxiety and depression (acupuncture effect, -1.83 and -2.13, respectively; both at  $P<0.001$ ), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at  $P<0.001$ ; Emotional Well-Being effect, 1.93; at  $P=0.001$ ; and Social Functioning Well-Being effect, 1.05;  $P<0.05$ ).

Real acupuncture versus sham acupuncture or wait list controls: Smith et al conducted a randomized controlled

trial (Smith et al., 2012), comparing acupuncture with a sham and a wait list control. Through sample size evaluation, 30 patients would be sufficient enough to provide valuable data. Fatigue was evaluated by BFI, including 9 items measuring the severity of fatigue on a scale between 0-10. Wellbeing was assessed using the W-BQ12 and MYCaW. Clinical outcomes were assessed at baseline 2, 4 and 6 weeks.

According to BFI, fatigue declined over time for all three groups. Reduction of fatigue was significant for women receiving acupuncture, compared with control after 2 weeks. Significance existed all the time for acupuncture compared with the wait list control. At 4 and 6 weeks there was a non-significant trend in reduced fatigue for the acupuncture and sham acupuncture groups. W-BQ12 scores also improved over time for all three groups, but no significant differences were found between groups. MYCaW had no significant changes at 2 and 4 weeks; but a significant change at 6 weeks with the overall score significantly improved for acupuncture compared with the other groups. Concerning the feedbacks from participants, remarkable improvements were reported in sleep, mood and relaxation.

#### *Therapeutic effect of moxibustion for CRF*

The result of FPS after treatment: Two RCTs (Qin et al., 2012; Yang et al., 2012) concentrated on the FPS, the corresponding results are as follows. The forest plots are shown in Table 2.

FPS (mild or none) after treatment: FPS (mild or none) means mild or none fatigue, score 0-3 points. Compared with routine care only, moxibustion plus routine care had no significant benefit in improving FPS (mild or none).  $I^2>50%$ , random model was adopted (OR=2.96, 95%CI: 1.00, 8.73,  $P=0.05$ ).

FPS (moderate) after treatment: FPS (moderate) means moderate fatigue, score 4-6 points. Compared with routine care only, the combination also had no significant benefit in improving FPS (moderate).  $I^2>50%$ , random model was adopted (OR=0.90, 95%CI: 0.12, 6.75,  $P=0.92$ ).

FPS (severe) after treatment: FPS (severe) means severe fatigue, score  $\geq 7$  points. Compared with routine care only, moxibustion plus routine care had relatively

significant benefit in improving FPS (severe).  $I^2 < 50\%$ , fixed model was adopted (OR=0.16, 95%CI: 0.07, 0.37,  $P < 0.0001$ ).

**The result of QLQ-C30 after treatment:** Two RCTs (Chen et al., 2011; Qin et al., 2012) referred to QLQ-C30 after treatment, meta analysis results showed that: compared with routine care alone, moxibustion plus routine care could improve emotional function (SMD=0.97, 95%CI: 0.72, 1.22,  $P < 0.00001$ ), global health status (SMD=0.81, 95%CI: 0.20, 1.43,  $P = 0.010$ ), and fatigue (SMD=-1.01, 95%CI: -1.31, -0.72,  $P < 0.00001$ ). The details show in Table 3.

#### *Descriptions on the improvement of KPS and immune function*

One RCT (Yang et al., 2012) focused on KPS and immune function. Moxibustion plus routine care could improve KPS, compared with routine care alone ( $P < 0.05$ ); In terms of immune function, the combination could promote it in some extent ( $P < 0.05$ ).

#### *Adverse effects*

**Acupuncture:** Balk et al (Balk et al., 2009) claimed no subjects experienced adverse events. Molassiotis et al (Molassiotis et al., 2007) (published in 2007) reported spot bleeding in 2/90 cases, bruise in one point in 1/90 patients, 1 patient feeling nauseous after the end of treatment, no severe ones were seen. Molassiotis et al (Molassiotis et al., 2012) (published in 2012) stated that therapists completed a form verifying adverse effects after each session, but no corresponding descriptions afterwards. Smith et al. (2012) did refer to adverse effects from cover to cover, but listing subjective feelings from patients (no one involved adverse effects).

**Moxibustion:** all the three studies (Chen et al., 2011; Qin et al., 2012; Yang et al., 2012) included in the systematic review did not attempt to mention or evaluate the adverse effects of moxibustion.

Nevertheless, on account of the small samples included in the review and certain missing data, we have no means to claim the safety of acupuncture and moxibustion. But they can be regarded as relatively safe therapies in some extent when performed properly.

## **Discussion**

Encountered with the highly prevalent and recalcitrant CRF, as well as absence of any official guidelines on how to manage it, numerous groups are always striving to seek and test alternative therapies (Weis, 2011). The acupuncture and moxibustion treatments have been applying to alleviate CRF in China since thousands of years ago (Lyons et al., 2012). Nowadays, when routine and classical therapies failed to treat CRF, or cannot tolerate them, more and more patients worldwide are willing to attempt acupuncture and moxibustion (Hou and Li, 2009; Arthur et al., 2012). However, different patients have various feedbacks; different clinical trials appeared various conclusions (Wen et al., 2009). Faced with the inconsistency above, to put forward more sufficient

evidence towards the therapeutic effect of acupuncture and moxibustion, and then guide clinical practice, we conducted this systematic review and meta-analyses, which is the first to our knowledge.

By means of relatively comprehensive search strategy, perhaps the most significant finding of the systematic review is that there exist few but rigorous RCTs aiming to test the effectiveness of acupuncture and moxibustion for CRF. No trials focused on moxibustion for CRF in English, the only three were all from China. Compared with acupuncture, moxibustion received fewer attentions worldwide, along with lower quality resulted from several risk of biases described above.

When real acupuncture versus sham acupuncture in Balk 2009 (Balk et al., 2009), goodish effects that subjects receiving true acupuncture may benefit more than those receiving sham one appeared (the reduction of fatigue and improvement of quality of life). Thus, we speculate that invasive form (real acupuncture) may be superior to non-invasive form (sham acupuncture). The process of penetrating into skin might play an irreplaceable role. When real acupuncture versus acupressure or sham acupressure in Molassiotis 2007 (Molassiotis et al., 2007), fatigue level appeared 36% improvement in the acupuncture group, while 19% in the acupressure group and 0.6% in the sham acupressure. Thus, we can also suppose that both the stimulus intensity and acupoints all influence therapeutic effect in some extent. When real acupuncture plus enhanced routine care versus enhanced routine care in Molassiotis 2012 (Molassiotis et al., 2012), the combination group improved mean General Fatigue score, as well as Physical and Mental Fatigue, anxiety and depression, and quality of life (Physical Well-Being effect, Functional Well-Being effect, Emotional Well-Being effect, Social Functioning Well-Being effect). Thus, we can conclude that real acupuncture may improve not only CRF, but also quality of life. With respect to the trial published in 2012 by Smith et al (Smith et al., 2012), the real acupuncture group displayed significant advantages over the wait list controls at 2 weeks in terms of fatigue improvement. And better well-being (MYCaW) effect appeared at 6 weeks for acupuncture compared with the sham and wait list control, not at 2 or 4 weeks. Meanwhile, numerous favorable feedbacks from participants arose. When moxibustion plus routine care versus routine care alone in Chen 2011 (Chen et al., 2011), Qin 2012 (Qin et al., 2012) and Yang 2012 (Yang et al., 2012), our meta-analyses demonstrated that: the combination had relatively significant benefit in improving severe fatigue, rather than mild or moderate fatigue. With respect to QLQ-C30, the combination appeared effective in promoting emotional function, global health status and fatigue,

Even though our systematic review has provided certain positive conclusions to suggest clinical practice, there still exist several limitations which may weaken the strength of recommendations. (1) The total numbers of RCTs and participants involved were too small to draw concrete conclusions on the therapeutic effect of acupuncture and moxibustion. (2) Four trials (Molassiotis et al., 2007; Balk et al., 2009; Molassiotis et al., 2012; Smith et al., 2012) concentrated on acupuncture possessed



relatively high quality, yet three studies (Chen et al., 2011; Qin et al., 2012; Yang et al., 2012) concerning moxibustion were noted not a few drawbacks, namely, the missing information of adverse effects and low methodological quality described above. Nevertheless, it cannot be avoided owing to the restriction of inherent literatures resource. (3) Most of the outcomes were subjective symptoms scales (except immune function measured by reagents and machines), which may be hard to control accurately on account of subjective feeling form participants. So it was important to use blinding towards the participants who received interventions. If blinding failed to work or work insufficiently, it would result in high implementation bias and measurement bias. (4) The specific and convictive mechanisms of acupuncture and moxibustion are still being elucidated. According to the theory based on Chinese traditional medicine, acupuncture and moxibustion are able to assist right qi, expel evil qi, and regulate the body's physiological functions (Shi, 2011; Wang et al., 2011). (5) Meta-analyses may be inappropriate for several important outcomes, on account of the obvious clinical heterogeneity and considerable variation among studies. Thus, descriptive analyses have to be conducted. (6) We made meta-analyses on FPS and QLQ-C30 to evaluate the therapeutic effect of moxibustion, the related literatures were all from China, together with moderate heterogeneity. For instance, the mean age, different types of cancer (reflecting different therapy protocols the patients had received), location of points and treatment source were not consistent among these studies. (7) In spite of relatively comprehensive search strategy, incomplete retrieval of identified research cannot be avoided, together with publication bias. In summary, the results of this systematic review may be exaggerated.

In conclusion, the notion that acupuncture and moxibustion appeared to be an efficacious auxiliary therapeutic method for CRF, is supported by the convictive but small amounts of data currently available, in spite of several inherent defects which included studies had but cannot avoid. Even so, no conclusion can be drawn about their advantage over other classical also conventional therapies treatment methods. When patients with terminal cancer are not able to tolerate conventional therapies, or loss confidence towards them, acupuncture and moxibustion could be a relatively ideal choice. Due to the considerable clinical heterogeneity and various outcome measures which cannot be merged by traditional statistical methods, we have on means to put forward further suggestions to guide clinical practice at present. Much more high-quality studies with adequate design and power are in need urgently, and on account of methodological limitation, much more systematic investigations in depth are also necessary to confirm the therapeutic value of acupuncture and moxibustion for CRF profoundly.

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