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A Systematic Review and Meta-Analysis of Randomized Controlled Trials on Acupuncture for Improving Post-Operative Cognitive Dysfunction (POCD) and Chemotherapy-Related Cognitive Impairment (CRCI)

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Objectives: This study was conducted to evaluate the efficacy of Korean Medicine Therapy (KMT) for the treatment of Chemotherapy-induced Cognitive Impairment (CICI) through systematic review and meta-analysis of randomized controlled trials (RCTs) as proceeding research to further research the efficacy of KMT for CICI patients.

Methods: We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA). The RCTs on the efficacy of KMT for treatment of CICI were searched by structured search strategies in MEDLINE, EMBASE, Cochrane library, CAJD, KISS, NDSL, KoreaMed, and OASIS. The searched RCTs were screened by inclusion and exclusion criteria. We evaluated the quality of the method in the included studies using the Jadad score and Cochran ROB tool. The efficacy outcomes were the Visual Analogue Scale (VAS) and the Clinical total Effective Rate (CER) of CICI. They were analyzed using mean difference for continuous variable or Relative Risk (RR) for Dichotomous variable in the random-effect model. The RevMan 5.3 program was used for meta-analysis.

Results: We included 19 RCTs, including 653 participants, in the systematic review and meta-analysis. There were favorable results for the KMT group after the intervention compared with the pharmacotherapy group, physiotherapy group, and combined treatment group. KMT group showed improvement using CER and VAS compared with exercises, but their heterogeneities were slightly significant. KMT was more effective compared to the Rehabilitation program in CER and the subgroup analysis results showed that KMT had a significant difference compared to other therapies in VAS, to Medication therapy in CER.

Conclusions: KMT presented reasonable evidence on improving the Clinical total Effective Rate and Visual Analogue Scale in CICI patients. However, further evaluation in future research is required.

Key Words: Chemotherapy induced cognitive impairment, Koeran medicine therapy, Randomized clinical trials, Systematic review, Meta-analysis.

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I. INTRODUCTION

Cancer survival rates have improved over the past decades, mainly due to two key factors. Earlier cancer detection and improvement of effective treatments[1]. Thus, most patients survive for decades under treatments, and a growing number of people are now beginning to complain about many aftereffects. One of the long-term or late effects of these cancer treatments is cognitive impairment[2,3]. Cancer-related cognitive dysfunction referred to impaired cognitive function in cancer diagnosis and treatment and was added in the National Comprehensive Cancer Network (NCCN) guideline as a treatment target in 2014[4].

Post-operative cognitive dysfunction (POCD) is a mild neurocognitive and reversible dysfunction. It occurs after major surgeries such as cancer removal surgery in some patients. After surgery, cancer patients complain about cognitive impairment and mental retardation, which are concerned with social communication, cognitive function, and orientation under the influence of anesthesia. These problems are manifested explicitly as anxiety, personality change, memory loss, abnormal cognitive ability, and disorders of mental system[5]. Evidence-based medicine studies have shown that general anesthesia can lead to morphologic and biological changes of neurons, thus causing apoptosis and cell loss. Elderly patients are especially vulnerable to the effects of general anesthesia, and the incidence of POCD is higher among them[6]. This condition also leads to persistent cognitive declining, so it is recognized as a significant problem for cancer surgery patients.

The problem of cognitive impairment that can occur in cancer patients is a chemotherapy-related cognitive impairment (CRCI), in addition to POCD. Early diagnosis and better treatments have increased cancer survivors, but their treatment-related cognitive impairment patients are also increasing. For example, up to seven out of ten cancer survivors experience changes in memory ability, learning new things, concentrating, planning, and making decisions about their everyday life, as a result of cancer treatment[7]. These symptoms are referred to as 'chemo-fog' or 'chemobrain' changes induced by non-localized, systemic long-term cancer treatment, such as chemotherapy[8].

This study included POCD and CRCI in cognitive impairment problems that may occur in cancer patients.

The study into the workings of acupuncture treatment is in progress, and many have been focused on neurology[9]. For instance, neuroimaging reports that acupuncture therapy increases hippocampal connectivity in Alzheimer's patients activates certain cognitive-related areas, and adjusts default network activity patterns[10]. In cognitively-impaired rat models, stimulating HT7 (神門) with laser acupuncture inhibited acetylcholinesterase expression in the hippocampus[11]. Naturally, attempts have been made to attempt acupuncture treatment for cognitive impairment in cancer patients.

Acupuncture therapy comprises various methods such as body acupuncture, electroacupuncture, transcutaneous acupoint electric stimulation, auricular acupuncture, etc. These methods are useful in caring for cognitive dysfunction[12]. Like as for preconditioning electroacupuncture at GV20 (百會) and GV14 (大椎) acupuncture points, it was reported that the stimulation alleviates cerebral ischemia-reperfusion injury-induced cognitive impairment in the elderly[13].

Thus, this study evaluates the effectiveness of acupuncture treatment on cognitive impairment in cancer patients who receive surgery or chemotherapy through scores evaluated using Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and incidence of symptoms concerned with subjective cognitive dysfunction.

II. METHODS

1. Data sources and searches

We conducted a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14].

The following databases were searched from their inception through October 15, 2020. The literature search was performed on October 1, 2020 by two investigators, who are Korean medicine doctors. Results published in English, Chinese, and Korean were considered. Data were recorded and assessed using Microsoft Excel 2014.

The gray literature was excluded. We also performed a manual search to find the ongoing clinical studies. The reference lists of included studies were screened to confirm that there are no missing relevant studies.

1) Identifying studies

International Electrical database (English)
- MEDLINE
- EMBASE
- Cochrane Library

Chinese database (Chinese)
- CAJD (China Academic Journal network publishing Database)

Domestic databases (Korean)
- KISS (Korean-studies Information Service System)
- NDSL (national discovery for science leaders)
- OASIS (Oriental Medicine Advanced Searching Integrated System)

2) Key words (Appendix 1)

2. Study selection

The study selection was performed independently by two reviewers and disagreements were resolved by discussion and adjudication. Duplication of studies was excluded using EXCEL database by comparing title, abstract, and author key words published. The CAJ Database did not allow logical searches with 'AND', so we used simple combinations of the search words. We selected acupuncture therapy as an intervention, but acupuncture therapy methods (such as traditional acupuncture, electroacupuncture, pharmacopuncture, auricular acupuncture) were not limited. Studies only with acupuncture therapy intervention were selected and acupuncture therapy combined with other treatments were excluded. Inappropriate articles were excluded by reviewing the title and abstract. Only papers that possess an abstract written in English were selected.

1) Types of studies

Studies mentioning randomized controlled trials (RCTs) of acupuncture therapy for improving cognitive impairment of cancer patient were considered and quasi-random method was allowed. Studies that did not mention RCTs or quasi-random methods at least, case series, observational, cohort, case control, qualitative studies, uncontrolled trials and laboratory studies were excluded.

2) Types of participants

The patients selected were diagnosed with various types of cancer clinically. Studies involving pediatric participants (<19 year) or participants who did not receive cancer therapy or who did not experience cognitive decline were excluded. No restrictions to gender and race were imposed.

3) Types of intervention

The intervention was only acupuncture therapy and methods of acupuncture therapy were included such as traditional acupuncture (TA), electroacupuncture (EA), pharmacopuncture (PA), auricular acu-

puncture (AA), transcutaneous acupoint electric stimulation (TAES) through experts advices whether it is applicable to the act of acupuncture therapy. Other forms of treatments (irrelevant to acupuncture therapy such as exercise, herbs, cupping, moxibustion etc.) were excluded. Studies that assessed the combined treatment with cancer operation or chemotherapy were not excluded due to the negative effect it might cause to the cancer patient's survival.

4) Types of control

We excluded studies that include controls that correspond to acupuncture therapy such as Cupping (control), Moxibustion (control), Mindfulness (control), MBSR (control), Herb(s) (control), Chuna (control), Tuina (control) and Meditation (control) including acupuncture therapy. Usual care or sham acupuncture, minimal acupuncture stimulation, electrical stimulation were included allowedly.

5) Types of outcome measures

The outcome measure was set to severity of cognitive function and clinical total incidence at the end of each session in treatment or evaluation phase reflected in the clinical trial protocol.

Primary outcomes including Cognitive function were measured by MMSE and MoCA calculated by the changes in Cognitive symptoms. And the incidence of cognitive decline symptoms after acupuncture treatment was Included in the evaluation instrument.

3. Data extraction

Data extraction was performed independently by two investigators and discrepancies were resolved through discussion. Data from the articles were validated and extracted using a predefined data extraction form. Study characteristics were study design, sample size, age, treatment duration, intervention, control, adverse event and outcome.

4. Risk of bias assessment

To assess the methodological quality of RCTs included, we used the Risk of Bias tool provided by the Cochrane Collaboration[15]. Because baseline imbalance in factors that are strongly related to outcome measures may cause other potential biases in the estimation of intervention effects in RCTs.

5. Data synthesis

The quantitative data of primary and secondary outcomes were combined and meta-analysis was performed according to effects of acupuncture therapy, using RevMan software version 5.4 (Cochrane, London, UK).

6. Identifying heterogeneity

A random-effect model was considered a possible analytical approach for clinical heterogeneity in the included studies using the chi-square test, the tau^2 test, and the Higgins I^2 statistics[16].

III. RESULTS

1. Study selection

Total 535 studies were screened, and full texts of 30 articles were reviewed (Fig. 1). Preferentially 178 duplicated studies were excluded. Ineligible studies after screening titles and/or abstracts were excluded (n=329). Of the 30 articles reviewed in full text, 2 studies were excluded which the original text was not available. Ineligible studies after screening full text were excluded (n=16). 1 study was not a clinical study (n=1). 7 studies were RCTs but not relevant to target disease (n=7). None RCTs studies (n=5), and Improper intervention (not related with acupuncture therapy) studies (n=3) were excluded in final. Under review, we checked that the data of 2 studies was duplicated. So, one of the 2 studies was excluded. Finally 11 studies

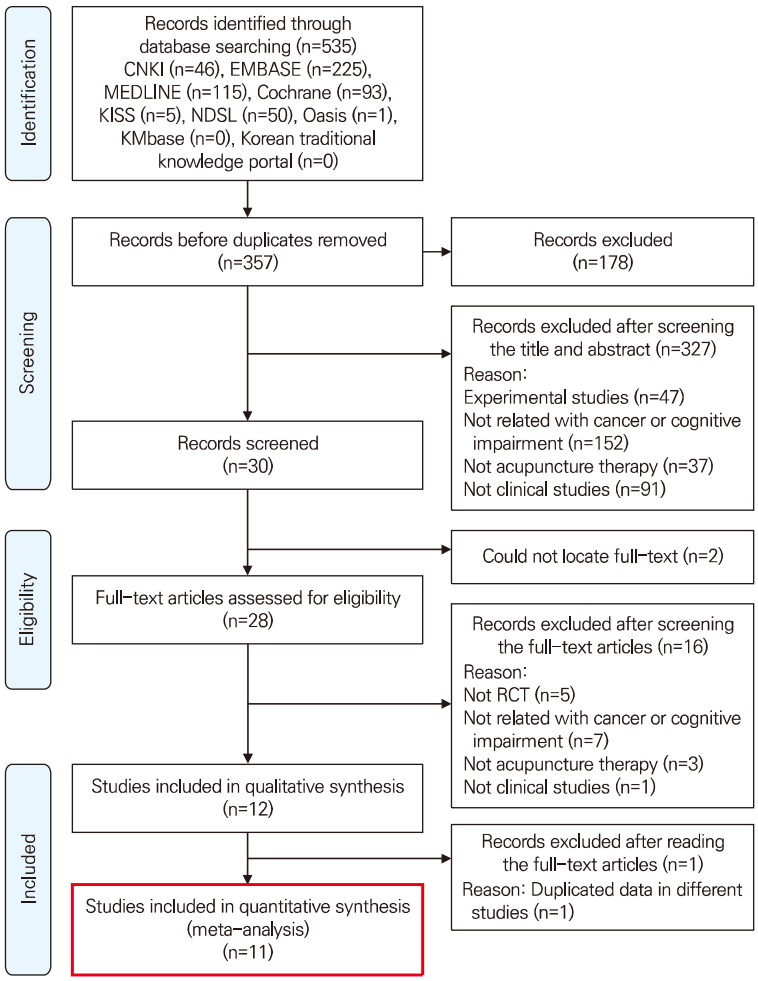


Fig. 1. PRISMA flowchart of study selection.

were identified for inclusion in meta-analysis (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Tong 2018), (Wang 2018), (Li 2018), (Zhang 2018), (Han 2018), (Zhang 2020)[17-27].

2. Study description

1) Characteristics of included studies

11 RCTs with 921 participants were included for the Systemic Reviews. They were all diagnosed with various cancers and participated in the studies. The average age of the control group was 60.98, and that of the KMT group was 62.19. Mean duration was 1 day to 8 weeks in range, and mean number of treatment was 1 to 40 times but it was difficult to define the characteristics of participants because some studies had lack of accuracy in description.

All the trials used acupuncture therapy. 10 trials were two-armed parallel group design (Lin 2013), (Ni 2015), (Li 2016), (Liu 2017), (Ton 2018), (Wang 2018), (Li 2018), (Zhang 2018), (Han 2018), (Zhang 2020), and 1 trials were 5-armed group design (Lin 2013*). 8 studies were designed as EA (electroacupuncture) versus usual care (Lin 2013), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Li 2018), (Han 2018), 1 trial designed as traditional acupuncture versus no treatment (Tong 2018), 1 trial designed as traditional acupuncture versus sham acupuncture (Zhang 2018) and

1 study designed as AT (electroacupuncture) versus MAS (Minimal Acupuncture Stimulation) (Zhang 2020).

Acupuncture therapy treatment duration time of 8 studies was 1 day (Lin 2013), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Li 2018), (Han 2018). and 8 weeks for 3 studies (Tong 2018), (Zhang 2018), (Zhang 2020).

2) Outcome measures

All studies were included for systematic review and analyzed for meta-analysis. 9 studies used Mini-Mental State Examination (MMSE) and 7 studies used incidence for measurement. Two of the studies using MMSE also measured Montreal Cognitive Assessment (MoCA). So MMSE, Incidence rate and MoCA were selected as a main outcome measurement. Summaries of RCTs included are presented in Table 1~3.

Only 1 study out of all RCTs was designed as a 5-arm study that was composed of comparison groups

Table 1. General Characteristics of included RCTs of AT for Cognitive Impairment in Cancer Patient

1st author (year) country	Study Design	Conditon	No. of participants (resgistered)	No. of participants (analysed)	Participants' age (Mean±SD)
Lin (2013) China	prospective, single-blind, randomized controlled 2-arm clinical study	Patients who have had surgery to remove a gastrointestinal tumor	75 (37/38)	75 (37/38)	(A) UC: 68.0±3.0 (B) EA: 69.0±4.0
Lin (2013)* China	prospective, single-blind, randomized controlled 5-arm clinical study	Patients who have had surgery to remove a gastrointestinal tumor	124 (24/26/25/24/25)	124 (24/26/25/24/25)	(A) UC: 67.3±2.7 (B) EA 2Hz: 68.8±2.8 (C) EA 2Hz/100Hz: 68.6±3.2 (D) EA 100Hz: 67.5±3.1 (E) TAES 2Hz/100Hz: 68.5±2.8
Ni (2015) China	prospective, single-blind, randomized controlled 2-arm clinical study	Patients who have had surgery to remove a colorectal neoplasms	60 (30/30)	60 (30/30)	(A) UC: 69.2±5.0 (B) TAES: 68.7±5.3
Li (2016) China	prospective, single-blind, randomized controlled 2-arm clinical study	Patients who have had surgery to remove thoracoscopic lung cancer	60 (30/30)	60 (30/30)	(A) UC: 66.5±3.95 (B) TAES: 65.7±6.12
Liu (2017) China	prospective, single-blind, randomized controlled 2-arm clinical study	Patients who have had surgery to remove neoplasms	98 (49/49)	98 (49/49)	(A) UC: 74.26±10.38 (B) TAES: 73.61±11.18
Tong (2018) China	prospective, single-blind, controlled 2-arm clinical study	Patients were diagnosed with early breast cancer (stage 0–II) and received chemotherapy.	80 (40/40)	75 (36/39)	(A) No treatment: 42.26±4.42 (B) TA: 43.11±4.23
Wang (2018) China	prospective, single-blind, randomized controlled 2-arm clinical study	Elderly patients that received general anesthesia for subtotal gastrectomy in gastric cancer	96 (48/48)	96 (48/48)	(A) UC 68.36±5.43 (B) EA 68.74±5.57
Li (2018) China	prospective, single-blind, controlled 2-arm clinical study	Patients that received elective general anesthesia thoracoscopic radical resection of lung cancer	70 (35/35)	67 (32/35)	(A) UC: 62.7±8.84 (B) TAES: 61.4±9.36
Zhang (2018) China	prospective, single-blind, randomized controlled 2-arm clinical study	Breast cancer patients who had evidence of cognitive impairment except dementia within 6 months after chemotherapy	100 (50/50)	93 (45/48)	(A) SA: 39.60±9.45 (B) TA: 41.50±9.12
Han (2018) China	prospective, single-blind, randomized controlled 2-arm clinical study	Elderly patients undergoing bowel cancer resection	90 (45/45)	90 (45/45)	(A) UC: 67.93±2.60 (B) EA: 68.52±2.44
Zhang (2020) China	prospective, an assessor-participant blinded, randomized controlled 2-arm clinical study	Breast cancer patients who had evidence of cognitive impairment within 2 weeks after the completion of chemotherapy	93 (47/46)	83 (43/40)	(A) MAS: 47.9±10.6 (B) EA/TNS+BA: 47.9±9.7

TA: traditional acupuncture, SA: Sham acupuncture, UC: usual care, EA: Electoacupuncture, TNS: Trigeminal Nerve Stimulation, MAS: Minimal Acupuncture Stimulation, TAES: Transcutaneous Acupoint Electric Stimulation, BA: body acupuncture.

Table 2. Intervention Characteristics of included RCTs of AT for Cognitive Impairment in Cancer Patient

First author (year)	intervention	comparison	No. of treatment/duration	follow up
Lin (2013)	(B) EA: 4 Hz/20 Hz, 5～7.5 mA, 20 min *Standardized point (GV20,PC6,ST36,SP6)	(A) UC: No TAES treatment	1 time/1 day	3 days
Lin (2013)*	4 intervention groups (B) EA2 Hz, 5～7.5 mA,30 min (C) EA2 Hz/100 Hz, 5～7.5 mA,30 min (D) EA100 Hz, 5～7,5 mA,30 min (E) TAES2 Hz/100 Hz, 5～7.5 mA,30 min *Standardized point (GV20,PC6,EX-HN3)	(A) UC: No TAES treatment	1 time/1 day	3 days
Ni (2015)	(B) TAES 2 Hz/100 Hz, 8～12 mA, 30 min *Standardized point (PC6,ST36,SP6)	(A) UC: No TAES treatment	1 time/1 day	1,3,5,7 days
Li (2016)	(B) TAES 2 Hz/100 Hz, 8～12 mA, 30 min *Standardized point (PC6,ST36)	(A) UC: No TAES treatment	1 time/1 day	1,3 days
Liu (2017)	(B) TAES 2 Hz/100 Hz, 5 mA, 30 min *Standardized point (GV20,PC6,ST36)	(A) UC: No TAES treatment	1 time/1 day	1,3 days
Tong (2018)	(B) TA: De-qi, 30 min *standardize dpoints (GV20,EX-HN1,KI3) and additional points (GV24,KI4,GB39,ST36)	(A) No treatment: No acupuncture needling	40 tims/8 weeks	2 months
Wang (2018)	(B) EA: De-qi, 80～90 Hz, 15～20 min *standardized points (ST36, PC6, LI4, ST37)	(A) UC: No EA treatment	1 time/1 day	1 day
Li (2018)	(B) TAES 2 Hz/100 Hz, 8～12 mA, 30 min *Standardized point (PC6,ST36)	(A) UC: No TAES treatment	1 time/1 day	1,3days
Zhang (2018)	(B) TA: De-qi, 30 min *Standardized point (GV20, EX-HN1, GV24, PC6, HT7, GB20, CV17, CV12, CV6)	(A) SA: Needled shallowly on non acupuncture points, away from TA points	16 times/8 week	48,16,24 weeks
Han (2018)	(B) EA: De-qi, 20 min, 4 Hz/20 Hz, 5～7.5 mA *Standardized point (GV20, PC6, ST36, SP6)	(A) UC: No EA treatment	1 time/1 day	6,12,24,36,72 hrs
Zhang (2020)	(B) EA/TNS+BA: De-qi, 2 Hz/100 Hz, 6 V, 48 mA, 30 min *Standardizedpoint (HT7, LI4, TE5, ST8, ST36, ST40, SP6, CV4, CV12, GV20, GV26, EX-HN1, EX-HN3, EX-HN5, GB6, GB15)	(A) MAS *Standardized point (BL7, BL17, BL59, LI10)	16 times/8 week	2,4,6,8 weeks

TA: traditional acupuncture, SA: Sham acupuncture, UC: usual care, EA: Electoacupuncture, TAES: Transcutaneous Acupoint Electric Stimulation, TNS: Trigeminal Nerve Stimulation, BA: body acupuncture, MAS: Minimal Acupuncture Stimulation.

of UC, EA (2 Hz frequency), EA (2/100 Hz frequency), EA (100 Hz frequency) and TAES (2/100 Hz frequency). There was a significant effect on relieving cognitive impairment on participants measured with MMSE, MoCA and Incidence. But according to Lin* (2013) and Tong (2018), Scores of MMSE had not improved compared with UC group. Also in Zhang (2020), There was no improved Incidence compared with the control (MAS) group.

8 studies compared acupuncture therapy with usual care. In Lin (2013), Lin* (2013), Ni (2015), Li (2016), Liu (2017), Wang (2018), Li (2018) and Han (2018), there were significant differences of score change on MMSE from baseline to each session in treatment or evaluation phase reflected in the clinical trial protocol ($p<0.05$ or $p<0.01$). Also there was certain effect on the Incidence rate of cognitive impairment in Lin (2013), Lin* (2013), Ni (2015), Li (2016), Liu (2017), Li (2018) and Han (2018). In two previously mentioned studies which used both MMSE and MOCA to analyze, there also was a significant difference in MoCA scores.

3 studies were designed for acupuncture therapy in chemotherapy related cognitive impairment of cancer patients. In Zhang (2018), traditional acupuncture therapy and Sham acupuncture (Needling shallowly on non acupuncture points, away from TA points) was compared. In this study, there was a substantial difference in MMSE and MoCA. In Zhang (2020), Trigeminal nerve stimulation and Body acupuncture were compared with minimal acupuncture stimulation, but

Table 3. Main Outcomes and Result of Intergroup Difference in RCTs

First author (year)	Intervention/ comparison	main outcomes	Intergroup difference	Adverse event (No. of participants)
Lin (2013)	UC/EA	(1) MMSE (2) Incidence	(1) EA > UC, ($p < 0.05$)* (2) EA > UC, ($p < 0.05$)*	n.r
Lin (2013)*	UC/EA1/EA2/ EA3/TAES	(1) MMSE (2) Incidence	(1) EA2 or TAES > EA1 or EA3, ($p < 0.05$)* (2) EA1 > UC, ($p < 0.05$)* EA2 > UC, ($p < 0.05$)* EA3 > UC, ($p < 0.05$)* TAES > UC, ($p < 0.05$)*	n.r
Ni (2015)	UC/TAES	(1) MMSE (2) Incidence	(1) Day 1,3,5 TAES > UC, ($p < 0.05$)* Day 7 TAES = UC, ($p > 0.05$) (2) Day 1,3 TAES > UC, ($p < 0.05$)* Day 5,7 TAES = UC, ($p > 0.05$)	n.r
Li (2016)	UC/TAES	(1) MMSE (2) Incidence	(1) Day 1 TAES > UC, ($p < 0.05$)* Day 3 TAES > UC, ($p < 0.05$)* (2) Day 3 TAES > UC, ($p < 0.05$)*	n.r
Liu (2017)	UC/TAES	(1) MMSE (2) Incidence	(1) Day 1 TAES > UC, ($p < 0.05$)* Day 3 TAES > UC, ($p < 0.05$)* (2) Day 1 TAES > UC, ($p < 0.05$)* Day 3 TAES > UC, ($p < 0.05$)*	n.r
Tong (2018)	No treatment/ TA	(1) MMSE, (2) FACT-COG, (3) PCI, (4) QOL, (5) OTH, (6) PCA, (7) AVLT1, (8) AVLT2, (9) AVLT3, (10) VFT, (11) SDMT, (12) CDT, (13) TMT-B	(1) TA = UC, ($p > 0.05$) (2) TA > UC, ($p < 0.05$)* (3) TA > UC, ($p < 0.05$)* (4) TA = UC, ($p > 0.05$) (5) TA = UC, ($p > 0.05$) (6) TA > UC, ($p < 0.05$)* (7) TA = UC, ($p > 0.05$) (8) TA = UC, ($p > 0.05$) (9) TA > UC, ($p < 0.05$)* (10) TA = UC, ($p > 0.05$) (11) TA = UC, ($p > 0.05$) (12) TA > UC, ($p < 0.05$)* (13) TA = UC, ($p > 0.05$)	n.r
Wang (2018)	UC/EA	(1) MoCA (2) MMSE	(1) EA > UC, ($p < 0.05$)* (2) EA > UC, ($p < 0.05$)*	n.r
Li (2018)	UC/TAES	(1) MMSE (2) Incidence	(1) Day 1 TAES > UC, ($p < 0.05$)* Day 3 TAES = UC, ($p > 0.05$) (2) (B) > (A), ($p < 0.05$)*	n.r
Zhang (2018)	SA/TA	(1) MMSE (2) MoCA	(1) 8 w: (B) > (A), ($p < 0.01$)* 16 w: (B) > (A), ($p < 0.05$)* 24 w: (B) > (A), ($p < 0.05$)* (2) 8 w: (B) > (A), ($p < 0.05$)* 16 w: (B) > (A), ($p < 0.01$)*	n.r
Han (2018)	UC/EA	(1) MMSE (2) Incidence	(1) 12 h,24 h,36 h EA > UC, ($p < 0.01$)* 6 h,72 h EA = UC, ($p > 0.05$) (2) EA > EA, ($p < 0.05$)*	n.r
Zhang (2020)	EA(TNS + BA)/ MAS	(1) MoCA (2) Forward digits pan test (3) Reverse digits pan test (4) Incidence	(1) No data of estimating (2) No data of estimating (3) No data of estimating (4) (B) = (A), ($p > 0.05$)	n.r

UC: usual care, SA: Sham acupuncture, EA: Electoacupuncture, TAES: Transcutaneous Acupoint Electric Stimulation, TA: traditional acupuncture, MMSE: Mini-Mental State Examination, FACT-COG: Functional Assessment of Cancer Treatment Cognition, PCI: Perceived Cognitive Impairments, QOL: quality of life, OTH: comments from others, PCA: perceived cognitive abilities, AVLT: the Auditory-Verbal Learning Test, VFT: the Verbal Fluency Test, SDMT: the Symbol Digit Modality Test, CDT: the Clock-Drawing Test, TMT-B: the Trail-Making Test part B, n.r: no reported.

almost all the data were unavailable for usage due to absence of raw data and only the transformed value was provided, making it unlikely to analyze. However, we were able to confirm the incidence rate and the data was used in this study. Similarly, from Tong (2018), only the MMSE data was used in our study.

All 11 studies were included for SR and meta-analysis. Summary of RCTs included are presented in Table 1, 2.

3. Risk of bias assessment

For evaluation of the methodological quality, modified Jadad score and Cochrane Collaboration's tool were used to assess risk of bias (ROB)[12,13]. Studies of 11 RCTs generated randomized sequence (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Zhang 2018), (Han 2018), (Zhang 2020) but the other 2 studies had not mentioned at all (Tong 2018), (Li 2018). All studies did not mentioned or showed no allocation concealment. Also only three studies mentioned blinding of outcome assessment (Tong 2018), (Zhang 2018), (Zhang 2020) and the other studies did not mentioned blinding of personnel (Lin 2013), (Lin 2013*) (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Han 2018), (Li 2018). 8 studies had no drop-out (Lin 2013), (Ni 2015), (Li 2016), (Liu 2017), (Tong 2018), (Wang 2018), (Han 2018), (Zhang 2020), and 1 study described the reasons for the drop-out (Zhang 2018). Other 1 study was reported as per-protocol (Li 2018), while the other 1 study was reported as per-protocol but incomplete (Lin 2013*). All RCTs were unclear in Selective reporting, and had no other bias (Fig. 2).

In accordance to the Jadad scoring system, 9 studies were randomized in various ways but 2 studies had no report (Tong 2018), (Li 2018). 8 trials used random number table (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Zhang 2018), (Han 2018), and 1 study used a computer-generated random block (Zhang 2020). 9 studies randomized as appropriate methods, but there were no mention of the randomized allocation sequence (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Zhang 2018), (Han 2018), (Zhang 2020).

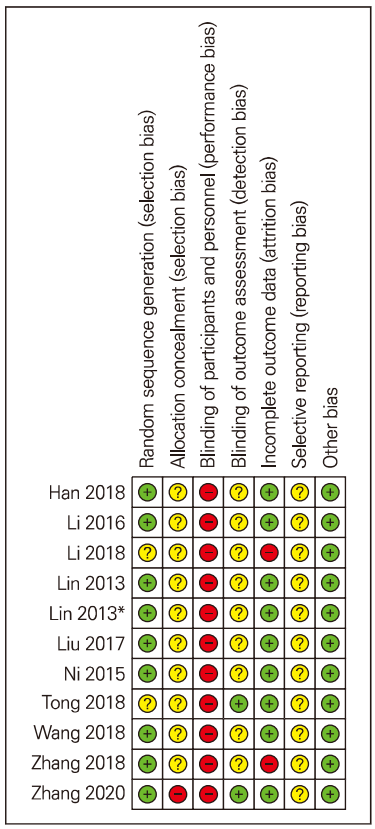


Fig. 2. Risk of bias summary
+: Low risk of bias, -: High risk of bias, ?: Unclear.

Due to the study protocol and patient's characteristics, 11 studies were not double-blinded. Beside 2 studies (Tong 2018), (Zhang 2020), 9 studies (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Li 2018), (Zhang 2018), (Han 2018) did not perform an evaluator blinding. Finally, 8 studies scored more than 3 positive points (Lin 2013), (Lin 2013*), (Ni 2015), (Li 2016), (Liu 2017), (Wang 2018), (Han 2018), (Zhang 2020).

4. Outcome results

1) AT versus UC for cognitive impairment after cancer surgery in MMSE

The data of 8 studies which compared AT with UC were synthesized in MMSE variations (Fig. 3). MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. In this study, MMSE was scored based on complaining symptoms in cognitive impairment of the cancer patients.

Total 684 participants were included, 325 were assigned to Acupuncture Therapy group whereas 295 were Usual Care group. The data analysis was using mean difference in random effect model. The results presented that AT was effective compared to UC (MD, 1.37; 95% CI, 0.97 to 11.78; $p<0.000001$). But, the heterogeneity was significant ($\chi^2=217.53$, $I^2=92\%$).

In 1 study included, they administered MMSE after 6, 12, 24, 36, 72 hours, in 6 studies after 1 day, in 7 studies checked after 3 days, and in another 1 study checked after 5 days or 7 days. So subgroup analysis was performed by the result in the subgroup using MMSE with intervention evaluated by the follow up time.

The intervention group which assessed changed results 6 hours after acupuncture treatment (Changes in 6 hrs group) was no effective (MD, -0.09; 95% CI, -0.46 to 0.28; p=0.64). Also Changes in 3 days group (MD, 1.08; 95% CI, -0.02 to 2.17; p=0.05) and 7 days group (MD, 0.30; 95% CI, -0.33 to 0.93; p=0.35) resulted no effective. On the other hand, Changes in 12 hrs group (MD, 1.22; 95% CI, 1.01 to 1.43; $p<0.00001$), Changes in 1 day group (MD, 2.07; 95% CI, 1.45 to 2.70; $p<0.00001$), Changes in 36 hrs group (MD, 1.50; 95% CI, 1.25 to 1.75; $p<0.00001$) and Changes in 5 days group (MD, 1.80; 95% CI, 1.12 to 2.48; $p<0.00001$) resulted effective. But, the heterogeneity of all subgroups were significant (Fig. 3).

2) AT versus UC for cognitive impairment after cancer surgery in incidence

The data of 7 studies which compared AT with UC were synthesized in Incidence variations (Fig. 4). In this study, incidence is a measure of the frequency of cognitive dysfunction after acupuncture treatment. Incidence was scored based on complaining symptoms in cognitive impairment of the cancer patients.

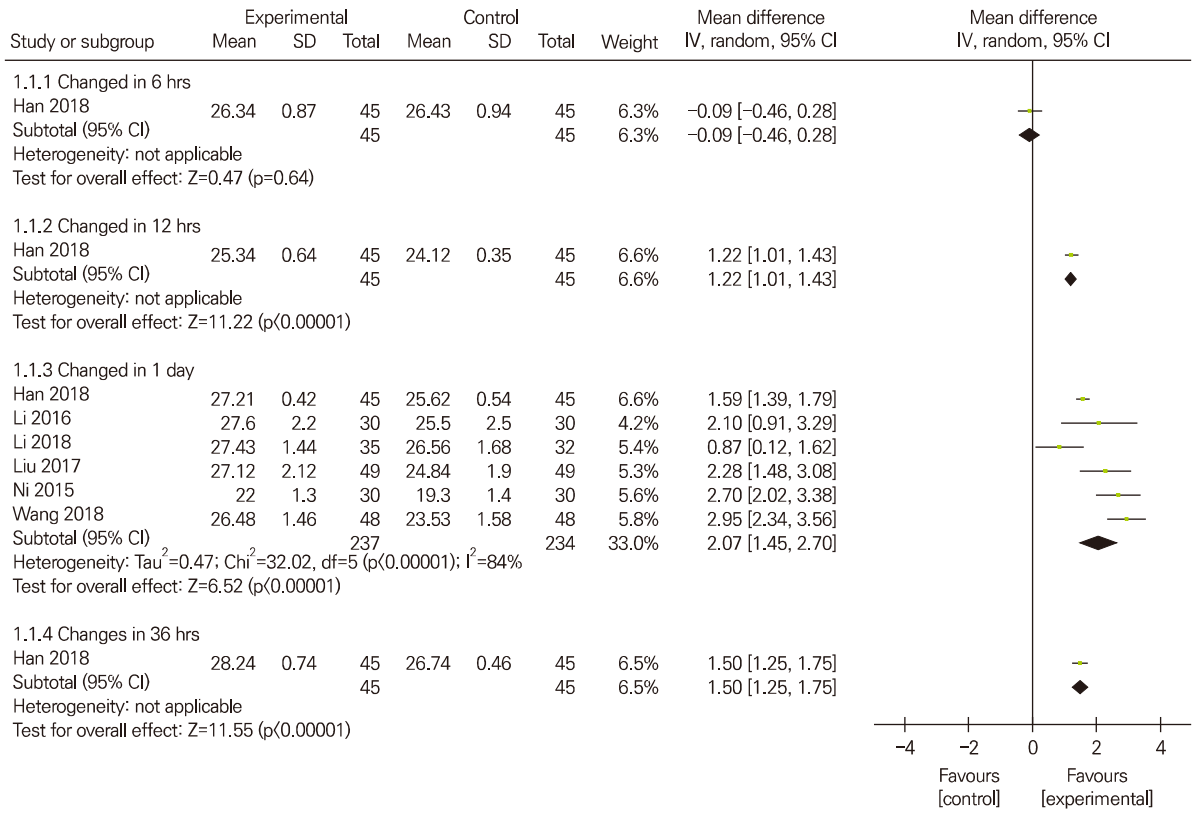
Total 574 participants were included, 251 were assigned to Acupuncture Therapy group whereas 248 were Usual Care group. The data analysis was using Risk Ratio in random effect model. The results were that AT was effective compared to UC (RR, 0.51; 95% CI, 0.39 to 0.66; $p<0.000001$). Also, the heterogeneity was not significant ($\chi^2=2.56$, $I^2=0\%$).

In 1 study, they checked Incidence after 1, 3, 5, 7 days, in another study after 1, 3 days, in 2 studies checked Incidence after 1 or 3 days respectively, and 4 studies after 3 days. So subgroup analysis was performed by the result in the subgroup using Incidence rate with intervention evaluated by the follow up time.

The intervention group which assessed changed results 1 day after acupuncture treatment (Changes in 1 day group) was effective (RR, 0.49; 95% CI, 0.32 to 0.74; p=0.0008) and heterogeneity was not significant ($\chi^2=0.12$, $I^2=0\%$). Also Changes in 3 days group was effective (RR, 0.49; 95% CI, 0.33 to 0.72; p=0.0002) and heterogeneity was not significant ($\chi^2=2.04$, $I^2=0\%$). But Changes in 5 days group (RR, 0.60; 95% CI, 0.25 to 1.44; p=0.25) and Changes in 7 days group (RR, 0.67; 95% CI, 0.21 to 2.13; p=0.49) were not effective.

3) AT versus UC for cognitive impairment after cancer surgery in MoCA

The data of only 1 study which compared AT with



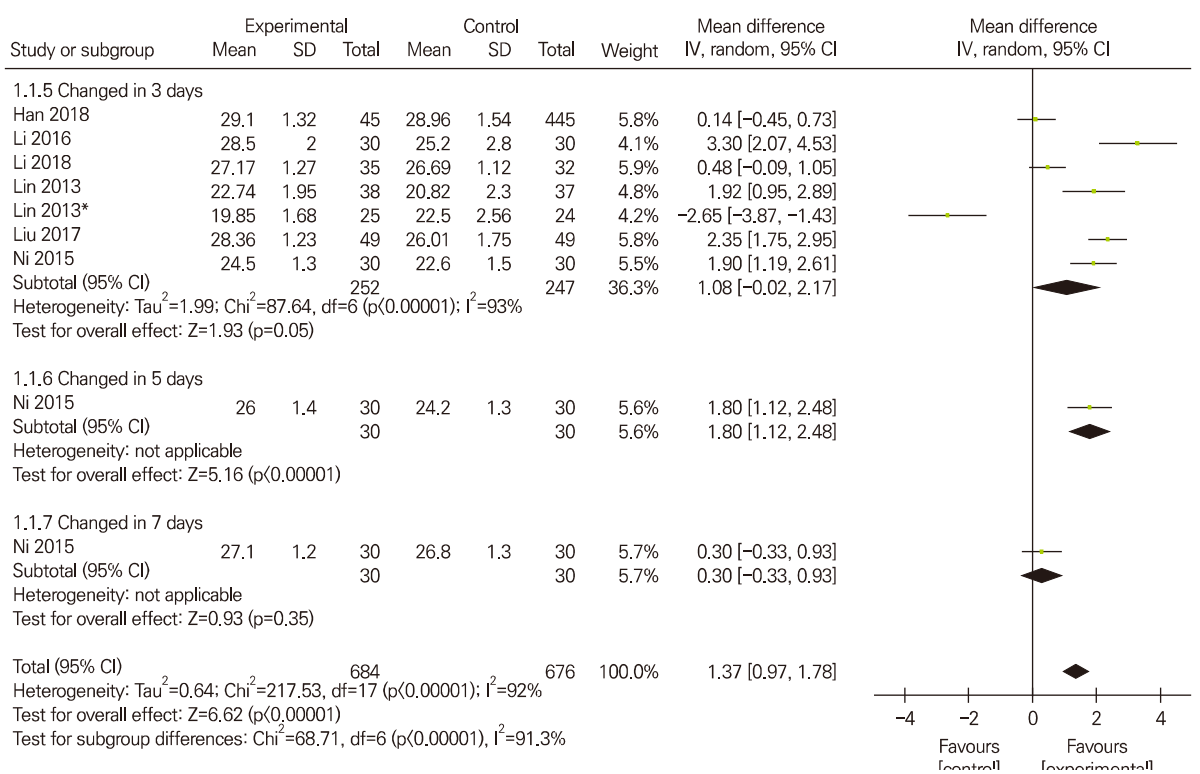


Fig. 3. The forest plot of MMSE : AT versus UC for cognitive impairment after cancer surgery.

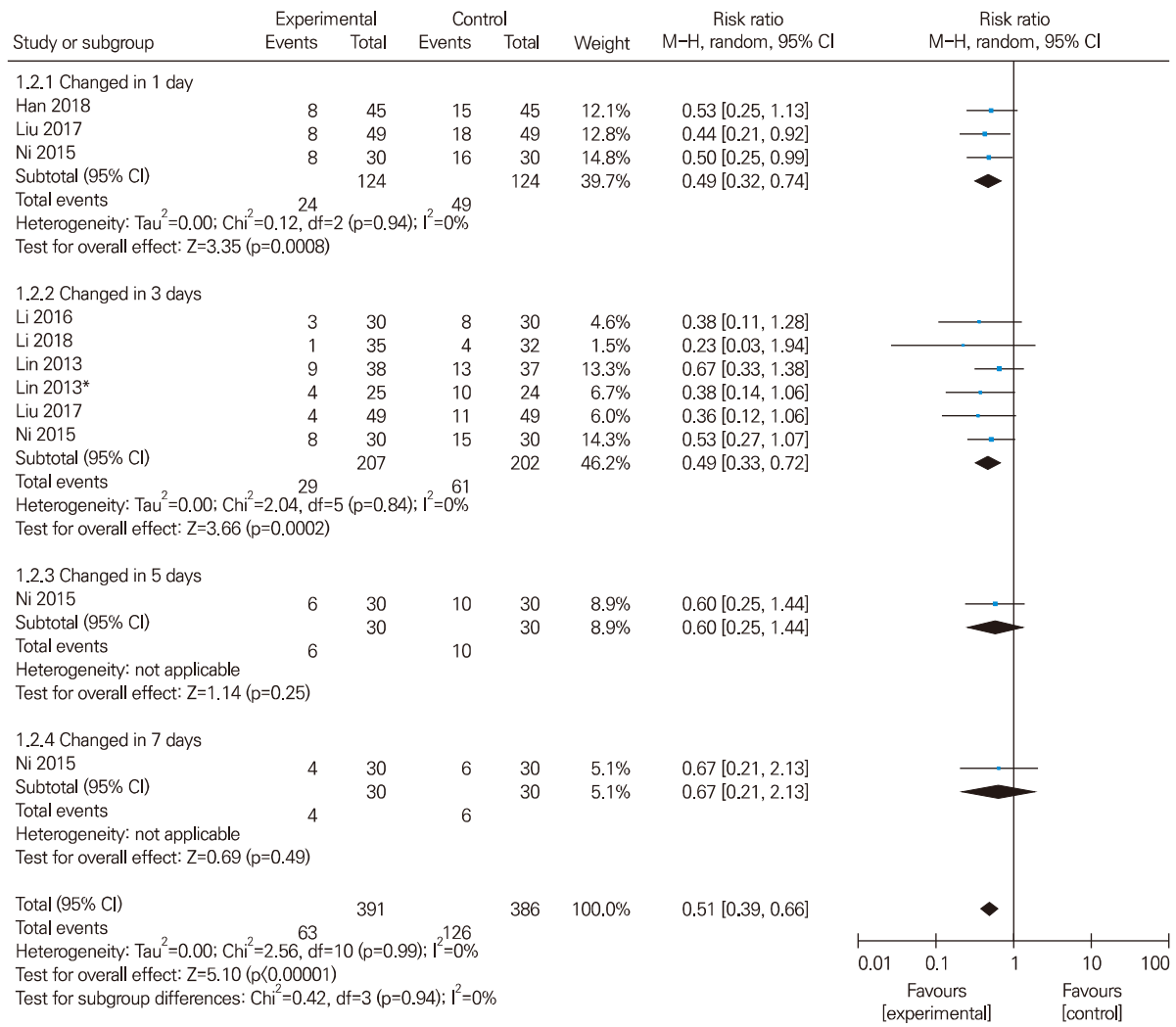


Fig. 4. The forest plot of Incidence : AT versus UC for cognitive impairment after cancer surgery.

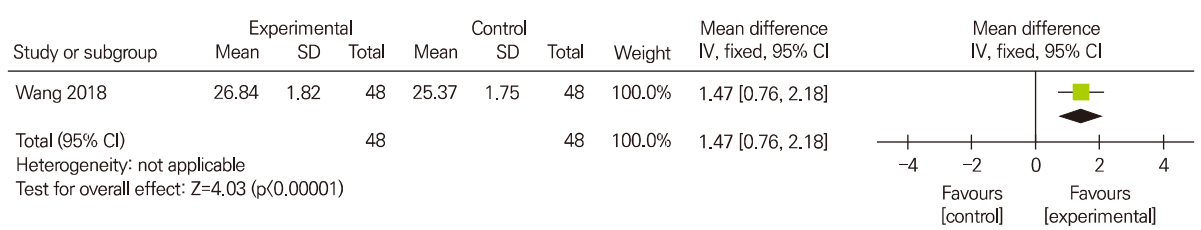


Fig. 5. The forest plot of MoCA : AT versus UC for cognitive impairment after cancer surgery.

UC were synthesized in MoCA (Fig. 5). The MoCA Test was validated in the setting of mild cognitive impairment (MCI), and has been subsequently adopted in numerous clinical settings. In this study, MoCA was scored based on complaining symptoms in cognitive impairment of the cancer patients.

96 participants were included, 48 were assigned to Acupuncture Therapy group whereas 48 were Usual

Care group. The data analysis was using mean difference in fixed effect model. The results were that AT was effective compared to UC (MD, 1.47; 95% CI, 0.76 to 2.18; p<0.000001). The heterogeneity was no applicable.

4) EA versus UC for cognitive impairment after cancer surgery in MMSE

The data of 2 studies which compared EA with UC were synthesized in MMSE variation (Fig. 6). Total 186 participants were included, 93 were assigned to EA group whereas 93 were UC group. The data analysis was using mean difference in fixed effect model. The results were that EA was effective compared to UC (MD, 1.27; 95% CI, 1.16 to 1.39; p<0.000001). But, the heterogeneity was significant (χ^2=148.72, I^2=95%).

In 1 study, they checked MMSE after 6, 12, 24, 36, 72 hours, and in another study after 1 day. So Subgroup analysis was performed by the result in the subgroup using MMSE with intervention evaluated by the follow up times.

The intervention group which assessed changed results 6 hours after EA (Changes in 6 hrs group) was not effective (MD, -0.09; 95% CI, -0.46 to 0.28; p=0.64). Also Changes in 3 days group was not effective too (MD, 0.15; 95% CI, -0.32 to 0.61; p=0.54). On the

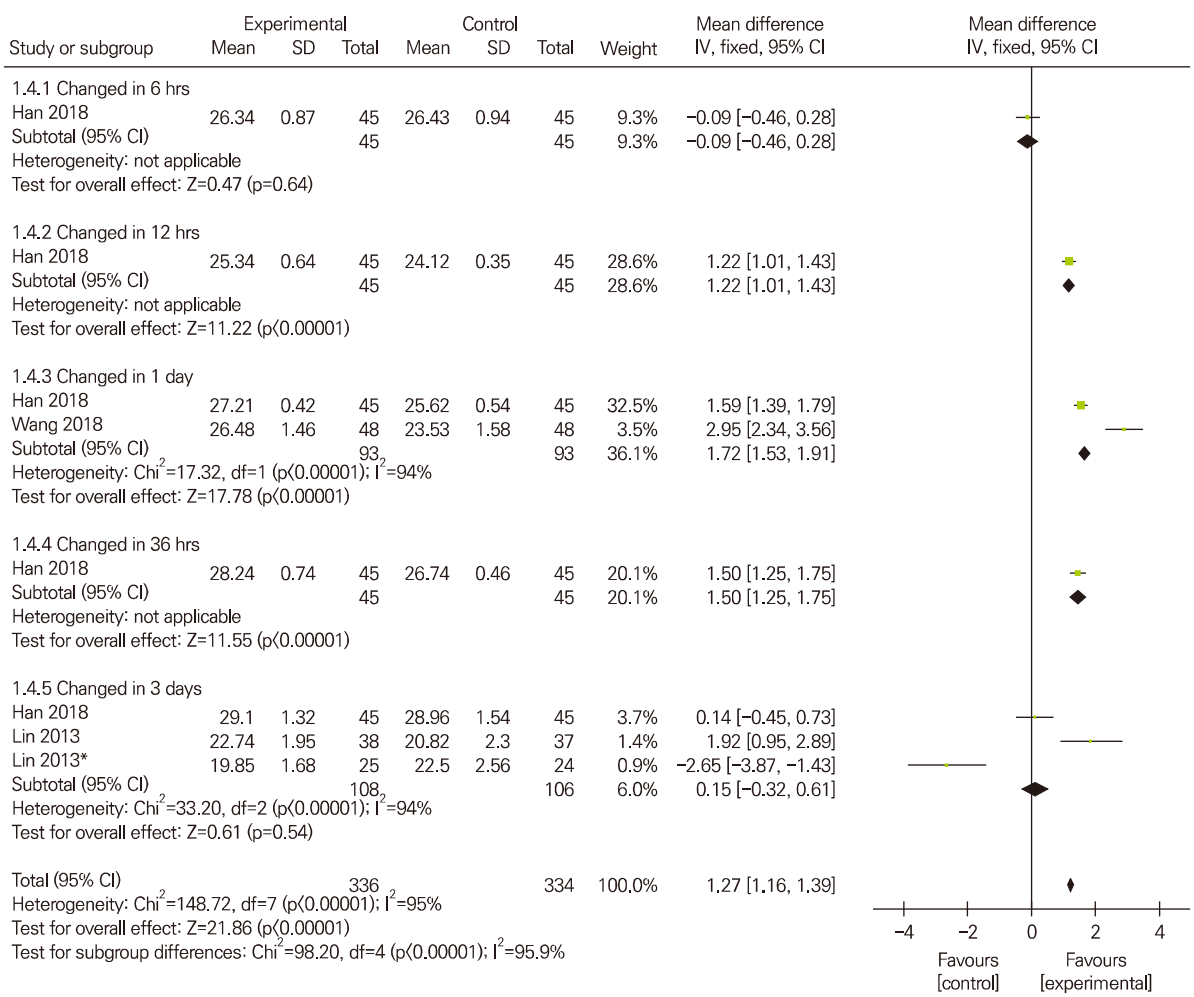


Fig. 6. The forest plot of MMSE : EA versus UC for cognitive impairment after cancer surgery.

other hand, changes in 12 hrs group (MD, 1.22; 95% CI, 1.01 to 1.43; p<0.00001), changes in 1 day group (MD, 1.72; 95% CI, 1.53 to 1.91; p<0.00001) and changes in 36 hrs group (MD, 1.50; 95% CI, 1.25 to 1.75; p<0.00001) were effective. But the heterogeneity of Changes in 6, 12, 36 hrs group was not applicable. Changes in 1 day group (χ^2= 17.32, I^2= 94%) and 3 day group (χ^2 = 33.20, I^2= 94%) were significant.

5) EA versus UC for cognitive impairment after cancer surgery in incidence

The data of 3 studies which compared EA with UC were synthesized in Incidence variations (Fig. 7). Total 214 participants were included, 108 were assigned to EA group whereas 106 were UC group. The data analysis was using Risk Ratio in fixed effect model. The results were that EA was effective compared to UC (RR, 0.54; 95% CI, 0.34 to 0.86; p=0.009). Also, the heterogeneity was not significant (χ^2=0.80, I^2=0%).

In 1 study, they checked Incidence after 1 day, and in 2 studies after 3 days. So subgroup analysis were performed by the result in the subgroup using Incidence rate with intervention evaluated by follow up time.

The intervention group which assessed changed results 1 day after EA (Changes in 1 day group) was not effective (RR, 0.53; 95% CI, 0.25 to 1.13; p=0.10) and heterogeneity was not applicable. But Changes in 3 days group was effective (RR, 0.55; 95% CI, 0.31 to 0.98; p=0.0002) and heterogeneity was not significant (χ^2=0.79, I^2=0%).

6) TAES versus UC for cognitive impairment after cancer surgery in MMSE

The data of 5 studies which compared TAES with UC were synthesized in MMSE variations (Fig. 8). Total 334 participants were included, 169 were assigned to TAES group whereas 165 were UC group. The data analysis was using mean difference in random effect model. The results were that TAES was effective compared to UC (MD, 1.42; 95% CI, 0.67 to 2.17; p=0.0002). But, the heterogeneity was significant (χ^2=106.18, I^2=91%).

In 1 study, they checked TAES after 1, 3, 5, 7 days,

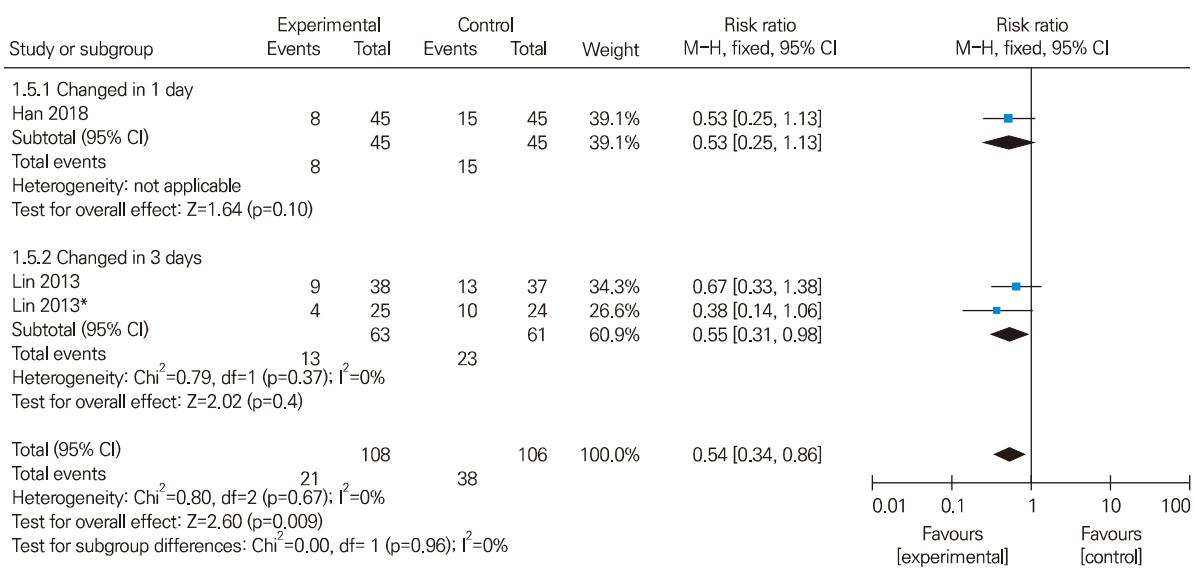


Fig. 7. The forest plot of Incidence : EA versus UC for cognitive impairment after cancer surgery.

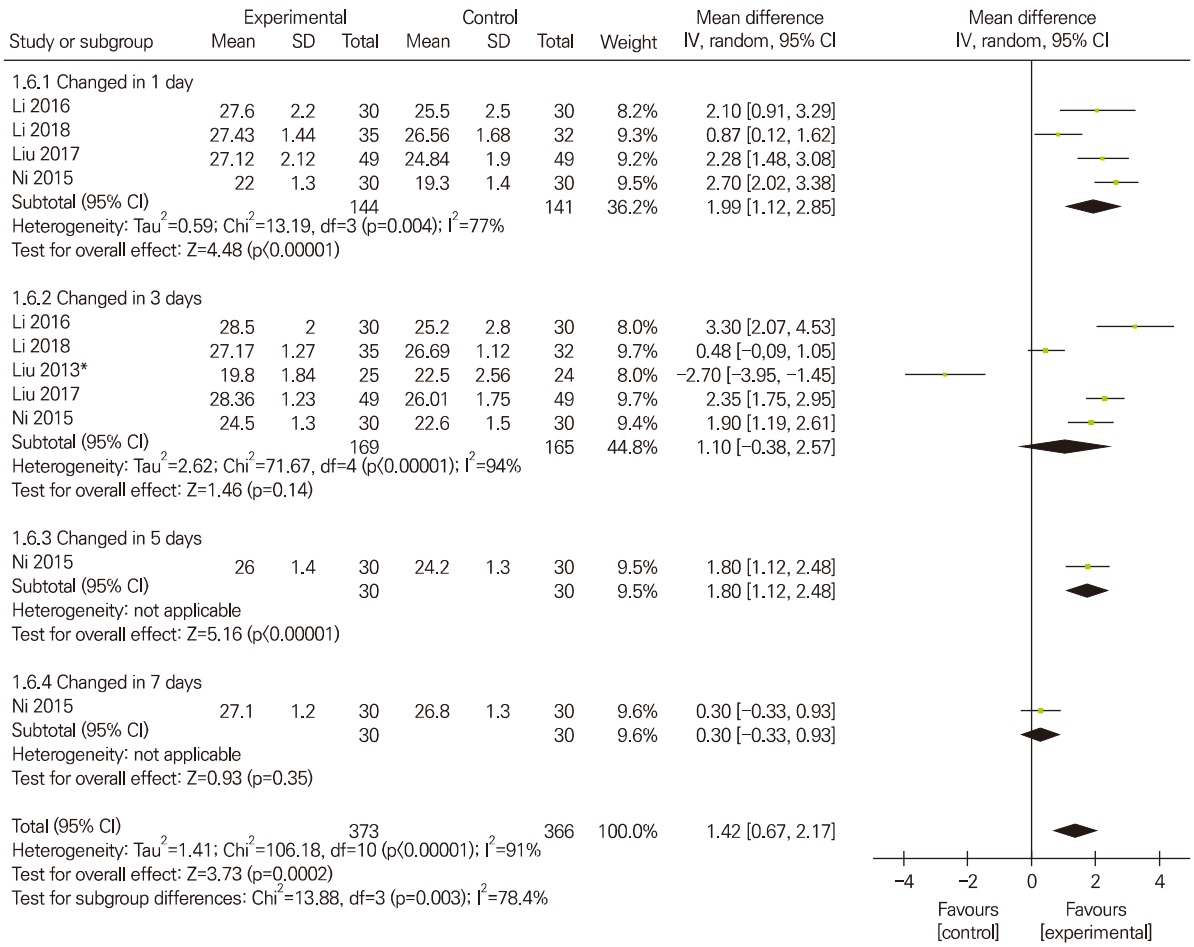


Fig. 8. The forest plot of MMSE : TAES versus UC for cognitive impairment after cancer surgery.

in another study after 3 days, and in 3 studies they checked MMSE after 1, 3 days respectively.

So subgroup analysis was performed by the result in the subgroup using MMSE with intervention evaluated by follow up time.

The intervention group which assessed changed results 1 day after TAES (Changes in 1 day group) was effective (MD, 1.99; 95% CI, 1.12 to 2.85; p=0.004) but heterogeneity was significant (χ^2=13.19, I^2=77%). Also Change in 5 day group was effective (MD, 1.80; 95% CI, 1.12 to 2.48; p<0.00001), and heterogeneity was not applicable. On the other hand, changes after 3 days group (MD, 1.10; 95% CI, -0.38 to 2.57; p=0.14) and 7 days group (MD, 0.30; 95% CI, -0.33 to 0.93; p=0.35) were not effective and heterogeneity was significant (χ^2=71.67, I^2=94%) or not applicable.

7) TAES versus UC for cognitive impairment after cancer surgery in incidence

The data of 5 studies which compared TAES with UC were synthesized in Incidence change (Fig. 9). Total 334 participants were included, 169 were assigned to TAES group whereas 165 were UC group. The data analysis was using Risk Ratio in random effect model. The results were that TAES was effective compared to UC (RR, 0.48; 95% CI, 0.35 to 0.65; p< 0.00001). Also, the heterogeneity was not significant (χ^2=1.78, I^2=0%).

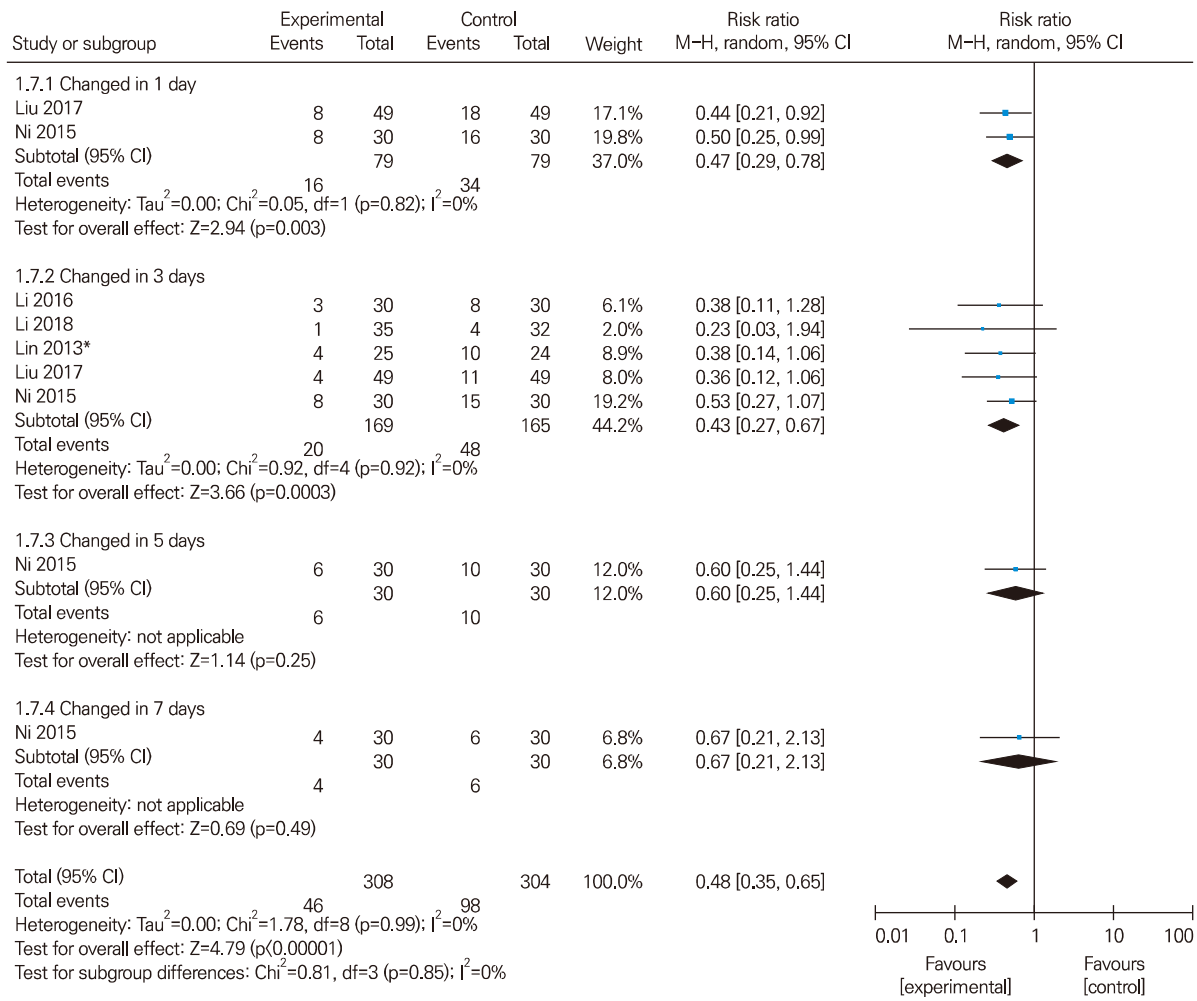


Fig. 9. The forest plot of Incidence : TAES versus UC for cognitive impairment after cancer surgery.

In 1 study, they checked Incidence after 1, 3, 5, 7 days, in another study after 1, 3 days, and the other 3 studies checked Incidence after 3 days.

So subgroup analysis was performed by the result in the subgroup using Incidence rate with intervention evaluated by follow up time.

The intervention group which assessed change results 1 day after TAES (Changes in 1 day group) (RR, 0.47; 95% CI, 0.29 to 0.78; p=0.003) and Changes in 3 days group (RR, 0.43; 95% CI, 0.27 to 0.67; p=0.0003) were more effective and heterogeneity of the 2 groups was not significant (χ^2=0.05, I^2=0%) (χ^2=0.929, I^2=0%). On the other hand, Changes in 5 day group (RR, 0.60; 95% CI, 0.25 to 1.44; p=0.25) and Changes in 7 day group (RR, 0.67; 95% CI, 0.19 to 2.13; p=0.49) were no effective, and heterogeneity was not applicable.

8) AT (by electric current) versus UC for cognitive impairment after cancer surgery in MMSE

The data of 7 studies which compared Electric current in electroacupuncture therapy with UC were synthesized in MMSE variation (Fig. 10). Total 499 participants were included, 251 were assigned to experimental group whereas 248 were UC group. The data analysis was using mean difference in fixed ef-

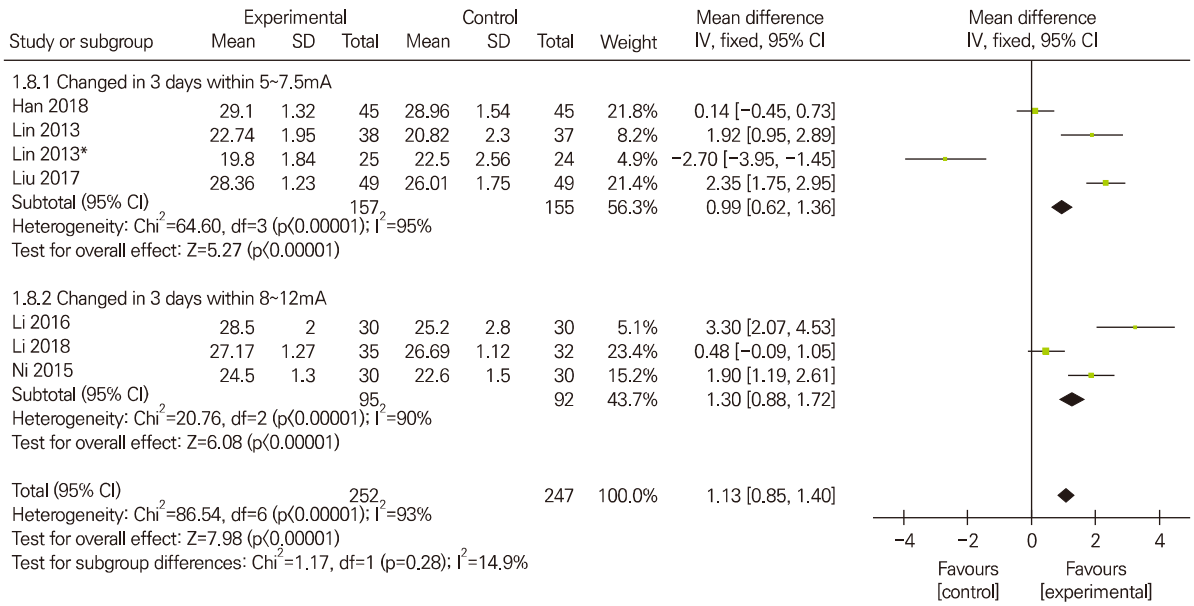


Fig. 10. The forest plot of MMSE : AT (by electric current) versus UC for cognitive impairment after cancer surgery.

fect model. The results were that Electric current in electroacupuncture therapy was effective compared to UC (MD, 1.13; 95% CI, 0.85 to 1.40; p<0.00001). But, the heterogeneity was significant (χ^2=86.54, I^2= 93%).

In 4 studies, they checked MMSE after electroacupuncture therapy of electric current within 5~7.5 mA and in 3 studies, after electroacupuncture therapy of electric current within 8~12 mA.

So subgroup analysis was performed by the result in the subgroup using MMSE with intervention of current strength of electro-acupuncture.

The outcome of the intervention subgroup that conducted electro-acupuncture with the current strength of electroacupuncture therapy within 5~7.5 mA was effective (MD, 0.99; 95% CI, 0.62 to 1.36; p<0.00001) and heterogeneity was significant (χ^2=64.60, I^2=95%). Also other subgroup within 8~12 mA came out effective (MD, 1.30; 95% CI, 0.88 to 1.72; p<0.00001) and heterogeneity was significant (χ^2=20.76, I^2=90%).

9) AT (by electric current) versus UC for cognitive impairment after cancer surgery in incidence

The data of 6 studies which compared Acupuncture therapy (Depend on Electric current in electroacupuncture therapy) with UC were synthesized in Incidence change (Fig. 11). Total 409 participants were included, 206 were assigned to experimental group whereas 203 were UC group. The data analysis was using Risk Ratio in fixed effect model. The results were that Electric current in electroacupuncture therapy was effective compared to UC (RR, 0.47; 95% CI, 0.32 to 0.69; p=0.0001). Also, the heterogeneity was not significant (χ^2=2.04, I^2=0%).

In 3 studies, they checked Incidence after electroacupuncture therapy of electric current within 5~7.5 mA and in other 3 studies, after electroacupuncture therapy of electric current within 8~12 mA.

So subgroup analysis was performed by the result in the subgroup using Incidence rate with intervention of current strength of electro-acupuncture current.

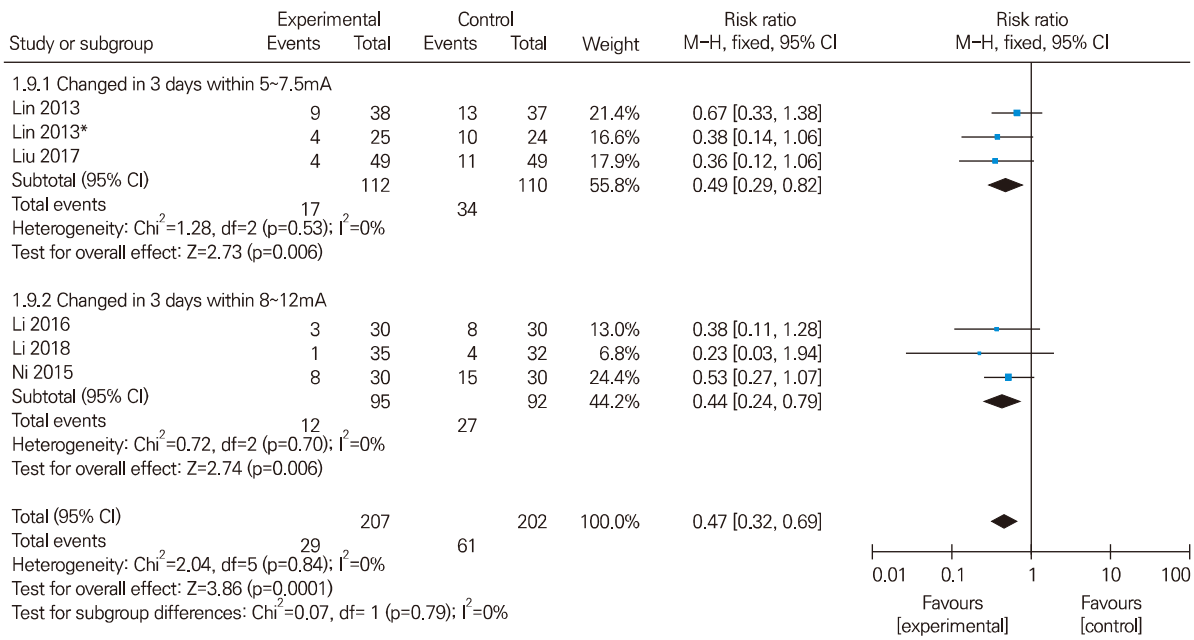


Fig. 11. The forest plot of Incidence: AT (by electric current) versus UC for cognitive impairment after cancer surgery.

The outcome of the intervention subgroup that conducted electro-acupuncture with the current strength of 5~7.5 mA was effective (RR, 0.49; 95% CI, 0.29 to 0.82; p=0.006) and heterogeneity was not significant (χ^2=1.28, I^2=0%). Also, other subgroup within 8~12 mA was effective (RR, 0.44; 95% CI, 0.24 to 0.79; p=0.006) and heterogeneity was not significant (χ^2=0.72, I^2=0%).

10) AT (by frequency) versus UC for cognitive impairment after cancer surgery in MMSE

The data of 7 studies which compared Electric frequency in electroacupuncture therapy with UC were synthesized in MMSE variations (Fig. 12). Total 524 participants were included, 276 were assigned to experimental group whereas 248 were UC group. The data analysis was using mean difference in random effect model. The total results were that Electric frequency in electroacupuncture therapy was not effective compared to UC (MD, 0.74; 95% CI, -0.35 to 1.84; p=0.18). And the heterogeneity was significant (χ^2=106.36, I^2=93%).

In 3 studies, they checked MMSE after electro-acupuncture therapy with Electric frequency of 2/20 Hz, and in 5 studies after electroacupuncture therapy with frequency of 2/100 Hz. So subgroup analysis was performed by the result in the subgroup using MMSE with intervention of degree of electro-acupuncture frequency.

The outcome of the intervention subgroup that conducted electro-acupuncture with frequency of 2/20 Hz was not effective (MD, 0.14; 95% CI, -1.15 to 1.87; p=0.87) and heterogeneity was significant (χ^2=21.67, I^2=91%). Also other subgroup within 2/100 Hz was not effective too (MD, 1.10; 95% CI, -0.38 to 2.57; p=0.14) and heterogeneity was significant (χ^2=71.67, I^2=94%).

11) AT (by frequency) versus UC for cognitive impairment after cancer surgery in incidence

The data of 6 studies which compared Electric frequency in electroacupuncture therapy with UC were

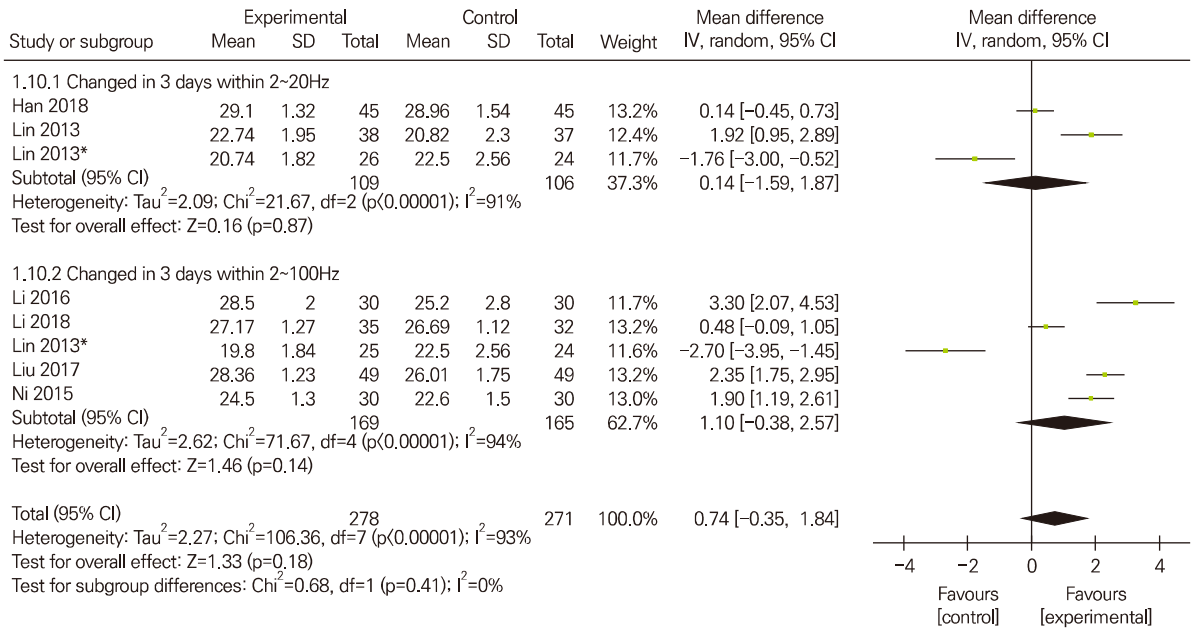


Fig. 12. The forest plot of MMSE : AT (by frequency) versus UC for cognitive impairment after cancer surgery.

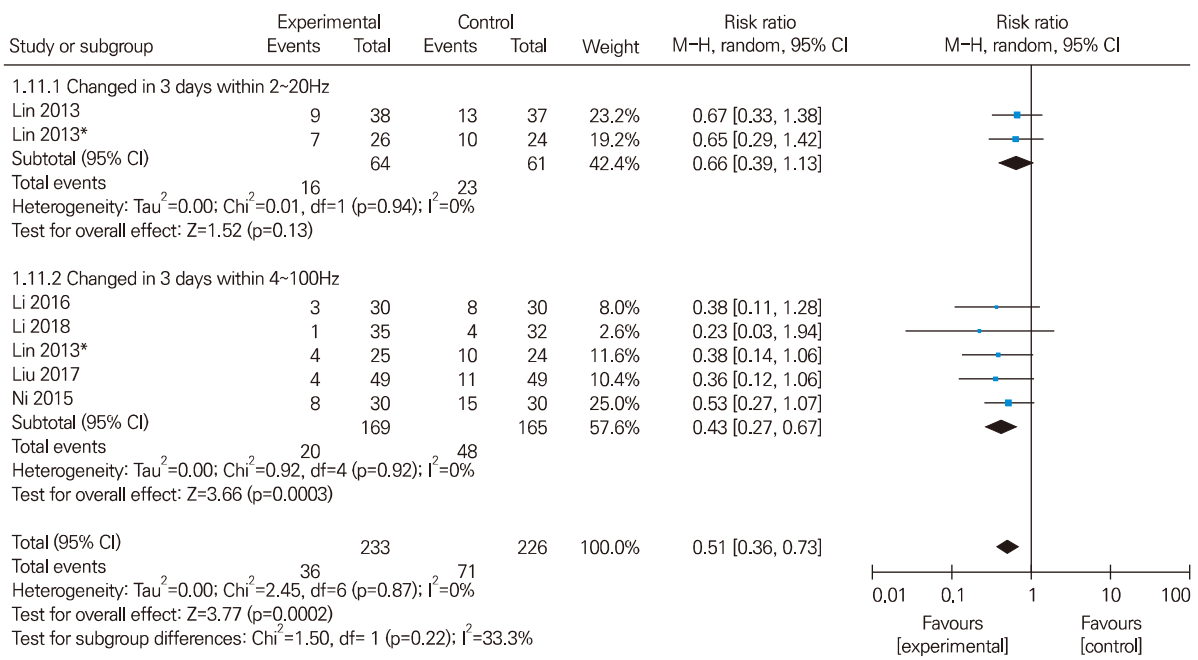


Fig. 13. The forest plot of Incidence : AT (by frequency) versus UC for cognitive impairment after cancer surgery.

synthesized in Incidence variations (Fig. 13). Total 479 participants were included, 231 were assigned to experimental group whereas 203 were UC group. The data analysis was using Risk Ratio in random effect model. The results were that Electric frequency in electroacupuncture therapy was effective compared to UC (RR, 0.51; 95% CI, 0.36 to 0.73; p=0.0002). Also, the heterogeneity was not significant (χ^2=2.45, I^2=

0%).

In 2 studies, they checked Incidence after electro-acupuncture therapy with Electric frequency of 2/20 Hz, and in 5 studies after electroacupuncture therapy with frequency of 4/100 Hz. So subgroup analysis was performed by the result in the subgroup using Incidence rate with intervention of degree of electro-acupuncture frequency.

The outcome of the intervention subgroup that conducted electro-acupuncture with frequency of 2/20 Hz was not effective (RR, 0.66; 95% CI, 0.39 to 1.13; p=0.13) and heterogeneity was not significant (χ^2=0.01, I^2=0%). On the other hand, the other subgroup within 2/100Hz was effective (RR, 0.43; 95% CI, 0.27 to 0.67; p=0.0003) and heterogeneity was not significant (χ^2=0.92, I^2=0%).

12) TA versus control group for CRCI in MMSE

The data of 2 studies which compared TA with Control group such as Sham Acupuncture and No needling, were synthesized in MMSE variations (Fig. 14). Total 168 participants were included, 87 were assigned to experimental group (TA) whereas 81 were control group. The data analysis was using mean difference in fixed effect model. The total result was that TA was effective compared to Control group (MD, 1.48; 95% CI, 1.23 to 1.73; p<0.00001) and the heterogeneity was significant (χ^2=47.09, I^2=92%).

13) TA versus control group for CRCI in MoCA

The data of just 1 study which compared TA with Sharm Acupuncture were synthesized in MoCA variations (Fig. 15). Total 80 participants were included,

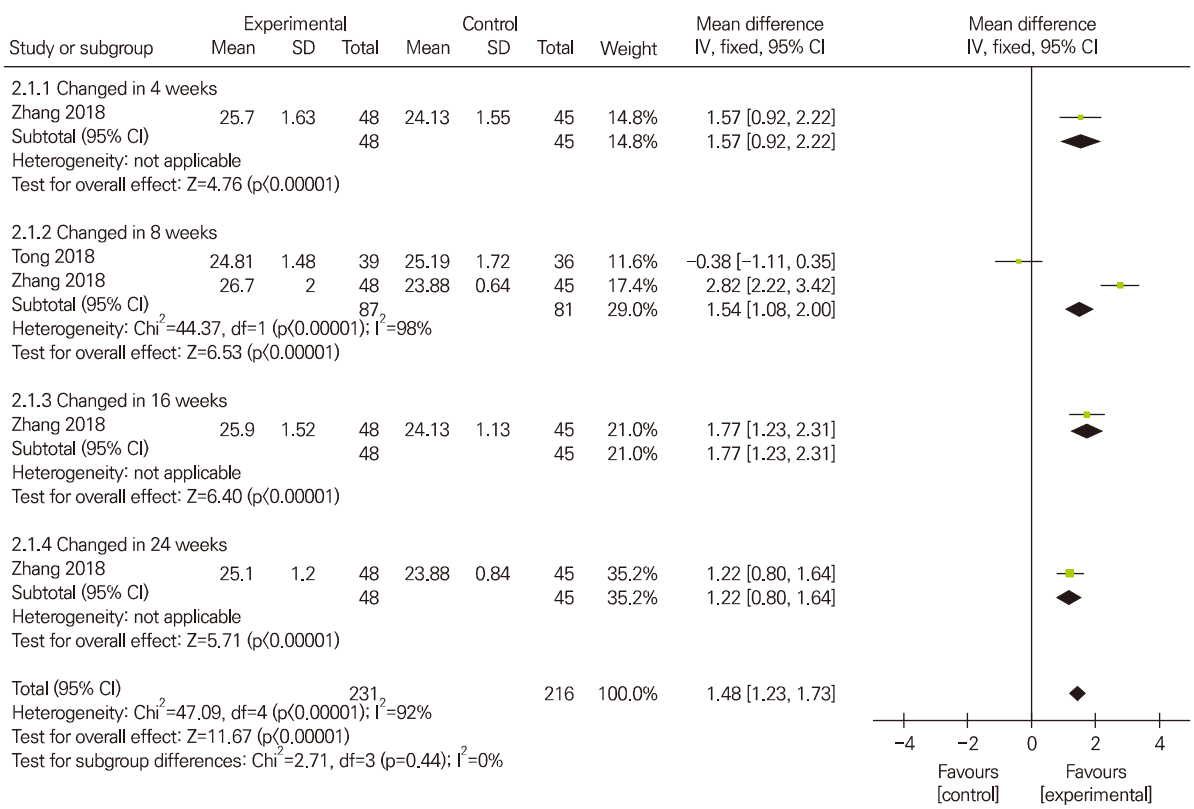


Fig. 14. The forest plot of MMSE : TA versus control group for CRCI.

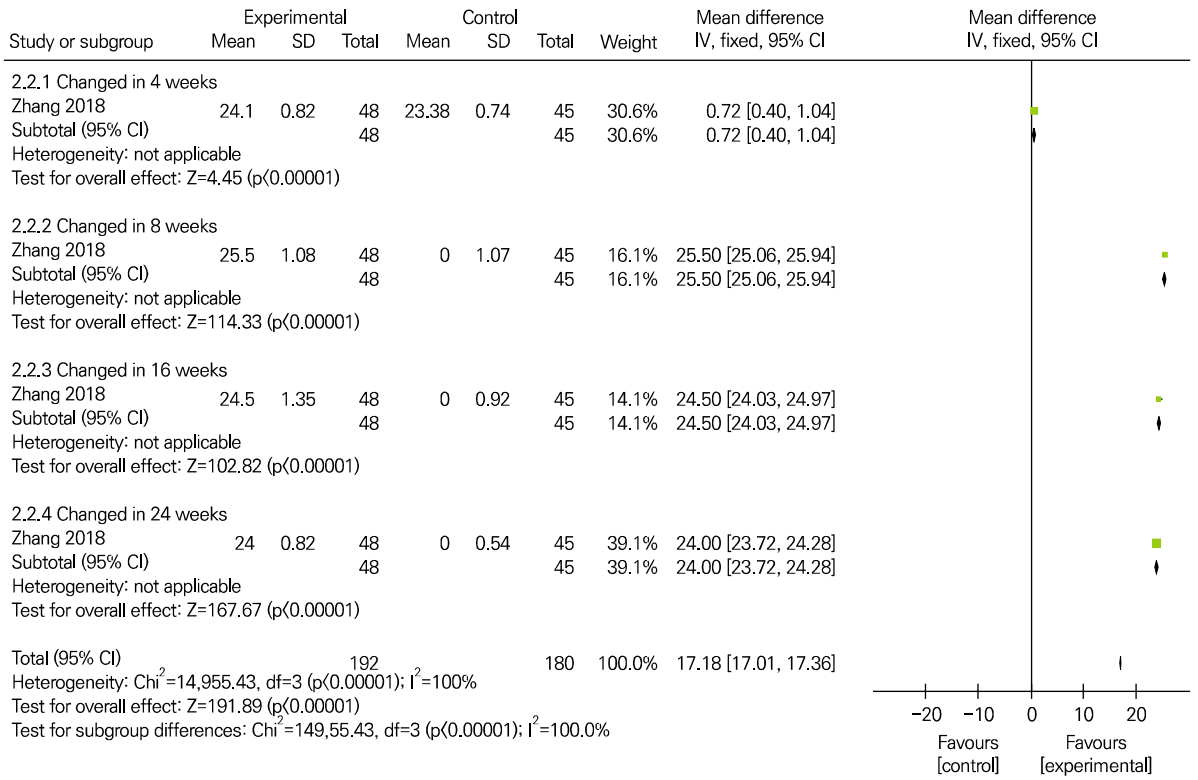


Fig. 15. The forest plot of MoCA : TA versus control group for CRCI.

40 were assigned to experimental group (TA) whereas 40 were control group (ST). The data analysis was using mean difference in fixed effect model. The total result was that TA was effective compared to Control group (MD, 17.18; 95% CI, 17.01 to 17.36; $p<0.00001$) and the heterogeneity was not applicable.

14) EA/TNS versus MAS for CRCI in Incidence

The data of just 1 study which compared Combined group of electroacupuncture, Trigeminal Nervous Stimulation (EA/TNS) and MAS (Minimal Acupuncture Stimulation) was synthesized in Incidence variations (Fig. 16). Total 83 participants were included, 40 were assigned to experimental group (EA/TNS) whereas 43 were control group (MAS). The data analysis was using Risk Ratio in random effect model. The total outcomes were that EA/TNS was effective compared to Control group (MD, 0.56; 95% CI, 0.31 to 0.99; p=0.04).

6) Safety

In enrolled and analyzed 11 studies, No studies reported adverse events.

IV. DISCUSSION

Development of new cancer treatments reduces the risk of recurrence and improves the survival rate, thereby increasing the life expectancy of cancer patients. As the survival of cancer patients increases, Many patients began to complain of decreased cognitive function[28-31]. As to reflect these newly increasing complaints, cancer related cognitive dysfunction was newly included in NCCN guideline as a target of treatment in 2014.

The problem of cognitive decline in cancer patients began to receive scientific attention only in the

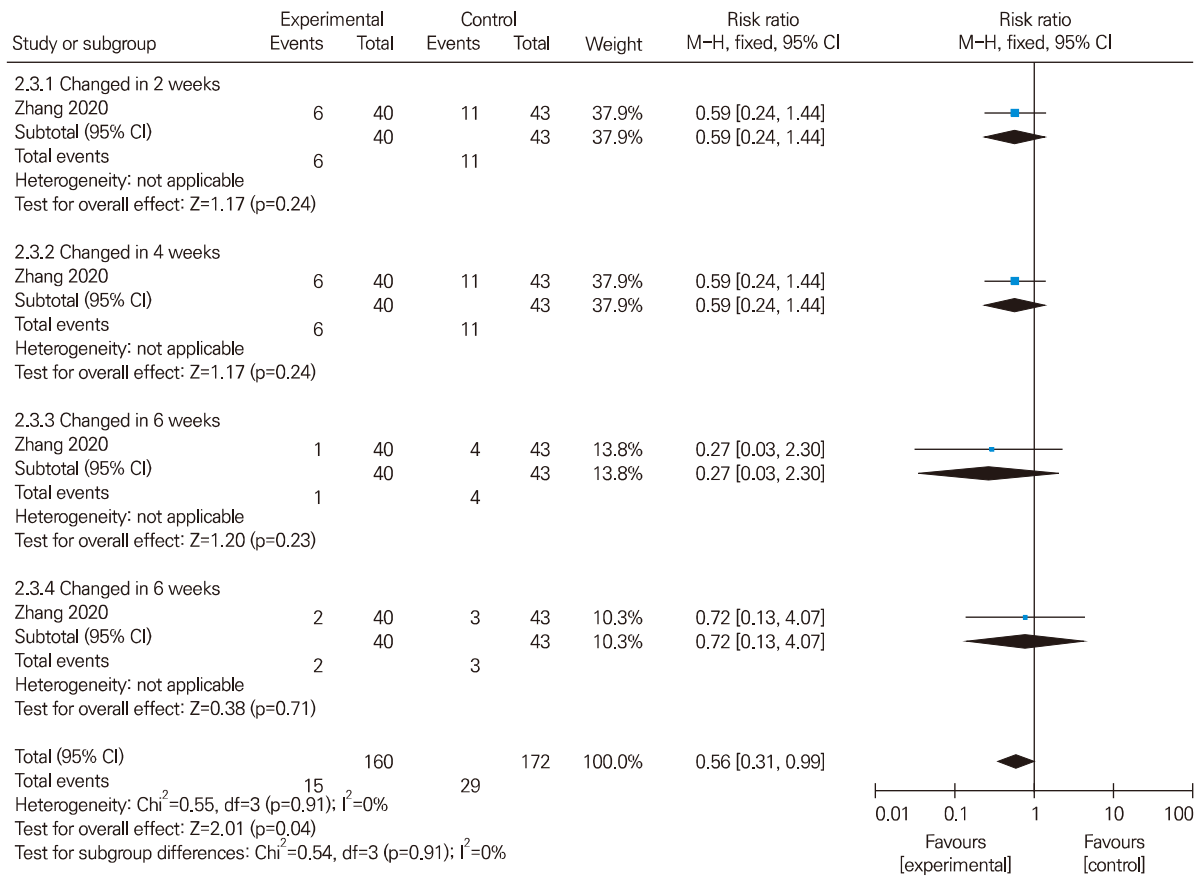


Fig. 16. The forest plot of Incidence : EA/TNS versus MAS for CRCI

late 1990s[32,33]. Thus, it has begun to be recognized as a treatment area relatively recently. All papers included in this study were also published after 2013, so it can be known that the research on this subject is recently attracting attention. In addition, cancer patients suffering from cognitive problems complain of significant deterioration in quality of life and deterioration in daily life performance. However, despite this situation, it is shown that the importance of the problem of cognitive decline in cancer patients is underestimated, and academic interest is insufficient[34].

The problem of cognitive decline that cancer patients complain of, can be seen mainly in postoperative cognitive dysfunction and Chemotherapy related cognitive impairment. In this study, we included POCD and CRCI in cognitive impairment problems that may occur in cancer patients.

Korean Medicine (KM) using acupuncture therapy explains a condition of health by maintaining physical and mental balance. Although there are still much to be revealed, many mechanisms including neurological explanations of acupuncture treatment are reported and this modality of treatment has been used widely in clinical practices to treat neuropsychiatric patients.

Many researchers reported that acupuncture therapy improves cognitive dysfunctions through clinical researches and in vitro/in vivo experiments. Moreover, it can effectively suppress the central nervous system, improve microcirculation and oxygen metabolism of brain tissues, increase cerebral blood supply,

relieve cerebral edema and reduce inflammatory responses in the hippocampus caused by inflammatory factors crossing the blood-brain barrier[35]. In addition, Acupuncture therapy has its effectiveness on reducing the accumulation of Ca^{2+} in brain neurons, preventing Ca^{2+} overload, mitigating or avoiding necrosis of the neurons and a protective influence on the ischemic injury of neurons[36]. So, it can be assumed that in the problem of cognitive decline, the use of acupuncture is highly recommendable.

Thus this study aims to evaluate the effectiveness of acupuncture treatment to cognitive impairment in cancer patients who receive surgery or chemotherapy through score evaluated using MMSE, MoCA and Incidence rate of symptoms.

In this study, selective intervention was determined as acupuncture therapy for cancer patients experiencing cognitive decline. Acupuncture therapy (including traditional acupuncture, body acupuncture, electroacupuncture, transcutaneous acupoint electric stimulation) was the selective intervention, and other treatment modalities such as herb remedies and other types of intervention were all excluded.

Only the studies which described the trials as RCTs were included and the studies which the description was not clear were excluded. However, the fact that allocation concealment was not mentioned or did not appear in all studies, that 2 studies had a high risk of incomplete outcome, can be assessed that the quality of the data is relatively poor.

This review aimed to evaluate the clinical effect of AT for cognitive decline in cancer patient compared to UC. The comprehensive search in this study involved 11 RCTs. Based on the results of this study, AT significantly improved cognitive decline in cancer patient, measured by MMSE, MoCA and Incidence of cognitive dysfunction after surgery or chemotherapy. EA group and TAES group showed improvement on cognitive impairment, compared to UC in MMSE and Incidence rate. The electro-acupuncture-related acupuncture treatment group was also effective regardless of the current's strength. However, AT with high/low frequency stimulation, was not effective assessed with MMSE, but AT with high/low frequency in Incidence rate was effective regardless of the frequency. Moreover, Traditional Acupuncture and EA/TNS was shown effective in both MMSE and MoCA.

Korean medicine treatment studies concerned with cognitive dysfunction in cancer patients have not been sufficiently conducted, until now. In fact, seeking papers for references, the variety of studies on cancer-related cognitive disorders were shallow.

Among the studies that included cognitive function evaluation, there were no studies that reported baseline values while independently evaluating cognitive function, so it was difficult to determine how Korean medicine treatment affects subjects with a certain degree of cognitive deficit. Although it was not reported whether the subjects included in the study had cognitive impairment from the baseline, changes in cognitive function were reported during clinical trials. Therefore, it is necessary to examine the effects of acupuncture on cognitive function in future studies.

MMSE and MoCA, used as indicators of cognitive function, are used as tools to evaluate subjective cognitive impairment. But because many of the questions are evaluated based on the patient's subjective condition, there is a certain limit to assess the cognitive function. Unfortunately, there were no studies in which objective neuropsychological tests such as Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and Controlled Oral Word Association test (COWA) have been conducted[37]. Thus it was difficult to evaluate the areas of detailed cognitive impairment and the areas recovered by Acupuncture Therapy. After being diagnosed with cancer, emotional problems as well as cognitive dis-

orders occur very frequently[38]. Therefore, not only cognitive evaluation but also emotional evaluation should be performed with cancer patients.

POCD is frequently occurred complications after surgery in cancer patient[39]. Some hypotheses have been suggested about the cause of POCD, but they are not yet clear. Typically, the systemic stress response induced by surgery may cause impaired brain function, resulting in POCD. According to Caza (2008), increased cortisol level and inflammatory response in the hippocampus are associated with the development of POCD[40]. Inflammatory response caused by surgery promotes the interleukin-1β (IL-1β) pathway in the hippocampus[41]. However, in a experiment with mice, even when only general anesthesia was performed without surgery, IL-1β increased and the learning ability of mice decreased[42]. In the past, it was expected that the incidence of POCD would vary depending on the type of anesthesia or the type of surgery performed, but recent studies concluded that there was no difference in the incidence of POCD according to the type of surgery or anesthesia[43]. Lee (2015) reported that the incidence rate of POCD was not significantly different by the level of sedation, so the study could not detect a significant association between the depth of sedation and the presence of POCD[44]. Lin (2014) reported that acupuncture-anesthetic composite could reduce the incidence of POCD and inhibit postoperative release of TNF-alpha, IL-1beta, and IL-6 in elderly patients undergoing colorectal cancer resection[45]. In summary, for cancer patients who suffer from POCD, acupuncture treatment is recommendable based on multi-studies such as clinical trials and in vitro/in vivo studies etc.

Also in recent review study on CRCI acupuncture treatment, it was reported that acupuncture therapy could help CRCI through recovery and protection of structural damage of the nervous system and relief of psychological distress[46] and suggest that physicians should support their patients interest to use acupuncture treatment for their chemotheraphy-associated cognitive dysfunction for there is evidence that acupuncture may effectively manage a range of psychoneurological conditions[47]. Additionally in vitro/in vivo studies, evidences for the effectiveness of acupuncture on cognitive decline are diverse. In the expresses mutated Amyloid Precursor Protein (APP) and presenilin-1 mouse model, electro-acupuncture at GV20 (百會) can reduce the abnormally high expression of b-amyloid-42, inhibit the apoptosis of nerve cells, enhance Brain Derived Neurotrophic Factor (BDNF) level and relieve cognitive impairment[48]. Moreover, experiments have shown that acupuncture on aging mice can induce cell proliferation and improve learning and memory in different brain regions[49]. Zhao (2013) reported that acupuncture up regulate the activity of phospho-isomerase in the hippocampus[50]. Nie (2014) and Wang (2017) reported AT regulates the function of cytoskeletal-related synapses, induce neurotransmitter secretion and promote the recovery of neuroplasticity[51,52]. Problems with memory and attention are not directly correlated with surgical adverse effects[53]. Acupuncture treatment may promote the physiological formation of BDNF, increasing levels of BDNF, which in turn, accelerates recovery of the central nervous system from chemotherapy damage, affecting attention, memory, executive function and other cognitive tasks. Acupuncture treatment may also provide other benefits, such as refining emotion, reducing pain and improving quality of life of cancer patients[53,54]. Therefore the clinical efficacy of Acupuncture Therapy for cognitive decline in cancer patients compared to Usual care are thought to be sufficient through clinical studies and basic studies.

For more convincing results of this study, better quality research, statistically more appropriate sample size and long-term follow up trials are needed. Furthermore, inclusion criteria for participant, inter-

vention, control and evaluation of quality have to be obviously specified to confirm which cancer patient is able to benefit from acupuncture therapy in detail and which method of acupuncture therapy is more effective according to each concrete cognitive dysfunction symptoms. Therefore, for better quality research, the studies of randomized clinical trials are suggested to follow Consolidated Standards Of Reporting Trials (CONSORT) statement[56]. Moreover, standardized monitoring of adverse events related to CMT and standardized acupuncture process for CRCI with studies comparing the effects of different skills of acupuncture therapy is also considered necessary. Given additional follow-up research or research related to efficacy of various acupuncture therapy modalities on CRCI, it will help physicians to make clearer decisions in clinical region.

V. CONCLUSION

11 RCTs were included in this study. The risk of bias was low overall, the effect sizes were various, and the ROB was poor. In Comparison to Usual Care Mainly, the efficacy of Acupuncture Therapies (such as electroacupuncture, Subcutaneous Acupoint Electric Stimulation, Traditional Acupuncture, Body Acupuncture/Trigeminal Nerveous Stimulation) for cognitive decline in cancer patient after surgery and chemotherapy were effective. Although Acupuncture Therapy was significant heterogeneous, it was usually more effective than Usual Care. Also electroacupuncture was effective, regardless of the high or low current. In accordance to recent evidence in clinical trials in vitro/in vivo, Acupuncture Therapy had benefits on cognitive decline problems in cancer patient who suffer from surgery or chemotherapy. However, the therapeutic effect according to high or low electric frequency was not confirmed in the subgroup analysis, thus further researches related with electric frequency are thought to be necessary. Therefore, Acupuncture Therapy has the potential of medical methods that can be used in cancer patients who suffer from cognitive dysfunction after surgery or chemotherapy. However, the sample sizes of including trials in this study were relevantly small, and many requirements are necessary to improve the quality of methods. So later on, well-designed studies are expected to strengthen these results, additionally.

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Appendix 1

· Medline

#1 "Neoplasms"[MeSH Terms]

#2 "cancer*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "carcinoma*"[Title/Abstract] OR "adenocarcinoma*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "leukemia*"[Title/Abstract] OR "leukaemia*"[Title/Abstract]

#3 "chemo*"[Title/Abstract]

#4 #1 or #2 or #3

#5 "Cognition"[Title/Abstract]

#6 "cognitive"[Title/Abstract]

#7 "attention"[Title/Abstract]

#8 "memory"[Title/Abstract]

#9 #5 or #6 or #7 or #8

#10 acupuncture[MeSH Terms]: "acupuncture"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms]

#11 "acupuncture*"[Title/Abstract]

#12 "electroacupuncture"[Title/Abstract]

#13 "acupoints"[Title/Abstract]

#14 "Pharmacopuncture"[Title/Abstract]

#15 "auricular acupuncture"[Title/Abstract]

#16 #10 or #11 or #12 or #13 or #14 or #15

#17 #4 and #9 and #16

· EMBASE

#1 "Neoplasms"[MeSH Terms]

#2 "cancer*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "carcinoma*"[Title/Abstract] OR "adenocarcinoma*"[Title/Abstract] OR "malignan*"[Title/Abstract] OR "leukemia*"[Title/Abstract] OR "leukaemia*"[Title/Abstract]

#3 "chemo*"[Title/Abstract]

#4 #1 or #2 or #3

#5 "Cognition"[Title/Abstract]

#6 "cognitive"[Title/Abstract]

#7 "attention"[Title/Abstract]

#8 "memory"[Title/Abstract]

#9 #5 or #6 or #7 or #8

#10 acupuncture[MeSH Terms]: "acupuncture"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms]

#11 "acupuncture*"[Title/Abstract]

#12 "electroacupuncture"[Title/Abstract]

#13 “acupoints”[Title/Abstract]
#14 “Pharmacopuncture”[Title/Abstract]
#15 “auricular acupuncture”[Title/Abstract]
#16 #10 or #11 or #12 or #13 or #14 or #15
#17 #4 and #9 and #16

· Cochrane Library(Central)

#1 MeSH descriptor: [Neoplasms] explode all trees
#2 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or leukemia* or leukaemia*):ti,ab,kw
#3 (chemo*):ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Cognition Disorders] explode all trees
#6 MeSH descriptor: [Attention] explode all trees
#7 MeSH descriptor: [Memory] explode all trees
#8 (cognition):ti,ab,kw
#9 (cognitive):ti,ab,kw
#10 (attention):ti,ab,kw
#11 (memory):ti,ab,kw
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 MeSH descriptor: [Acupuncture] explode all trees
#14 MeSH descriptor: [Acupuncture Therapy] explode all trees
#15 MeSH descriptor: [Electroacupuncture] explode all trees
#16 MeSH descriptor: [Meridians] explode all trees
#17 (acupuncture*):ti,ab,kw
#18 (electroacupuncture):ti,ab,kw
#19 (Pharmacopuncture):ti,ab,kw
#20 (acupoints):ti,ab,kw
#21 (auricular acupuncture): ti,ab,kw
#22 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #4 and #12 and #22

· CNKI

#1 癌
#2 neoplasm
#3 tumor
#4 tumour
#5 chemo*
#6 cancer

#7 or/#1-6
#8 认知
#9 认识
#10 cognition
#11 cognitive
#12 memory
#13 attention
#14 OR/#8-13
#15 针*
#16 刺*
#17 针刺
#18 穴位
#19 电针
#20 针药*
#21 蜂毒
#22 蜂疗
#23 穴位注射
#24 耳针
#25 acupuncture
#26 electroacupuncture
#27 auricular acupuncture
#28 OR/#15-27
#29 #7 AND #14 AND #28

· KISS, NDSL and OASIS

#1 acupuncture:ab
#2 electroacupuncture:ab
#3 acupoints:ab
#4 pharmacopuncture:ab
#5 auricular acupuncture:ab
#6 #1 or #2 or #3 or #4 or #5
#7 cancer:ab
#8 cognitive:ab
#9 cognition:ab
#10 memory:ab
#11 attention:ab
#12 #8 or #9 or #10 or #11
#13 #6 and #7 and #12