



## Acupuncture Prevent Progression of Cachexia in Breast Cancer in Outpatients of Dr. Saiful Anwar General Hospital Malang East Java Indonesia

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### Abstract

**Objective:** This study was aimed to assess effect of acupuncture in progression of cachexia in breast cancer patient. Indicator progression of cachexia in this study is level of BMI, FM and FFM was measured before and after eight session of acupuncture procedure. **Methods:** Seven patients were diagnosed breast cancer provide eight acupuncture session before chemotherapy and radiotherapy procedure. Acupuncture procedure was done every 2 days, with duration 30 minutes for every session. Bioelectrical impedance analysis (BIA) measurements were taken at before and after eight acupuncture session to evaluate the body composition of patients. BIA is fast, inexpensive and noninvasive method for evaluating Body Mass Index (BMI), Fat Mass (FM) and Fat-Free Mass (FFM). **Results and Conclusion:** All patients were including in the analysis were complete the acupuncture intervention and BIA measurements. Average age was 54 years, with rang 47-58 years. Most of patients in advanced cancer, 28.5% stage 3 and 43% in stage 4. In this study acupuncture could prevent progression of breast cancer cachexia, with maintain body composition during procedure. BMI was relative constant after eight session of acupuncture ( $20.25 \pm 3.1$ ;  $p > 0.00$ ). Similarly, from BIA measurement, FFM decrease only 0.4% ( $p > 0.05$ ) and FM increase 0.4% ( $p > 0.05$ ). The constant value of body composition mean acupuncture could maintain the metabolism rate in cachexia patients. These studies indicate acupuncture could prevent progression of cachexia in breast cancer.

**Keywords:** Acupuncture, Cachexia, Breast Cancer, Body composition.

### Introduction

Cachexia is a wasting syndrome which is common conditions in advance breast cancer patients and metastasis [1]. Cancer cachexia cause reduce effectivity of cancer therapy, decreasing quality of life and worse prognosis [2]. Cachexia directly responsible for 20 percent of cancer death, being present 32-48 percent of breast cancer patient [1]. The cachexia syndrome is characterized by progressive loss of skeletal muscle mass with or without loss of fat mass that cannot be

fully reversed only by nutritional support and leads to progressive functional impairment. Two inflammatory cytokines, tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6) have been more proposed to be involved in cachexia progression [3]. Cancer cachexia is a complex condition that is not yet fully understood and some therapy have been developed to prevent or treat of cancer-associated muscle wasting, but not obtained satisfying result [4].

Therefore cachexias still a predictor of death in cancer [5]. Complementary and alternative medicines (CAM) are widely used for cancer in community although base on experience from previous generation [6]. Although CAM is not standard therapy, WHO notes 80% cancer patient use complementary and alternative therapy with various reasons [7]. Acupuncture is one therapy that is often used in breast cancer patients. Previous studies show the role of acupuncture in anti-inflammatory pathway with activating vagus nerves and work in hypothalamus-pituitary adrenal (HPA) axis. [8, 9].

Moreover, acupuncture had dual effect depend on the acupuncture technique used. Manual acupuncture or electro acupuncture (EA) with low frequency (10Hz), cause anti-inflammatory effect [10, 11]. Clinical evaluation is needed to evaluate of effectivity of therapy by evaluation of body mass index (BMI), and body composition such as fat mass (FM) and fat-free mass (FFM). Bio-impedance analysis (BIA) is body composition assessment tool that has been widely used in clinical and community due to its low cost, ease to use and no-invasive [12].

## Materials and Methods

### Study Design

This research is an exploratory and experimental study with a pretest-posttest design to examine the effect of acupuncture to body composition in breast cancer patients with cachexia. The study was approved by General Hospital of Dr. Saiful Anwar Malang of the institution where the study was conducted and registered to ethical clearance (No.070/1336/302/2019). Informed consent was obtained from all individual participants includes in the study.

### Sample and Setting

Patients were recruited from Unit/ SMF Surgery / General Hospital Dr. Saiful Anwar Malang, Sub Division of Oncology. Inclusion criteria included patients who diagnosed breast cancer (1) live in Malang East Java, (2) weight loss of at least 5% over the last 6 months, (3) ability to follow the research protocol, (4) There are no operational plans for the next 20 days, (5) never had chemotherapy and there are no chemotherapy and radiotherapy plans for the next 20 days.

Exclusion criteria included those (1) patients who have Diabetes Mellitus and (2) afraid of acupuncture needles and its procedures.

### Acupuncture Protocol

Manual acupuncture is performed on patients eight sessions was provide every two days. Acupuncture needles were single-use, sterile stainless steel, and disposable, brand of Huan Qiu made in China measuring 0,25 x 25 mm for acupuncture point Hegu (LI-4), Zusanli (ST36), Sanyinjiao (Sp6), Xuehai (Sp10), Neiguan (P6) and Dazhui (GV14) and needle size 0,13 x 20 mm for Acupuncture point of Dicang (ST4).

Acupuncture points were located using standard anatomical location and needle at proper needling depth (0.5-1,5cm) bilaterally and needle were retained for 30 minutes. Acupuncture was provided to all patients by an acupuncturist who is trained and certified no. 01175/XII/UK/XII/2010.

### Measurement

Demographic information including cancer type, age, education, gender, marital status, ethnicity and insurance type was collected at baseline. Body composition was measured using the BIA (Omron Karada Scan HBF-375).

BIA device is to be reproducible and noninvasive methods to measure body composition. It is an objective tool to measure Body Weight, Body Mass Index (MBI), Free-Fat Mass (FFM) and Fat Mass (FM). Body composition values were measured 2 days before and after eight acupuncture session.

### Statistical Analysis

The *Wilcoxon* signed-rank tests with  $p < .05$  were used for statistical comparisons (SPSS version 16.0). All data were analyzed using Microsoft Excel 2013.

### Result

Patient characteristics are shown in table 1. The mean age of this study was  $54 \pm 3$  years. Most of them have low educational level and have advanced and metastatic cancer (stage 3 and 4, 71.5%) at the time of diagnosis. The mean of body weight loss from previous 6 month and start at study more than 10% (11.63%,  $p < 0.00$ ) as well as BMI (19.4,  $p < 0.00$ ).

**Table 1: Patients characteristics**

		Patient (n=7)		<i>p value</i>
		No	%	
Age (y)	Mean	54±3		
	Range	47-58		
Education	Year 10 or below	4	57	
	Year 12	3	43	
Marital status	Married	5	71	
	Widowed	2	29	
Tumor stage at diagnosis	Stage 2	2	28,5	
	Stage 3	2	28,5	
	Stage 4	3	43	
Body weight (BW)	Normal BW (before diagnosed) (mean; kg)	53.3±7,6		
	Start at study (mean; kg)	47.1±5,1		
	BW decreasing		11,63	<i>p&lt;0.00*</i>
Weight loss previous 6 month	≤ 10% (CWL)	4	57	
	> 10% (non CWL)	3	43	
BMI	Normal BW (before diagnosed) (mean; kg/m <sup>2</sup> )	25.3±3,6		
	Start at study (mean; kg/m <sup>2</sup> )	20.4±2,9		
	BMI decreasing		19,4	<i>p&lt;0.00*</i>

\*Significantly different,  $p<0.005$  (wilcoxon test)

### The Effect of Acupuncture in Body Mass Index (BMI)

We use BIA to measure body composition, especially BMI, FM and FFM. Same basic data patients we need no enter in BIA instrument before measurement such us age, gender and height from the direct measurement. Before intervention, we calculate BMI all patient in from data

previous six month to determine the presence of cachexia ( $25.3\pm3.6$  kg/m<sup>2</sup>). All patients had BMI>20 kg/m<sup>2</sup> in 6 month ago, its mean they had normal BMI. BMI was decrease during the process of disease. In the day start of this study, mean BMI of patient were  $20.35\pm2.9$  lower than baseline ( $p<0.00$ ). BMI was relative constant after eight session of acupuncture ( $20.25\pm3.1$ ,  $p>0.00$ ) (Fig. 1).

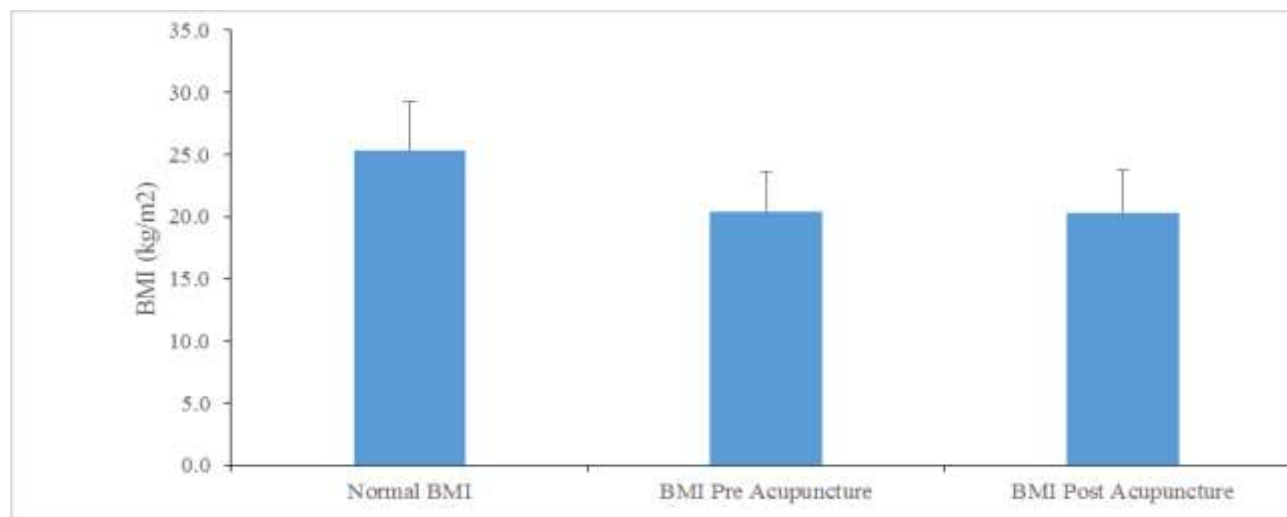


Fig.1: Relative change in normal BMI, pre acupuncture and after eight session of acupuncture. M±SD, n=7

### The Effect of Acupuncture in Fat-Free Mass (FFM)

Fat-free mass refers to all body components except fat. Therefore, we use subtraction of fat from total body mass to determine fat-free mass (FFM). In this study, measure FFMI to know the relation muscle mass to height and weight. In our study, FFM after eight session

of acupuncture was decrease 0.4% ( $p>0.00$ ) than before acupuncture. Its mean, FFM in this study have constant value. This study indicate acupuncture for eight session could maintain fat-free mass or lean body mass in breast cancer patient with cachexia. Therefore acupuncture can maintain the metabolic activity and prevent progression and severity of cachexia.

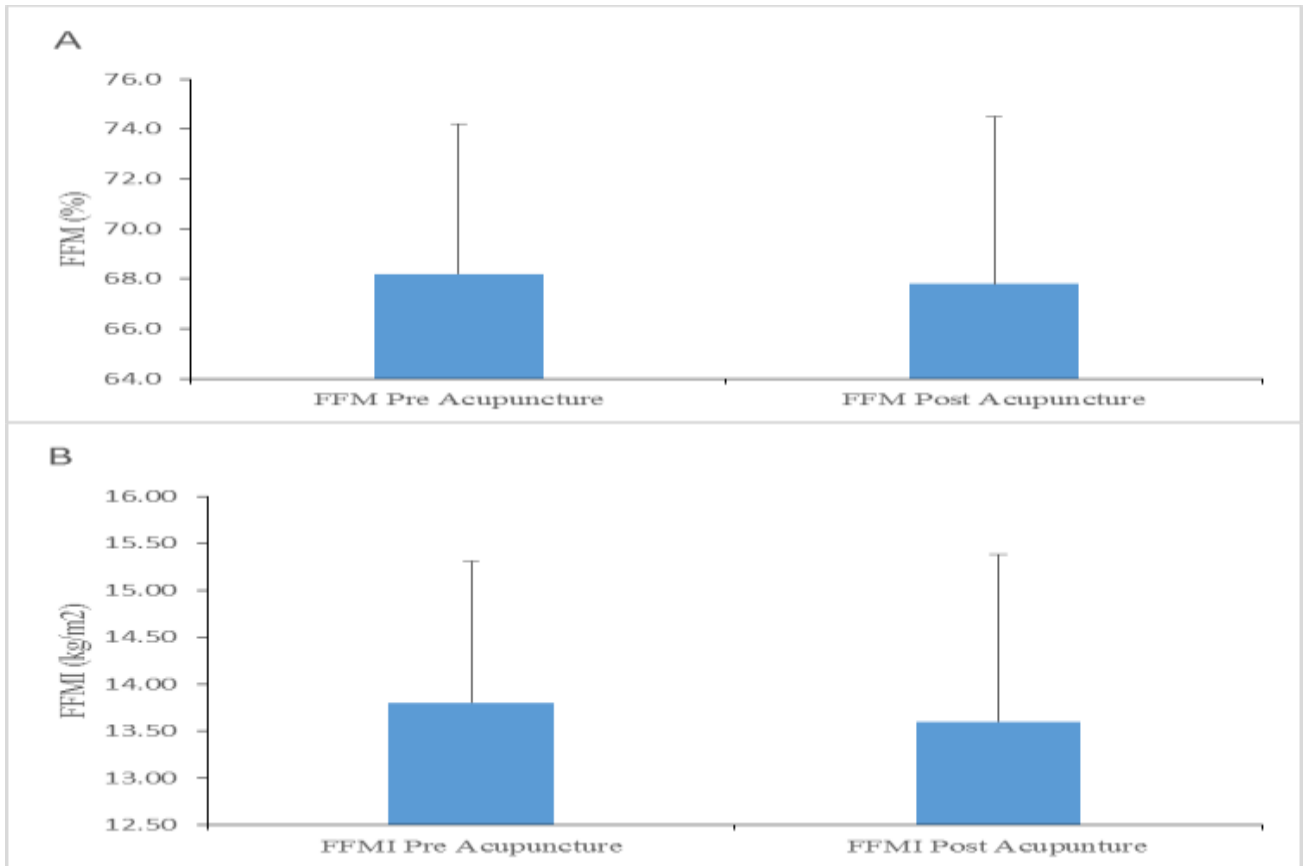


Fig. 2: Percentage fat-free mass (FFM) and fat-free mass index (FFMI) pre and post acupuncture (A) Relative change (in %) FFM pre and post acupuncture, (B) Relative change FFMI pre and post acupuncture

### The Effect of Acupuncture in Fat Mass (FM)

In this study, measurement of fat mass with BIA to estimate body adiposity of breast

cancer patient with cachexia. Percentage of fat mass in this study decrease 0.4% ( $p>0.00$ ) after eight session of acupuncture.

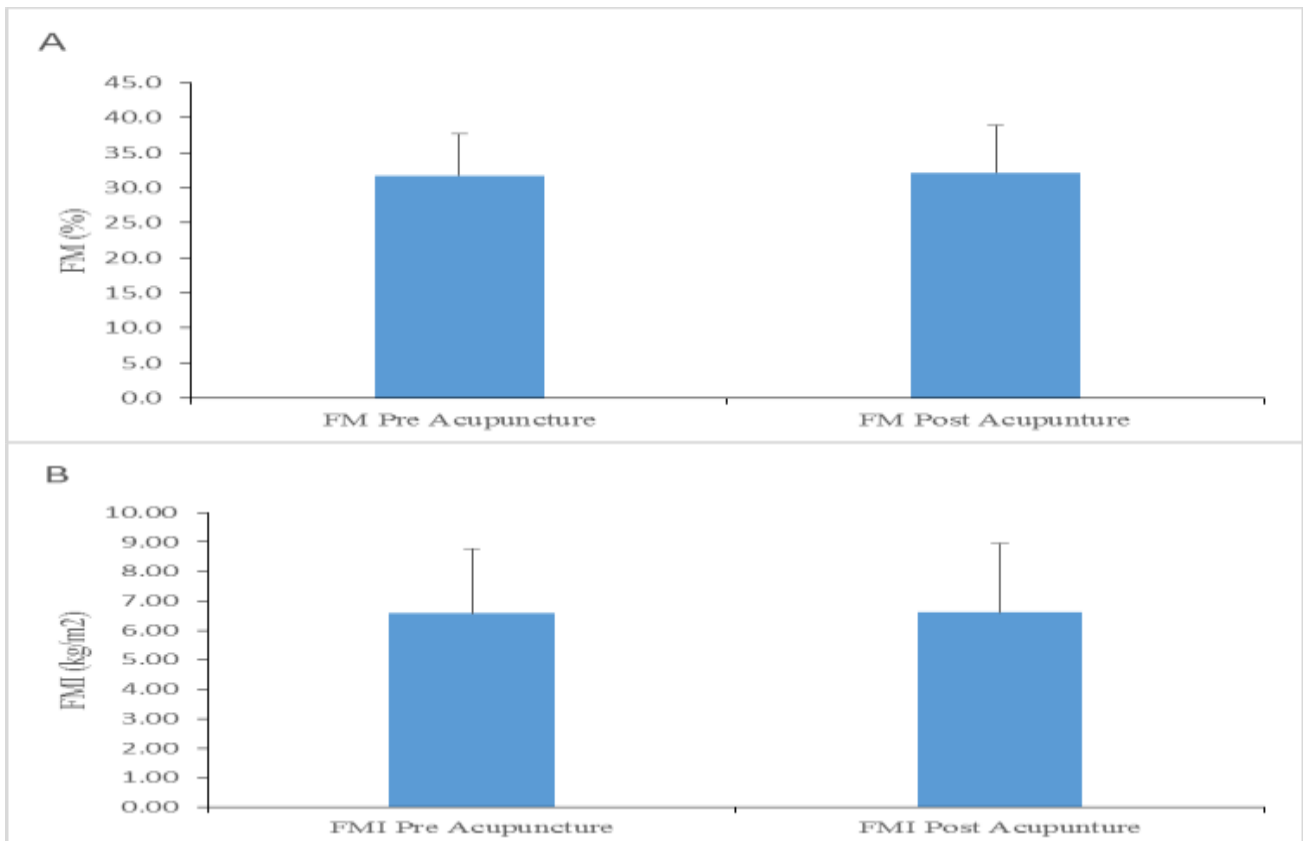


Fig. 3: Percentage fat mass (FM) and fat mass index (FMI) pre and post acupuncture (A) Relative change (in %) FM pre and post acupuncture, (B) Relative change FMI pre and post acupuncture

## Discussion

The result of this study indicate that acupuncture is well tolerate and feasible in patients breast cancer with cachexia; indeed there is no negative side effect based on researcher's observation and also subjective from patients during the intervention period. This is study that investigates the effect acupuncture to body composition in breast cancer patient with cachexia. Same factors contributing cachexia are elevated energy expenditure, decreased food intake and alterations circulating levels of hormones including insulin, leptin and catecholamine.

High energy demand due to progression of cancer as well as elevated catabolism and produce inflammatory mediators also contributing factors in cachexia [13]. This study showed that acupuncture procedure can prevent progression and severity of breast cancer cachexia. In this study, there are 3 patients (43%) had Critical weight loss (CWL), BMI<21.5 patients (71%) and FFMI<15 for 5 patients (71%). After eight session of acupuncture, patient had weight loss only 0.57% than body weight before acupuncture. Similarly with body weight, BMI in previous six month ( $25.3 \pm 3.6$ ) dramatic decrease ( $20.4 \pm 2.9$ ,  $p < 0.05$ ) in start of study and could be maintain after eight session of acupuncture ( $20.25 \pm 3.1$ ,  $p > 0.05$ ).

Relative constant change of BMI in patient show in Figure 1. In this study body weight and BMI were no increase in patient with acupuncture, but the average weight loss was only 0.57%, which is less than average weight loss of 1.3% in previous study about the effect acupuncture in GI tract [14] and 5% in patient with palliative chemotherapy [15]. Critical weight loss that occurs in previous 6 month before this study may as a result of the process of diseases. Most of patients showed that 71.43% of all patients had last stages of the disease and metastasis.

Loss of appetite most experience in breast cancer patients that cause food intake disorder [16]. In this study show FAACT score increase during intervention, indicate nutritional status to be better during intervention. In this study improvement of nutritional status cause maintain quantity of nutrition but still not enough to increasing body weight and BMI. Study in gastrointestinal tract, acupuncture is feasible to improve appetite and slow weight loss.

Physiologically, acupuncture inhibit  $\alpha$ -MSH, decrease cortisol levels, improved GI motility, decrease of pro inflammatory cytokines and increased opioid peptides. Therefore acupuncture benefit to increased appetite, higher caloric intake, and weight gain [17]. In cachexia, there are condition that FFM was decrease, its stimulate presence of elevated or abnormal fat mass (FM). The condition of low FFM and elevated FM may led higher risk for metabolic syndrome, cardiovascular disease and decrease physical functioning [18].

In this study, FFM lightly decrease only 0.4% or remained at relative constant levels throughout the intervention period, indicating metabolic activity not deteriorate along intervention. Similarly, FFM remained stable for acupuncture group in gastrointestinal tract cancer at the end of the study in another study [19]. Lowering FFM in cancer cachexia indicates that pro inflammatory cascade use proteins to maintaining muscle mass [15]. In this study acupuncture maintained FFM in breast cancer patients with cachexia (figure 2A), indicate acupuncture prevent the progression of muscle wasting. However, mechanism of acupuncture in muscle wasting in human was very limited.

Previous study in mice, acupuncture with low frequency electrical stimulations (Acu-LFES) stimulated the expression inflammatory cytokines (IL-6, TNF- $\alpha$  and TNF- $\gamma$ ) in normal and denervation muscle. Production of the muscle-specific microRNAs miR-1 and miR-206 was increase; indicate acupuncture with low electrical stimulations effective in counteracting denervation-induced skeletal muscle atrophy and increasing muscle regeneration [20]. Another study, Electro acupuncture in mice prevented the muscle atrophy by IGF-1/AKT pathway and myostatin gene expression [21].

Previous study in 28 cachectic patients reported that IL-6 was the only cytokine measured was elevated in all patients and the increased IL-6 levels always experience in patients as they approached death [22]. Acupuncture signal from acupuncture point was transmission via afferent vagus nerve to brain. Thus, acupuncture stimulates release of ACTH from the brain to activating humoral anti-inflammatory pathway. Acupuncture also decreasing pro inflammatory (TNF, IL-1 $\beta$ , IL-6, and IL-18)

and increasing anti-inflammatory (IL-10) cytokines to controlling the anti-inflammatory response [8]. Study in human proved that level of TNF- $\alpha$  in serum of healthy women is very low, but levels would increase in breast cancer patients. Where low levels of TNF- $\alpha$  present in the serum of women who experience breast cell hyperplasia and begin to increase in the serum of women with primary breast cancer [23]. In studies of animals liver cancer with cachexia, it was found that TNF- $\alpha$  receptors in skeletal muscle and adipose tissue have increased and is associated with muscle wasting during tumor development [24].

Studies in inflammatory rat models found an effect of acupuncture on the levels of TNF- $\alpha$  cytokines in serum. Manual acupuncture for 30 minutes at the ST36 point after 60 minutes induction of lipopolysaccharide (LPS), indicate reduction of TNF- $\alpha$  levels in serum in the treatment group compared to the control group [11]. FFMI is predictor mortality was stronger than BMI. Low BMI not increases mortality risk beyond depressed of FFMI.

In women, cachexia is defined as a BMI<21 and an FFMI<.15; semi starvation is defined as a BMI<21 and an FFMI $\geq$ .15; muscle atrophy is defined as a BMI $\geq$  and FFMI<.15; and no impairment is defined as a BMI $\geq$ 21 and an FFMI $\geq$ .15 [25]. BMI alone cannot provide information about the respective contribution of FFM or fat mass to body weight [26]. At the start of this study, patients had average FFMI 13.8 $\pm$ 1.51 and after eight session acupuncture, FFMI 13.6 $\pm$ 1.78. Relative change FFMI in this study show in Figure 2B.

The decreasing value of FFMI in this study may cause of disease progression, most of patient in advance stage and metastasis and skeletal wasting that has been going on for a long time. In another study had reported patients with Critical weight loss (CWL) and normal FFMI were not increased one year mortality risk, but patients with CWL and low FFMI had increases mortality risk.

## References

1. Tuca A, Jimenez-Fonseca P, Gascón P (2013) Clinical evaluation and optimal management of cancer cachexia. *Critical Reviews in Oncology/Hematology*, 88(3): 625-636.

Mortality risk also increased in patients with combination of CWL, high BMI/low FFMI but not in CWL, high BMI and high FFMI. The patient in CWL condition if weight loss >5% in previous month or >10% in previous six moth. That condition can be explained by the fact that patients with a low BMI and low FFMI are already depleted in energy and protein reserves [27]. Fat loss is associated with reduced adipocytes tissue that occurs in both visceral and subcutaneous depots. Fat loss in cancer caused from increased lipolysis and fat oxidation, impaired lipogenesis and lipid deposit. Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ), and interleukin-1 beta (IL-1 $\beta$ ) is inflammatory cytokines contributed to depleting of adipose in cachexia [28].

In this study, the level of FM was slight more than normal level (25-30%) before acupuncture (31.7%  $\pm$ 5.9) and after acupuncture (32.1% $\pm$ 6.7). Relative change of FM and FMI in patient was show in figure 3. The slight level of FM and FMI in this study may cause intake nutrition especially protein in patient less than needed for their metabolism. Another study was showed that in cachexia and sarcopenia was potential to obesity sarcopenia, it mean percentage fat mass was increase but percentage fat-free mass was decrease [25].

## Conclusion

Present no effective therapy against to cancer cachexia. Acupuncture could maintain BMI and body composition mean acupuncture could maintain metabolism in breast cancer patients. Constant body weight, BMI, FM and FFM after acupuncture in this study indicated that acupuncture could prevent cachexia progression.

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2. Barton MK (2017) Cancer cachexia awareness, diagnosis, and treatment are lacking among oncology providers. *CA: Cancer Journal for Clinicians*, 67(2): 91-92.

3. Tsoli M, Robertson G (2013) Cancer cachexia: Malignant inflammation, tumorkines, and metabolic mayhem. *Trends in Endocrinology & Metabolism*, 24(4): 174-183.
4. Fox K M, Brooks J M, Gandra S R, Markus R, Chiou CF (2009) Estimation of Cachexia among Cancer Patients Based on Four Definitions. *Journal of Oncology*.
5. Consul N, Guo X, Coker C, Lopez-Pintado S, Hibshoosh H, Zhao B, Acharyya S (2016) Monitoring Metastasis and Cachexia in a Patient with Breast Cancer: A Case Study. *Clinical Medicine Insights. Oncology*, 10: 83-94.
6. Adams M, Jewell AP (2007) The use of complementary and alternative medicine by cancer patients. *International Seminars in Surgical Oncology*, 4: 10.
7. Liao G S, Apaya M K, Shyur L F (2013) Herbal Medicine and Acupuncture for Breast Cancer Palliative Care and Adjuvant Therapy. *Evidence-Based Complementary and Alternative Medicine*, e437-948.
8. Kavoussi B, Ross B E (2007) The neuroimmune basis of anti-inflammatory acupuncture. *Integrative Cancer Therapies*, 6(3): 251-257.
9. Panagiotis Z, Vasileios G, Anastasios V, Konstantinos S, Georgios V, Stamatios T, Dimitrios R (2017) Acupuncture Treatment for Allergic Rhinitis: Why should Physicians Recommend it? *Journal of Clinical & Experimental Neuroimmunology*, 2(1): 1-4.
10. Zijlstra F J, van den Berg-de Lange I, Huygen F J P M, Klein J (2003) Anti-inflammatory actions of acupuncture [Research article].
11. Lim H D, Kim M H, Lee C Y, Namgung U (2016) Anti-Inflammatory Effects of Acupuncture Stimulation via the Vagus Nerve., *PLOS ONE*, 11(3): e0151-882.
12. Xiao J, Purcell S A, Prado C M, Gonzalez M C (2018) Fat mass to fat-free mass ratio reference values from NHANES III using bioelectrical impedance analysis. *Clinical Nutrition*, 37(6): 2284-2287.
13. Tisdale M J (2002) Cachexia in cancer patients. *Nature Reviews. Cancer*, 2(11): 862-871.
14. Grundmann O, Yoon S L, Williams JJ (2015) Influence of acupuncture on bioelectrical impedance measures in patients with gastrointestinal cancer: Results of a pilot study. *Acupuncture in Medicine: Journal of the British Medical Acupuncture Society*, 33(1): 16-22.
15. Buskermolen S, Langius JAE, Kruijenga H M, Ligthart-Melis GC, Heymans M W, Verheul H M W (2012) Weight loss of 5% or more predicts loss of fat-free mass during palliative chemotherapy in patients with advanced cancer: A pilot study. *Nutrition and Cancer*, 64(6): 826-832.
16. Solheim T S, Blum D, Fayers P M, Hjermstad M J, Stene G B, Strasser F, Kaasa S (2014) Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: Three peas in a pod? - Analysis from a multicenter cross sectional study. *Acta Oncologica (Stockholm, Sweden)*, 53(4): 539-546.
17. Yoon S L, Grundmann O, Williams J J, Carriere G (2015) Novel intervention with acupuncture for anorexia and cachexia in patients with gastrointestinal tract cancers: A feasibility study. *Oncology Nursing Forum*, 42(2): E102-109.
18. Prado C M M, Wells J C K, Smith S R, Stephan B C M, Siervo M (2012) Sarcopenic obesity: A Critical appraisal of the current evidence. *Clinical Nutrition.*, 31(5): 583-601.
19. Grundmann O, Yoon S L, Williams J J, Gordan L, George T J (2019) Augmentation of Cancer Cachexia Components With Targeted Acupuncture in Patients With Gastrointestinal Cancers: A Randomized Controlled Pilot Study. *Integrative Cancer Therapies*, 18.
20. Su Z, Hu L, Cheng J, Klein J D, Hassounah F, Cai H, Wang X H (2016) Acupuncture plus low-frequency electrical stimulation (Acu-LFES) attenuates denervation-induced muscle atrophy. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 120(4): 426-436.
21. Takaoka Y, Ohta M, Sugano A (2011) Molecular Evidence: EA May Inhibit the Muscle Atrophy. *Acupuncture - Clinical Practice, Particular Techniques and Special Issues*.
22. Iwase S, Murakami T, Saito Y, Nakagawa K (2004) Steep elevation of blood

- interleukin-6 (IL-6) associated only with late stages of cachexia in cancer patients. *European Cytokine Network*, 15(4): 312-316.
23. Martinez-Reza I, Diaz L, Garcia-Becerra R (2017) Preclinical and clinical aspects of TNF- $\alpha$  and its receptors TNFR1 and TNFR2 in breast cancer. *Journal of Biomed Science*, 22: 90
  24. Figueras M, Busquets S, Carbó N, Almendro V, Argilés JM, López-Soriano FJ (2005) Cancer cachexia results in an increase in TNF-alpha receptor gene expression in both skeletal muscle and adipose tissue. *International Journals of Oncology*, 27(3):855-860.
  25. Schols A M, Broekhuizen R, Weling-Scheepers C A, Wouters E F (2005) Body composition and mortality in chronic obstructive pulmonary disease. *The American Journal of Clinical Nutrition*, 82(1): 53-59.
  26. Kyle U G, Schutz Y, Dupertuis Y M, Pichard C (2003) Body composition interpretation. Contributions of the fat-free mass index and the body fat mass index. *Nutrition (Burbank, Los Angeles County, Calif.)*, 19(7-8): 597-604.
  27. De van der Schueren M A E, de Smoker M, Leistra E, Kruizenga H M (2018) The association of weight loss with one-year mortality in hospital patients, stratified by BMI and FFMI subgroups. *Clinical Nutrition (Edinburgh, Scotland)*, 37(5): 1518-1525.
  28. Ebadi M, Mazurak V C (2014) Evidence and Mechanisms of Fat Depletion in Cancer. *Nutrients*, 6(11): 5280-5297.