Original Article:

Profile of Cachexia Parameters and Dietary Intakes in Advanced Stage of Nasopharyngeal Cancer Patients: Study inThree Hospitals in Semarang, Central Java, Indonesia

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Abstract

Background: Nasopharyngeal cancer (NPC) patients have high risk of cachexia. It is important to notice cachexia parameters in the beginning of their treatment in order to predict and anticipate unexpected outcomes. This study aimed to describe the profile of advanced stage NPC patient receiving first chemotherapy, especially in cachexia parameters and dietary intakes. ***Methods*:** A cross-sectional study was conducted involving advanced stage of NPC patients who would receive their first chemotherapy aged 20-70 years. Subjects with distant metastatic, acute infection, history of past chemotherapy or radiotherapy, were excluded. Parameters of cachexia being studied were inflammation markers (NLR and CRP level), anorexia and fatigue scores, body composition (fat and muscle mass) and hand grip strength (HGS), meanwhile dietary intakes were energy and protein. Frequency distribution, descriptive statistic, and Pearson correlation test were used in data analyses. ***Results*:** Forty-three subjects were participated. Average age was48.1±9.8 years old and 63% were males. NLR and CRP level were high, i.e.4.8±5.0 and 13.3±20.6 mg/dL, respectively. Anorexia and fatigue scores were 32.4±9 and 35.9±11.8, respectively, with 70% subjects were anorexic and 30% subjects experienced severe fatigue. Less than 20% were malnourished but 35% subjects had central obesity and 37% subjects classified to have very high fat mass. Most subjects had low muscle mass (77%) and classified to have weak HGS (77%). Energy and protein intakes were 26.7±8.9 kcal/kgBW/d and 1±0.4 g/kg BW/d respectively. Some variables had strong correlation (r≥0.80), i.e. BMI with visceral fat (r=0.94), fat with muscle mass (r=-0.89), energy with protein intakes (r=0.80), and moderate correlation (r=0.60–0.79) between anorexia and fatigue scores. ***Conclusions****:* Advanced stage of NPC patients receiving first chemotherapy had high inflammation status, anorexia and fatigue. Many subjects had low muscle mass and weak HGS. BMI with visceral fat, fat with muscle mass, energy with protein intake, were strongly correlated.

Keywords: cachexia; nasopharyngeal cancer; chemotherapy; dietary intake; Indonesia.

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of the nasopharyngeal epithelium with a relative low frequency in the world (0.1 per 100,000 population per year)[1], more common in men (ratio 2.3:1) with the highest population in Southeast

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Asia (age-standardized rates [ASR] 6.4 for men, 2.4 for women) and in Polynesia, East Asia, and South Africa where rates are above 2 for men and 1 for women[2]. In Europe and the United States the incidence of NPC is around 0.5 – 2 per 100,000. However, in South China, Southeast Asia, North Africa and Alaska, the incidence is 30 – 80 cases per 100,000[1]. In Indonesia, research conducted at RSUP dr. Cipto Mangunkusumo (RSCM) Jakarta, of all head and neck cancers treated between 2000-2005, the prevalence of NPC was around 28.35% (948 of 3344), with a male: female ratio of 2.4:1 (70.4% male and female). 29.6% women)[3]. The most frequent malignancy (>90%) occurring in the head and neck region is squamous cell carcinoma, which is the seventh most malignant cancer worldwide[4]. In 2012, there were an estimated 51,000 deaths due to NPC, which constituted 0.6% of all cancer deaths[2].

Head and neck cancer (HNC), including NPC, is one of the 4 cancers most at risk for cachexia. Other cancers are upper gastrointestinal, lung, and prostate cancers[5]. Cachexia is not always present in all malnourished patients, but all cachexia patients are malnourished. Cancer cachexia is a multifactorial metabolic syndrome associated with underlying malignancy. Its main characteristics is negative energy balance resulting from decreased appetite, weight loss, metabolic changes (increased lipolysis, proteolysis, resting energy expenditure and insulin resistance), and increased inflammatory status that can originate from the host or tumor itself. Clinically, patients with cachexia lose fat tissue, skeletal muscle mass and function, resulting in weight loss. Furthermore, cancer cachexia is associated with decreased quality of life, toxicity due to the treatment, reduced treatment response, and poor prognosis[4,6,7]. Therefore, it is necessary to recognize early on the condition of NPC patients at the beginning of therapy so that clinicians can have strategies and can anticipate the worse condition, then therapy would be successful.

In our knowledge, there was no publication yet that specifically explained about the profile of advanced stage NPC patients who will do their first cycle of chemotherapy in Indonesia. Therefore this study aimed to describe the profile of advanced stage NPC patient undergoing chemotherapy for the first time in some cachexia parameters, which were NLR, CRP level, anorexia and fatigue scores, body composition (fat mass and muscle mass) and hand grip strength (HGS), as well as dietary intake (energy and protein intakes). Furthermore, the correlation between two numeric variables were analyzed.

Material and Methods

Design and study population

This cross-sectional study was carried out in 3 hospitals which have chemotherapy facilities. Forty three advanced stage of NPC patients in aged 20-70 years gave consent to be the subject of this study. All the patients were hospitalized and beginning to receive their first chemotherapy. Subjects with distant metastatic, acute infection, history of past chemotherapy or radiotherapy program were excluded.

Demographic characteristic, cachexia parameters, and nutrition intakes

The demographic characteristics included age, gender, and race were collected from medical record. Status inflammation indicators were neutrophil lymphocyte ratio (NLR) and C-reactive protein (CRP), also collected from medical record.

The anthropometric measurements included height, middle upper arm circumference (MUAC), waist circumference (WC) and calf circumference (CC). Height was measured were using stature-meter and recorded to the nearest 0.5 cm. The remaining anthropometrics measurements assessed using non-elastic measuring tape and recorded to the nearest 0.1 cm. MUAC was measured in the non-dominant arm. The midpoint was between acromion and olecranon, with bended position at 90° angle, then the circumference was measured with arm hanged free (180° angle) in the body side. To measure WC, the subject stood upright with feet apart shoulder width, then the inspector measured participants' the midpoint of lower end of the last rib and the upper ridge of the iliac crest. CC was measured when subject in sitting position and hold the foot down with leg folded to 90° angle. With a tape measure, the circumference of the calf at its widest point.

Weight and body composition (% body fat and fat free mass) were assessed with Karada Scan Omron® HBF-375. The subject stepped on the main unit, stand with the knees and the back straight, and extended the arms straight horizontally at a 90° angle of the body. The result would be displayed automatically and recorded manually.

Anorexia and fatigue scores were assessed with the Functional Assessment of Anorexia/Cachexia Therapy-Anorexia/Cachexia Subscale (FAACT-A/

CS) and the Functional Assessment of Chronic Illness Therapy (FACIT-F) questionnaires, respectively. Anorexia questionnaire has 12 items with range score 0-48, meanwhile fatigue questionnaire has 13 items with range score 0-52. The higher the score the better the condition. Participants were asked according to their real condition for each item in the questionnaires during the past 7 days.

Functional capacity indicator was hand grip strength (HGS) measured using dynamometer Camry® EH-101. The participants were asked to apply the maximum grip strength three times for their left and right hands individually. The participants were instructed to hold the grip continuously with full force for more than 3 second. At least 30 second of rest was allowed between each measurement. Hand grip strength was defined as the maximally measured value among the six measurements in both hands.

All measurements above were conducted by clinical nutrition physicians, except for laboratory analyses, and dietary intakes were collected with food frequency questionnaire (FFQ) and calculated using Nutrisurvey® software by dietisiens.

Statistical analysis

Data were analyzed and presented with frequency distribution and descriptive statistic to show the profile of the subjects, and Pearson correlation test to analyze some numeric variables, using software of IBM SPSS Statistics 25.

Ethical clearance

The study was approved by the Health Ethics Committee of Sultan Agung Islamic Hospital and dr. Kariadi Hospital with approval ref: 02/EC/KEPK/2020 and 541/EC/KEPK-RSDK/2020, respectively. Written informed consent was obtained from all the participants after explaining the study procedures.

Results

During period April 2020 until July 2021, 43 subjects who met inclusion and exclusion criteria were participated. General characteristics and dietary intakes of the subjects were presented in **Table 1**. More than a half of the subject were males and average age was 48.1±9.8 years old. Anthropometric measurements results show that most of the subject within normal range of BMI and without central obesity or normal visceral fat. More than two-third of the subjects had better hemoglobin level (>11 mg/dL). Energy and protein intakes were displayed in total intake per day and per kilogram body weight per day.

Table 1. General characteristics of the subjects

Variable	n (%)	Mean	SD	Range (min. – max.)
Gender				
- Males	27 (63)			
- Females	16 (37)			
Age (years)		48.1	9.8	21 – 68
Race: Javanese	43 (100)			
Anthropometric measurements				
Height (cm)		157.83	8.0	142 – 175
Weight (kg)		56.2	15.7	29.1 – 99.2
Body mass index (kg/m^2)				
- Malnutrition (<18,5)	8 (19)			
- Normal (18.5 – 22.9)	19 (44)	22.4	5.1	12.9 – 36.4
- Overweight (23 – 24.9)	6 (14)			
- Obese (≥25)	10 (23)			
Mid upper arm circumference (cm)		26.3	4.7	16 – 36
Waist circumference[a] (cm)				
- Non central obese	28 (65)	79.8	14.0	50 – 115
- Central obese	15 (35)			
Calf circumference (cm)		31.7	5.3	21 – 46
Laboratory test				
Hemoglobin level (g/dL)				
- Non-anemia (>11 mg/dL)	36 (84)	12.6	1.5	8.9 – 15.5
- Anemia (≤11 g/dL)	7 (16)			
Dietary intakes				
Energy (kcal/day)		1442.2	440.6	503 – 2302
- Energy (kcal/kgBW/day)		26.7	8.8	10.8 – 45.1
Protein (g/day)		55.4	24.7	14.6 – 137
- Protein (g/kgBW/day)		1.0	0.4	0.31 – 2.2

SD Standard deviation;[a]Waistcircumference ≥80 cm for females or ≥90 cm for males was classified as central obese

Table 2 shows some cachexia parameters of the subjects. The subjectshad high level of CRP (≥3.0 mg/L) and NLR 4.8±5.0, as inflammation markers. About two-third subjects were anorexic and 30% subjects experienced severe fatigue. Body composition result showed that more than one-third of the subjects had very high fat mass and more than 75% subject had low muscle mass. Moreover, more than 75% of the subjects had weak HGS.

Table 2. Cachexia parameters of the subjects

Variable	n (%)	Mean	SD	Range (min. – max.)
Laboratory test				
Neutrophil Lymphocyte Ratio (NLR)		4.8	5.0	1.03 – 25.17
CRP level (mg/L)				
- Normal (<3 mg/L)	14 (33)	13.3	20.6	0.6 – 84.3
- High (≥3 mg/L)	29 (67)			
Anorexia score				
- Non-anorexia (>37)	13 (30)	32.4	9.0	14 – 48
- Anorexia (≤37)	30 (70)			
Fatigue score				
- Non severe fatigue (≥30)	30 (70)	35.9	11.8	12 – 52
- Severe fatigue (<30)	13 (30)			
Body composition measurements				
Fat mass[a] (%)				
- Low	6 (14)			
- Normal	11 (26)	25.4	9.2	5.8 – 43.3
- High	10 (23)			
- Very high	16 (37)			
Visceral fat				
- Normal (0.5 – 9.5)	31 (72)			
- High (10.0 – 14.5)	6 (14)	7.5	6.1	0.5 – 26.5
- Very high (15.0 – 30.0)	6 (14)			
Muscle mass[b] (%)				
- Low	33 (77)			
- Normal	7 (16)	28.0	4.2	20.4 – 38.4
- High	1 (2)			
- Very high	2 (5)			
Hand Grip Strength[b] (kg)				
- Weak	33 (77)	23.3	8.7	10.6 – 48.1
- Normal	10 (23)			

SD Standard deviation;[a]Fat mass and muscle mass were classified according to their gender; [b]HGSwas classified according to subject's gender and age

Table 3 shows that some variables had strong correlation (r≥0.80), i.e.BMI with visceral fat (r=0.94), fat mass with muscle mass (r=-0.89), energy with protein intake (r=0.80), and moderate correlation (r=0.60–0.79), i.e. between anorexia and fatigue scores, meanwhile other variables were low and very low correlation (r=0.4–0.59 and r<0.40, respectively).

Discussions

According to our results in Table 1, all the subjects were Javanese with more males than females (1.7 times), and the mean age was 48.1±9.8. It is similar to the 2012 publication by Adham*et al.* Males are about 2.6 times more than females, and the age group of 41-50 years dominates as much as 69%, although they mentioned that other studies refiled that the age group was 50-60 years. Some studies found different results could be explained by three factors that cause NPC, i.e. genetic susceptibility, early exposure to chemical carcinogens, and latent Epstein Barr Virus (EBV) infection[3].

The inflammatory status of the subjects increased as indicated by NLR > 3.441[8] and CRP > 3 mg/L[9]. Several previous studies have shown that a higher NLR has a lower prognostic value, although with different cut-offs for NLR, e.g. 2.25[10]; 2.28[11]; 3.441[8]; and 3.6[9]. Similarly for CRP, high CRP has a worse prognostic value than low CRP[9]. The laboratory used a cut-off of 3, while some references in the meta-analysis used a higher cut-off. Amano *et al.* divided into 4 groups: low CRP (< 1mg/L), moderate CRP (1-<5 mg/L), high CRP (5 - <10 mg/L), and very high CRP (≥10 mg/L)[12], and our CRP results was very high, 13.3±20.6 mg/L.

The mechanism by which elevated NLR is associated with poor prognosis remains unclear. Neutrophils, an inflammatory cell type, are involved in various stages of tumor development through the production of various cytokines, such as oncoctatin M, hepatocyte growth factor, and transforming growth factor (TGF)-β. In addition, neutrophils stimulate tumor angiogenesis through the release of angiogenic factors, such as vascular endothelial growth factor (VEGF), angiopoietin-1, and fibroblast growth factor-2. On the other hand, lymphocytes are also responsible for immune surveillance in eliminating tumor cells. The involvement of lymphocytes, such as T cells, in tumor infiltration is associated with a better prognosis and has also been used as a therapeutic target. Therefore NLR can impact the tumor microenvironment and immune system to influence the survival of NPC patients[11].

Cancer cachexia is experienced by most patients with advanced cancer. Proinflammatory cytokines play an important role in the mechanism of cachexia, and cancer cells may depend on them for growth, protection from apoptosis, and stimulating angiogenesis/metastasis. Thus, inflammatory cytokines stimulate chronic systemic inflammation and CRP synthesis in hepatocytes, resulting in elevated CRP levels, although it is not known whether the increased CRP is produced by the tumor,

Table 3. Correlation matrix of selected study variables

	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	1											
2. BMI	0.02 (0.89)	1										
3. NLR	-0.03 (0.83)	-0.10 0.52	1									
4. CRP	0.02 (0.92)	-0.05 (0.76)	-0.02 (0.92)	1								
5. Anorexia score	-0.26 (0.10)	0.32* (0.03)	-0.23 (0.15)	-0.06 (0.73)	1							
6. Fatigue score	-0.23 (0.14)	0.45** (0.00)	-0.21 (0.17)	-0.24 (0.13)	0.61** (0.00)	1						
7. Fat mass	0.16 (0.31)	0.43** (0.00)	-0.03 (0.86)	0.32* (0.04)	0.20 (0.20)	0.04 (0.81)	1					
8. Visceral fat	0.12 (0.43)	0.94** (0.00)	-0.07 (0.68)	-0.04 (0.78)	0.27 (0.82)	0.41** (0.01)	0.35* (0.02)	1				
9. Muscle mass	-0.15 (0.33)	-0.25 (0.10)	-0.06 (0.73)	-0.17 (0.27)	-0.07 (0.67)	0.09 (0.57)	-.89** (0.00)	-0.13 (0.40)	1			
10. Energy intake	-0.26 (0.10)	-0.49** (0.00)	-0.09 (0.55)	-0.22 (0.16)	0.20 (0.20)	-0.03 (0.83)	-0.42** (0.01)	-0.44** (0.00)	0.34* (0.03)	1		
11. Protein intake	-0.03 (0.87)	-0.26 (0.10)	-0.07 (0.65)	-0.39* (0.01)	0.20 (0.21)	0.12 (0.45)	-0.30 (0.06)	-0.18 (0.26)	0.26 (0.09)	0.80** (0.00)	1	
12. HGS	-0.11 (0.48)	0.33* (0.03)	-0.09 (0.56)	-0.19 (0.23)	0.20 (0.191)	0.40** (0.01)	-0.21 (0.187)	0.38* (0.013)	0.40** (0.01)	-0.02 (0.92)	0.17 (0.29)	1

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

the liver, or both. CRP levels can reflect the degree of cancer cachexia and be a prognostic marker in advanced cancer[12].

Anorexia is frequently suffered by cancer patients caused by various factors, both peripheral and central. Peripheral mechanisms can include several aspects, including (a) tumors that cause dysphagia or directly affect digestive function; (b) tumors that produce substances that alter food intake, e.g. lactate, tryptophan, or parathormone-associated peptides; (c) tumors that lead to changes in nutrients that can cause anorexia, e.g. zinc; (d) tumors that produce inflammation and cause the release of cytokines. Peripherally, chemotherapy can alter taste perception and cause nausea, vomiting, mucositis, abdominal cramps, bleeding, and ileus. Central mechanism describes that the main cause of anorexia can be depression, pain, or changes in central neurotransmitters. The neurotransmitter changes in depression leading to anorexia appear to be reflected in changes by serotonin and corticotrophin releasing factor. Characteristics of this disorder include fatigue, weakness, social withdrawal, drowsiness, sadness, lack of motivation, hyperalgesia, failure to concentrate, and anorexia. Hypoxia is thought to cause anorexia in patients with HNC[13].Research conducted by Blauwhoff-Buskermolen*et al.* using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire to assess anorexia in cancer patients stated that the cut off was 37[14]. In this study, 70% subjects had anorexia score ≤37.

Cancer-related fatigue is defined as a persistent and subjective sense of stressful or pressure that the patient feels in the form of physical, emotional, and/or cognitive fatigue, which is associated with cancer or cancer therapy and not proportional to current activity and affects daily functioning[15]. Several factors that contribute to fatigue, such as the production of inflammatory cytokines, changes in muscle metabolism, sleep disturbances, stress, and depression[16]. This study used the FACIT-F questionnaire which states that a score <30 (range 0-52) indicates severe fatigue[17] and 30% subjects of this study complained on severe fatigue. Other study in lung cancer also complaining on fatigue as the fourth top symptom[18]. Table 3 show a moderate correlation between anorexia and fatigue (r=0.61, p<0.001). This study is similar with previous study by Yennurajalingam *et al.* withr=0.29 (p<0.001). They found that fatigue was associated with anxiety,

anorexia, drowsiness, and feelings of well-being in advanced cancer patients, but no association between fatigue and age or gender[19]. Fatigue also had correlation with pain, sleep disturbance, sadness, and stage of the cancer[18].

Previous studies have shown that 70% of weight loss in HNC patients is associated with lean body mass or fat free mass (FFM). Loss of FFM is an important prognostic factor, which can affect therapeutic toxicity, risk of recurrence and mortality, decreased muscle strength and physical activity, and functional performance. These show that in HNC patients, a decrease in FFM can provide additional and relevant information as a predictor of outcome, in addition to weight loss alone, even in high or low BMI, including patients with sarcopenic obesity. Sarcopenia is characterized by low muscle strength or low physical activity performance, which may be particularly prominent in patients with HNC. Low FFM has an impact on the incidence of complications, length of hospital stay, and low survival. Weight loss alone cannot predict a decrease in FFM, so it is important to evaluate body composition in HNC patients[20]. In this study, according to their gender and age, 77% subjects had low muscle mass and 77% subjects had low hand grip strength. This is similar to the research conducted by Kowshik*et al.* in India who found that the HGS of HNC patients was lower than that of healthy people. This low HGS is related to body composition parameters, such as body fat percentage and muscle percentage[21]. Steemburgo *et al.* also stated that hospitalized cancer patients have low functional capacity. The dynamometer for the measurement of HGS is a useful tool for evaluating functional capacity and low nutritional status, and can be included when evaluating cancer patients with other nutritional assessment instruments[22]. HGS is also used to evaluate muscle function in cancer patients which is an early sign of malnutrition and can be an outcome variable in nutritional intervention studies[23].

Our result found that BMI was correlated with visceral fat and fat mass was inversely correlated with muscle mass, the higher fat mass the lower muscle mass (Table 3). With the increase of obesity in HNC population, many cancer patients may have BMI within or above normal range though they lose their weight and experience muscle wasting. Patient who has combination of sarcopenia and obesity has worse prognosis and higher risk of chemotherapy-related adverse effects. Therefore, body composition assessment is recommended to guide clinical decision making and chemotherapy dosing[20].

Table 2 shows that the energy and protein intakes of the subjects in this study were relatively sufficient, i.e., 26.7±8.8 kcal/kgBW and 1.0±0.4 g/kgBW, respectively. The energy intake recommended by the European Society in Enteral and Parenteral Nutrition (ESPEN) for cancer patients is 25-30 kcal/kg/day while protein intake is 1-1.5 g/kg/day[7]. However, total intakes of energy and protein of the subjects, i.e. 1442.2±440.6 kcal and 55.4±24.7 g are lower than to RDA for Indonesian, i.e. 1550-2650 kcal and 58-65 g, respectively[24]. Our results similar with previous study in HNC patients. It is difficult for cancer patients to meet recommended intakes, unless they consume fortified foods[25].

In 2017 de Vries *et al.* found that dietary intake in breast cancer patients before receiving chemotherapy was relatively the same as in women without cancer, but diet intake decreased after patients received chemotherapy[26]. Other study in HNC patients showed that average daily energy and protein intake significantly decreased from baseline to post-treatment[25]. Chemotherapy-induced symptoms, such as a subjective taste perception, appetite and hunger, and experiencing a dry mouth, difficulty chewing, lack of energy and nausea, are associated with lower dietary intake. Therefore it is important to monitor nutritional status and symptom burden during chemotherapy to ensure an optimal dietary intake during cemotherapy in cancer patients[26].

Energy intake has strong correlation with protein intake (Table 3), the higher energy intake the higher protein intake. Energy and protein intake can affect the clinical outcome of cancer patients. Hsieh *et al.* conducted a retrospective study to determine nutritional status and clinical outcomes based on energy intake after nutritional recommendations were made. They classified cancer patients based on their dietary intake, whether less (<50% of the recommendation), moderate (50-79%), or adequate (≥80%). They concluded that cancer patients who met moderate energy intake (50-79%) for at least 28 days could limit weight loss and improve nutritional status and clinical outcomes[27]. Weight loss in cancer patients depends on a combination of inadequate dietary intake and metabolic imbalance. In HNC patients, including NPC, inadequate dietary intake is associated with various symptoms, including dysphagia, odynophagia, and anorexia, which can lead to weight loss. During cancer therapy, such as

chemotherapy, radiotherapy, or a combination of both, the development of mucositis, xerostomia, dysphagia, dysgeusia, and depression can lead to decreased dietary intake, weight loss, and 20% of patients withdraw from therapy[28].

This study has described the profile of advanced NPC cancer patients in the first time they are receiving chemotherapy in Indonesia that have not been reported. We also found some correlations among variables. Unfortunately there was no information about weight loss which is very useful as one of indicators cachexia[5]. We also missed some micronutrients that may have role in improving cancer, e.g. vitamin D[29], Zn[13].

Conclusions and Recommendations

Advanced stage of NPC patients receiving first chemotherapy were found to have high inflammation status, anorexia and fatigue, low muscle mass and weak HGS. Energy and protein intakes were adequate according to ESPEN guidelines. Likewise, some variables, i.e. BMI and visceral fat, fat and muscle mass, energy and protein intake, anorexia and fatigue score were significantly correlated.

Regarding to the result from this study, in clinical application, it is advisable that all NPC patients should be referred to clinical nutrition physician to have dietary counselling as early as possible before they start their cancer treatment, in order to reduce their inflammation status and to improve nutrients intakes, especially those which anti-inflammation or antioxidant properties. Further studies to investigate the progress of the patients during treatment program, or the influencing factors of clinical outcomes (survival rate, prognosis, quality of life, etc.), are warranted. In addition, some nutrients markers in the blood that related to cancer development and progression need to be studied since they are more precise than nutrients intakes.

Authorship Contributions:

MF, HWS, S, SF, YWP, NM made contributions to the conception and design of the study

S and YWP provided clinical guidance

MF conducted the data analysis with supported from HWS, SF, and NM

MF, HY, and SP conducted the study in each hospital

HWS, SF, NM made substantial contributions to the interpretation of the findings

All authors contributed to drafting and revising the manuscript for intellectual content, and approved the final version for submission.

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