Association Between Nutritional Status and Neutrophil Lymphocyte Ratio in Patients with Lung Cancer at Persahabatan Hospital, Indonesia

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Abstract

Context: Systemic inflammation in patients with lung cancer can be seen by the increase of neutrophil lymphocyte ratio (NLR) where these examinations are common in hospitals. Systemic inflammation can cause anorexia resulting in decreased nutrition intake of patients with lung cancer and affecting their nutritional status. One of the diagnostics of nutritional status for patients with lung cancer is using the American Society for Parenteral and Enteral Nutrition (ASPEN) criteria that consist of decreased nutritional intake, weight loss, decreased muscle mass and subcutaneous fat mass, general or local fluid accumulation, and functional capacity. Malnutrition can be diagnosed if there are two of the six criteria. **Aims:** The study aims to determine the relationship between nutritional status and NLR in patients with lung cancer at Persahabatan Hospital in East Jakarta, Indonesia. **Settings and Design:** This cross-sectional study included 52 patients with lung cancer in oncology outpatient clinic of Persahabatan Hospital. **Methods and Material:** Data of characteristics subject were taken from interviews, physical examinations, laboratory analysis, and patients medical records in the oncology outpatient clinic of Persahabatan Hospital. Statistical analysis used chi-square or Fisher exact test to assess relationship between nutritional status and NLR ($P < 0.05$). **Results:** Based on nutrient intake, more than 50% of the subjects had low energy and protein intake. Based on patient generated subjective global assessment, 38.5% of subjects were at risk of malnutrition or moderate malnutrition, while 67.3% of them were malnutrition based on ASPEN. There was no statistically significant association between nutritional status and NLR ($P = 0.35$). **Conclusions:** There was no association between nutritional status and NLR, and so further research with larger samples is needed.

Keywords: Lung cancers, malnutrition, neutrophil lymphocyte ratio, nutritional status, systemic inflammation

Key Messages: NLR is a laboratory assessment that is commonly used in hospitals and can be used to see nutritional status in patients with lung cancer so that with proper nutrition management the incidence of malnutrition in patients with lung cancer can be prevented.

INTRODUCTION

Lung cancer is the dominant cause of mortality worldwide for both males and females. Based on the data from Global Burden of Cancer (Globocan) in 2020, the mortality rate of lung cancer was in the first position (18%), followed by liver cancer (8.3%), gastric cancer (7.7%), breast cancer (6.9 %), and colon cancer (5.8%) throughout the world. In Indonesia, a total of 34,783 people were diagnosed with lung cancer and it was in the third position after breast and cervical cancer.[1] The research conducted by Komalawati in 2016 stated that the number of patients with lung cancer at Persahabatan Hospital in 2013 was 616 and it increased to 880 people in 2014.[2] A delayed diagnosed of lung cancer stages is the main cause of the

Access this article online	
Quick Response Code:	**Website:** www.ijnpnd.com
	DOI: 10.4103/ijnpnd.ijnpnd_16_21

increased of mortality rate for patients with lung cancer. Commonly, patients are diagnosed at the III-1V of its stage.[3]

Chronic systemic inflammation often occurs in patients with lung cancer. Pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin 1 (IL-1), IL-6, play a central role in the inflammatory process. To detect the presence of inflammation, it can be done by calculating the neutrophil lymphocyte ratio (NLR).[4] Neutrophils are active nonspecific mediator that trigger the body's protective response, while lymphocytes are a protective component of inflammation. Neutrophil counts will increase and lymphocyte counts will decrease in responding to the body's inflammation.[5]

High NLR in patients with lung cancer can be the indicator of inflammation that will affect nutritional status. This occurs because systemic inflammation can cause anorexia, thereby reducing the food intake. Furthermore, if it is not being treated, it will affect malnutrition.[5] Patients with lung cancer can be categorized as one of the groups with the highest prevalence of malnutrition.[6] In a longitudinal prospective study about the prevalence of malnutrition of patients who come to Australian oncology clinics before chemotherapy or radiotherapy treatment, 69% of patients with lung cancer had malnutrition, higher than patients with colorectal cancer (57%) or head and neck cancer (45%). Hébuterne *et al*.[7] found a 45% overall rate of malnutrition in inpatients with lung cancer.

The nutritional status is assessed based on clinical, physical, and anthropometric, as well as laboratory, examinations. Diagnosis of malnutrition may be made by the criteria of American Society for Parenteral and Enteral Nutrition (ASPEN), which consists of inadequate energy intake, weight loss, decreased subcutaneous fat mass, decreased muscle mass, local or general fluid accumulation, and functional status assessed by using hand grip strength. Malnutrition can be diagnosed if there are two of the six criteria.[8]

The association between nutritional status and NLR has attracted the interest in recent years for its routine and readily available test. Tan *et al*. stated that there was a positive relationship between malnutrition in cancer patients based on the results of the patient generated subjective global assessment (PG-SGA) and NLR.[9]

Prior research discussed more about the relationship between prognosis and NLR of patients with lung cancer. However, topic about the relationship between nutritional status and NLR is still limited. This study aims to identify nutritional status of patients with lung cancer that is linked to inflammatory status by using NLR.

SUBJECTS AND METHODS

Study participants

This cross-sectional study with consecutive sampling method was conducted from August 2020 to October 2020 at Persahabatan Hospital. This study had received approval from the Dr Cipto Mangunkusomo Hospital Faculty of Medicine Universitas Indonesia ethical committee (KET-174/UN2.F1/ETIK/PPM.00.02/2020) and Persahabatan Hospital ethical committee (78/KEPK-RSUPP/7/2020). The research consisted of 52 subjects. The patients were able to stand, primary lung cancer stage III-IV, males and females, 40 to 65 years old, and were willing to participate in the study by signing the informed consent. Subjects with the additional diseases such as diabetes mellitus, infection, steroids consumed, chronic heart disease, and immunodeficiency diseases were excluded.

Interview of subjects

Subjects were interviewed by using the subject characteristics, food intake, screening for malnutrition by using PG-SGA, and status therapy.

Dietary intake

Dietary data were collected from each participant using validated semiquantitative food frequency questionnaire (SQ-FFQ) for the intake of energy and protein over the past 1 month. It is analyzed by using NutriSurvey 2007.

Nutrition status examination

Nutrition status examination consisted of history taking of weight loss and physical examination including weighing by using SECA 876 digital weighing scale to nearest 0.1 kg, examination of subcutaneous fat in the orbital area, upper arm circumference (triceps and biceps), chest and back area (ribs, lower back, midaxillary line), examination of muscle mass in temples (*m.temporalis*), clavicle bone area (*m.pectoralis major*, deltoid, *m.trapezius*), clavicle and acromion (*m.deltoid*), scapular area (*m.trapezius, m.supraspinus, m.infraspinus*), back of hands (*m.interosseous*), knees, upper thighs, calves, fluid accumulation (see the presence or absence of oedema), as well as examination of grip strength by using the Jamar dynamometer.

Laboratory analysis

Complete peripheral blood test is carried out to determine NLR. The result is categorized into high NLR (NLR >3.0) and low NLR (NLR <3.0).[5]

Statistical analysis

To assess association between subject characteristics with nutritional status and association between nutritional status with NLR using Chi-square or Fisher exact test with The Statistical Package for the Social Sciences (SPSS) version 20.1. The result states that there is a significant relationship if $P < 0.05$.

RESULTS

Characteristics of the subjects in this study include age, gender, smoking status, smoking rate, energy and protein

Table 1: Subject characteristics

Parameter	Results N = 52	<50 years old	15 (28.8)
50-60 years old	20 (38.5)		
>60 years old	17 (2.7)		
Gender, *n* (%)			
Male	32 (61.5)		
Female	20 (38.5)		
Smoking status, *n* (%)			
Active smoker	3 (5.8)		
Former Smoker	29 (55.8)		
Passive Smoker	18 (34.6)		
Nonsmoker	2 (3.8)		
Smoking degree, *n* (%)			
Heavy smoker (≥600 cigarettes)	16 (30.8)		
Medium smoker (200–599 cigarettes)	12 (23.1)		
Light smoker (<200 cigarettes)	4 (7.7)		
Energy intake, *n* (%)			
Low <25 kcal/kg (body weight)	43 (82.7)		
Normal 25-30 kcal/kg ((body weight)	9 (17.3)		
Over >30 kcal/kg (body weight)	0 (0)		
Protein intake, *n* (%)			
Low <1 g/kg (body weight)	42 (80.8)		
Normal 1-1.5 g/kg (body weight)	10 (19.2)		
Over >1 g/kg (body weight)	0 (0)		
PGSGA score, *n* (%)			
Stage C severe malnourished	15 (28.8)		
Stage B moderate malnourished	20 (38.5)		
Stage A well nourished	17 (32.7)		
Therapy status, *n* (%)			
Without therapy With therapy	10 (19.2)42 (80.8)		

PGSGA, patient-generated subjective global assessment.

Table 2: Incidence of malnutrition at Persahabatan Hospital

Nutritional status	Result
Malnourished, *n* (%)	35 (67.5)
Well nourished, *n* (%)	17 (32.5)

intake, PG-SGA screening, and therapy status. The data can be seen in Table 1.

Patients with lung cancer who were willing to participate in this study consisted of 61.5% men and 38.5% women, and the most common age range was 50 to 60 years. As many as 55.8% of subjects are former smokers and 30.8% cancer patients were former heavy smokers.

In this study, 61.5% of subjects had low energy intake based on European Society for Clinical Nutrition and Metabolism (ESPEN) recommendation, which is less than 25 kcal/body weight per day. For protein intake, it showed 69.2% of subjects were less than 1 g/kg body weight per day. Based

on screening by using PG-SGA, 38.5% subjects were found at risk of malnutrition or moderate malnutrition, while 28.8% had severe malnutrition.

As for this study, there were 10 new patients diagnosed with a therapy plan and 42 patients were being treated with oral chemotherapy or intravenous chemotherapy. The visits of lung cancer patients to the oncology clinic at the Persahabatan Hospital have been decreasing due to the coronavirus (COVID-19) pandemic. This study found that 67.5% of subjects had malnutrition [Table 2].

Table 3 showed subject characteristics based on nutritional status. There was no significant association between age, gender, smoking status, smoking degree, and protein intake with nutritional status in this study ($P = 0.647$, $P = 0.476$, $P = 0.797$, $P = P.072$, $P = 0.076$, respectively). Otherwise there was significant association between energy intake, PG-SGA, and therapeutic status with nutritional status ($P = 0.001$, $P < 0.001$, $P = 0.02$, respectively).

We found that there was no significant association between nutritional status and NLR in patients with lung cancer ($P = 0.35$) [Table 4].

DISCUSSION

In this study, the biggest age range was between 50 and 60 years. These results almost similar to the data from Burhan *et al*.[10] showed that 57% incidence of lung cancer at Persahabatan Hospital from 2015 to 2016 had the highest number of cases in the age range of 40 to 60 years old. Middle-aged people are susceptible to cancer due to the accumulation of cancer risk factors that cause genetic and epigenetic mutations.

In this study, patients with lung cancer were mostly males, which were 61.5%. This is in line with the research conducted by Sholih *et al*.[11] and Pierzynski,[12] which stated that the incidence rates of lung cancer based on gender were 76.7% and 53.46%, respectively, in males. It is assumed that men tend to have a previous smoking history in which smoking is one of the main factors of having lung cancer.[13] 55.8% of patients with lung cancer were former smokers. In line with the study conducted by Pierzynski,[12] 63.8% of patients with lung cancer had a history of smoking. The risk of lung cancer increases with the duration of smoking.[13] Among the subjects in this study, 30.8% had a heavy Brinkman index in line with the research conducted by Burhan *et al*.[10] at Persahabatan Hospital, which stated that as many as 33.7% of patients with lung cancer had a heavy Brinkman index.

Table 3: Characteristics of subjects based on nutritional status

Parameter	Nutritional status		P value
	Malnourished	Well nourished	
Age, n (%)			0.647
<50 years old	11 (73.3)	4 (26.7)	
50-60 years old	14 (70.0)	6 (30.0)	
>60 years old	10 (64.7)	7 (35.3)	
Gender, n (%)			0.476
Male	20 (62.5)	12 (35.5)	
Female	15 (75.0)	5 (25.0)	
Smoking status, n (%)			0.797
Active smoker	2 (66.7)	1 (33.3)	
Former smoker	19 (65.5)	10 (34.5)	
Passive smoker	12 (66.7)	6 (33.3)	
Nonsmoker	2 (100.0)	0 (0.0)	
Smoking degree, n (%)			0.072
Heavy smoker (≥600 cigarettes)	9 (56.2)	7 (43.8)	
Medium smoker (200–599 cigarettes)	11 (91.7)	1 (8.3)	
Light smoker (<200 cigarettes)	2 (50.0)	2 (50.0)	
Energy intake, n (%)			0.001*
Low <25 kcal/kg (body weight)	27 (84.4)	5 (15.6)	
Normal 25-30 kcal/kg ((body weight)	8 (40.0)	12 (60.0)	
High >30 kcal/kg (body weight)	0 (0.0)	0 (0.0)	
Protein intake, n (%)			0.076
Low <1 g/kg (body weight)	27 (75.0)	9 (25.0)	
Normal 1-1.5 g/kg (body weight)	8 (50.0)	8 (50.0)	
High >1 g/kg (body weight)	0 (0.0)	0 (0.0)	
PGSGA score, n (%)			<0.001*
Stage C severe malnourished	15 (100.0)	0 (0.0)	
Stage B moderate malnourished	20 (100.0)	0 (0.0)	
Stage A well nourished	0 (0.0)	17 (100.0)	
Therapy status, n (%)			
Without therapy	10 (100.0)	0 (0.0)	
With therapy	25 (59.5)	17 (40.5)	0.021*

PGSGA, patient-generated subjective global assessment. *The association is considered to be significant if $P < 0.05$ (there is a significant association).

Table 4: Association between nutritional status and neutrophil lymphocyte ratio

Nutritional status	Neutrophil lymphocyte ratio		P value
	High (>3)	Low (<3)	
Malnourished, n (%)	15 (42.9)	20 (57.1)	0.35
Well nourished, n (%)	5 (29.4)	12 (70.6)	

Energy intake based on ESPEN recommendation is 25 kcal/kg body weight per day until 30 kcal/kg body weight per day.[14] Low energy intake in lung cancer patient can be caused by systemic inflammation that can affect metabolism, suppressing the hunger center in the arcuate hypothalamus nucleus, which result in anorexia and decreased intake. Previous study at Dharmais Hospital with 49 patients with lung cancer showed that 53.1% of them had low energy intake.[15] Protein intake based on ESPEN was 1 to 2 g/kg/day.[14] For protein intake, this study showed that 69.2% of patients with lung cancer were less than 1 g/kg/day. The same thing is also found in research conducted by Amanda[15] at Dharmais Hospital, 42.9% of their protein intake were less than 1 g/kg/day. The lack of protein intake in this study was because the subjects did not know how much protein should have been consumed according to their needs.

In this study, 38.5% of our respondents were in the moderate malnutrition category or at risk of malnutrition. Supported by Silva *et al*.[16] which had a cross-sectional study in Brazil on all types of cancer, figuring out of 32 patients with lung cancer, 17.3% had been screened by using PG-SGA were in the moderate malnutrition category or at risk of malnutrition and 10.1% of the patients were in the category of severe malnutrition. A study conducted in China by Ge *et al*.[17] found that of 495 patients with advanced lung cancer, 264 (53.3%) needed nutritional support.

Nutritional status in this study is assessed based on ASPEN criteria, consisting of weight loss, energy intake, subcutaneous fat, muscle mass, local/general fluid

accumulation, and functional status (grip strength). Malnutrition can be seen if there are two of the six criteria. It is found that 67.5% of patients with lung cancer who were the subjects of this study had malnutrition. Based on another study, the prevalence of malnutrition in lung cancer was 45% to 69%.[6] Malnutrition of patients with lung cancer affects the clinical condition, decreases quality of life, decreases functional status, and effects the prognosis. Appropriate and fast nutritional therapies are expected to improve the quality of life of patients with lung cancer.

There was no significant result between age and nutritional status ($P = 0.866$). This result is different from the research conducted by Silva *et al*.,[16] which found that there was a significant relationship between age and nutritional status of patients with lung cancer. The difference in results can be attributed to different criteria for malnutrition. In a study conducted by Silva *et al*.,[16] the criteria for malnutrition are based on WHO criteria [using body mass index (BMI)]. Diagnosis of malnutrition using body mass index does not assess weight loss, only uses actual weight. For gender, no significant relationship with nutritional status ($P = 0.476$) toward patients was found. This is in line with a study conducted at the University of Pennsylvania Hospital by Hudson *et al*..[18] There was no significant connection between gender and nutritional status ($P = 0.1355$) of all inpatients from 2013 to 2015. This occurred because both males and females had the same risk of malnutrition. Another study conducted by Silva *et al*.[16] found a significant relationship ($P < 0.05$) between smoking status and malnutrition. In contrast to this study, there was no significant relationship between smoking status and nutritional status. This is because of the homogeneous data on the distribution of smoking status of patients.

Malnutrition in cancer patients can occur due to anorexia as well as metabolic and endocrine changes due to tumor factors and inflammatory cytokines produced by cancer cells or host or due to chemotherapy effects such as nausea, vomiting, dry mouth, greening disorders, and it can also be due to the effects of cancer itself. Cancer cells stimulate the release of inflammatory cytokines so as to stimulate the effects of satiety in the central nervous system, result in reduced feeding intake, and can lead to malnutrition.[19-21] Research conducted by Darmawan and Adriani[22] on cancer patients at Dr. Ramelan Hospital Surabaya revealed that there is a significant association between energy intake and nutritional status ($P = 0.024$). In this study, 75% of subjects were malnourished with protein intake less than 1 g/kg/day, but there was no significant relationship with nutritional status ($P = 0.076$). This occurred because in case of the subjects who were well nourished, their protein intake were assessed by the SQ-FFQ below 1 g/kg/day.

In this study, there is a significant relationship between patient-generated subjective global assessment (PGSGA) and nutritional status ($P < 0.001$). This is in line with the study conducted by Ge *et al*.[17] in China in which there was a significant relationship between PGSGA and nutritional status ($P < 0.001$) in 495 patients with lung cancer. This indicates the importance of screening so that patients who are at risk of malnutrition would be immediately given the nutritional therapy, both counselling and other nutritional therapies. Nutritional therapy, which is done earlier, can affect overall survival.

In this study, there was a significant relationship between therapeutic status and nutritional status ($P = 0.02$). Kiss *et al*.[23] found that out of 207 patients with lung cancer, 33% were malnourished prior to therapy, which increased to 50% after treatment. Malnutrition that occurs in patients who are being treated is from the side effect of the therapy itself. The side effects of chemotherapy that often occur and affect the nutritional status are nausea and vomiting. Chemotherapy causes the release of neurotransmitters such as dopamine, serotonin, and substance P that send signals through the chemoreceptor trigger zone in the postrema area to the vomiting center.[21]

This study showed that there was no association between nutritional status and NLR in patients with lung cancer. This result is different from the study conducted by Pessanha *et al*.[5] in 87 patients with gastrointestinal cancer in which it was found that there was a relationship between nutritional status assessed based on weight loss, NRI, and SGA with NLR ($P=0.002$, $P=0.001$, and $P=0.009$). Weight loss categorized as weight loss in >10% for 6 months and ≤10% for 6 months, nutrition risk index (NRI) and screening by using SGA with NLR of patients ($P = 0.002$, $P = 0.001$, and $P = 0.009$). Weight loss is one of the diagnostic criteria for malnutrition based on ASPEN. In this study, there was no significant relationship between weight loss and the value of NLR. This is stated, probably, because the total patients in this study had weight loss of >10% or ≤10% for 6 months, not as many as in the study conducted by Pessanha *et al*.[5] NRI is a nutritional status screening that is assessed based on serum albumin and body mass index, but does not assess food intake, weight loss, or physical and functional status examinations that allows a different diagnosis of nutritional status. In the screening with the SGA method, the components of the examination are not as complete as the examination of nutritional status by using ASPEN criteria. In ASPEN, there is an examination of functional capacity by assessing grip strength and there is an assessment of intake as well, and so those patients screened using SGA are not malnourished. However, based on the ASPEN criteria, there is an examination of grip strength and intake assessment can be diagnosed with malnutrition.

In previous studies, there was linking of nutritional status to the NLR conducted in cancer patients who had not received therapy. In this study, the patients being treated have a NLR value below three. However, malnutrition occurred due to the side effect of the therapy itself. Neutrophils release cytokines

and chemokines that play a role in the growth and proliferation of tumor cells and the spread of tumor cells (metastasis), while the lymphocytes have a role to press cancer cells and prevent the spread of cancer cells. In a study conducted by Lee *et al*.,[24] there were 199 patients with lung cancer who received chemotherapy, the decrease in the NLR after having a therapy, where there was a decrease also in the number of neutrophils, and an increase in the number of lymphocytes was attributed to a good tumor response and an effect on the survival of patients with lung cancer. The decrease in inflammatory response, as seen from the decrease in the NLR, shows the shrinkage of cancer cells as well as the success of therapy and the sensitivity of it.

Anticancer therapy aims to press neutrophil activity by suppressing chemokine receptors (CXCR2), which plays a role in the spread of cancer. The suppression of CXCR2 and CXCR1 activity is able to influence the clinical state of cancer. In addition, cancer therapy aims to inhibit IL-23 and IL-17, which stimulate the increase in neutrophils mediated by granulocyte-colony stimulating factor (G-CSF). G-CSF plays a role in the maturation of neutrophils.[25] Taken together, neutrophil is an important indicator for anticancer therapy.

There are strengths of this study. This study assessed food intake using SQ-FFQ method so that it can examine the usual intake of the subject and diagnostic malnutrition using ASPEN criteria is more detail than using WHO criteria based on body mass index, which has more often been used in other studies. However, this study had a limitation, which was the length of therapy for patients with lung cancer. In this study, it varied considerably and it could affect the result of the study.

CONCLUSION

There was no significant association between nutritional status and NLR in patients with lung cancer at Persahabatan Hospital. Therefore, it is necessary to conduct a similar study with the criteria for diagnosis of malnutrition by using ASPEN with a larger number of samples of pre-treatment cancer patients, which can affect the NLR.

Acknowledgement

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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