Prognostic Nutritional Index (PNI*)* as a Prognostic Factor in Stage IV Lung Adenocarcinoma

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ABSTRACT

Background. Based on nutritional and immunological indicators, the Prognostic Nutritional Index (PNI) is one of the prognostic indicators besides the Platelet-to-Lymphocyte Ratio (PLR) and Glasgow Prognostic Score (GPS). PNI can serve as a biomarker to help guide clinical practice and promote clinical outcomes for lung cancer patients. PNI was superior to Neutrophil- to- Lymphocyte Ratio (NLR) in the prediction of progression-free survival (PFS) and overall survival (OS).
Objectives. To analyze the association between a low PNI score (PNI <40) and increased risk of mortality among stage IV pulmonary adenocarcinoma patients.
Methods. A cohort-retrospective study was performed by extracting PNI data from medical records and the mortality of patients with stage IV pulmonary adenocarcinoma. A total of 265 patients met the inclusion and exclusion criteria, based on the medical records of patients with stage IV pulmonary adenocarcinoma who were hospitalized at Dr. Sardjito hospital Yogyakarta between January 1st, 2016 and July 1st, 2019. PNI score were calculated as follows: 10 x serum albumin (g/dl) + 0.005 x lymphocyte count (per $mm^{3)}$. Mortality was considered six months since the diagnosis. Chi-square tests were used to analyze the proportions of mortality and confounders. Multiple logistic regression tests were used to analyze the association between PNI and mortality.
Results. Subjects with PNI score <40 were at risk of mortality three times higher than subjects with PNI score ≥40 (adjusted OR 3.356, 95% CI 1.165 - 9.670, p = 0.025).
Conclusion. PNI score significantly affected the mortality in patients with stage IV pulmonary adenocarcinoma.

Keywords. PNI (Prognostic Nutritional Index), pulmonary adenocarcinoma, mortality

Abstrak

Latar Belakang. *Berdasarkan indikator gizi dan imunologi,* Prognostic Nutritional Index *(PNI) merupakan salah satu indikator prognostik selain* Platelet-to-Lymphocyte Ratio *(PLR) dan* Glasgow Prognostic Score *(GPS). PNI dapat berfungsi sebagai biomarker panduan dalam praktik klinis dan meningkatkan perbaikan luaran klinis untuk pasien kanker paru-paru. PNI lebih unggul dari* Neutrophil-to-Lymphocyte Ratio *(NLR) dalam memprediksi* progression-free survival *(PFS) dan kelangsungan hidup secara keseluruhan (*overall survival/*OS.)*
Tujuan Penelitian. *Penelitian ini bertujuan untuk menganalisis hubungan antara nilai PNI yang rendah (PNI<40) dengan peningkatan risiko mortalitas pasien kanker paru adenokarsinoma stadium IV.*
Metode. *Penelitian ini dilakukan dengan metode kohort retrospektif, dengan melihat data status PNI di catatan medis dan kemudian menghitung mortalitas pasien kanker paru adenokarsinoma stadium IV. Jumlah sampel penelitian ini sebanyak 265 yang telah memenuhi kriteria inklusi dan eksklusi, diambil dari catatan medis pasien adenokarsinoma paru stadium IV yang dirawat di RSUP dr. Sardjito Yogyakarta kurun waktu 1 Januari 2016 – 1 Juli 2019. Nilai PNI dihitung dengan rumus 10 x serum albumin (g/dl) + 0,005 x angka limfosit (per mm^3). Data mortalitas dihitung 6 bulan sejak tegak diagnosis. Uji statistik dengan Chi-Square digunakan untuk menganalisis beda proporsi mortalitas dan variabel pengganggu. Uji regresi logistik multipel digunakan untuk menganalisis keeratan hubungan antara PNI dengan mortalitas.*
Hasil. *Subyek yang memiliki skor PNI < 40 berisiko mengalami kematian 3 kali dari subjek yang memiliki skor PNI ≥40 (*adjusted OR *3,356, 95% CI 1,165-9,670, nilai p = 0,025).*
Kesimpulan. *Skor PNI terbukti berpengaruh secara bermakna terhadap prognosis mortalitas pada pasien kanker paru jenis adenokarsinoma stadium IV.*

Kata Kunci. *PNI (*Prognostic Nutritional Index*), adenokarsinoma paru, mortalitas*

Introduction

The prognosis of lung cancer depends primarily on the disease stage. Approximately 75% of lung cancer patients die due to thoracic complications, 25% due to extrathoracic complications, and 2% died from central nervous system disorders. Nearly 40% of adenocarcinoma and large cell carcinoma patients die from thoracic complications, 55% due to extra thoracic complications, 15% metastasize to the brain, 8-9% die from central nervous system abnormalities. The average life expectancy of patients with metastatic tumors varies from 6 months to 1 year.

Studies of potential prognostic biomarkers in lung cancers are an ongoing field. Several nutritional and immunological indices, such as Prognostic Nutritional Index (PNI), Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), and Glasgow Prognostic Score (GPS), have been developed as means to predict the outcome of cancer patients and to determine the optimal treatments. Of these nutritional and immunological-based indices, PNI is frequently used.[1] Other potential biomarkers are Systemic Inflammatory Index (SII), Advanced Lung Index (ALI), and Lymphocyte-to-Monocyte Ratio (LMR).

Two components of the PNI calculation are albumin and lymphocytes. Albumin is a marker of estimated protein content and has been frequently used to measure nutritional status. Lymphocytes play an important role in cellular immunity in various cancers, and inflammation is also critical for cancer progression. The immune response against tumor depends on lymphocytes; thus, a low leukocyte count may predict poor survival.[2]

PNI calculation is as follows: 10 x serum albumin (g/dl) + 0.005 x lymphocyte count (per mm^3). PNI ≥50 PNI is considered normal, PNI between 45-49 mild malnutrition, PNI between 40-44 moderate malnutrition, and PNI <40 severe malnutrition.[3] Therefore, the current study used a cut-off PNI <40 and ≥40 as an independent variable.

Studies suggested low PNI scores as a prognostic factor for complications during the early postoperative period and worse long-term outcomes in various cancers, such as gastric, colorectal, and esophageal cancers. Malnutrition is a condition that is often associated with malignancy.[4]

The low PNI was significantly associated with low overall survival of NSCLC patients in a study.[5] Other studies also suggested that low PNI is associated with poor survival of advanced NSCLC patients who received EGFR-TKIs.[6]

Our study used mortality as a dependent variable. This is different from previous studies that used overall survival (OS). Mortality was used in this study since some literature suggested that mortality is more appropriate for an outcome study than overall survival.[7,8,9] We performed a study to assess PNI as a prognostic factor of mortality among patients with stage IV pulmonary adenocarcinoma.

Methods

The study was performed using a retrospective cohort design, extracting the PNI from the medical records of stage IV

adenocarcinoma patients hospitalized in Dr. Sardjito Hospital between January 1st, 2016 and July 1st, 2019. Patients who met the inclusion and exclusion criteria were recruited as subjects.

Inclusion criteria were patients with stage IV lung adenocarcinoma, ≥18 years of age, had complete baseline characteristics data (age, sex, weight, height, and performance status), complete pre-treatment supportive data (platelet count, neutrophil count, monocyte count, WBC count, albumin level), never received treatment before (chemotherapy, targeted therapy, and radiotherapy), and non-recurrent cases. Meanwhile, the exclusion criteria for the study were comorbidity of other malignancies, hematological disorder, autoimmune diseases, HIV/AIDS, and patients who refused chemotherapy.

The independent variable was the PNI value. Variable dependent was mortality, whereas age, sex, performance status, and mutation were considered potential confounders.

Results

A total of 265 subjects were recruited for the study, comprising 170 (64.2%) men and 95 (35.8%) women. The age range was 27-84 years, but the majority were ≥ 59 years old (51.3%). There were 130 (50.9%) subjects with BMI <19.42 and the rest (49.1%) had a BMI ≥19.42. Univariate analysis of other variables is presented in Table 1 below.

The 186 (70.19%) subjects had ECOG performance scores <2, and 79 (29.81%) patients had ECOG performance scores ≥ 2. Most subjects had positive mutation in the EGFR (46.4%), albumin level ≥3.14 (52.5%), platelet count ≥100.000 (94.3%), and neutrophil count ≥2,300 (94.7%). Comorbidities such as diabetes mellitus, tuberculosis, and COPD showed in 84 subjects (31.7%), and 15 (5.7%) subjects had diabetes mellitus. Of the subjects, 186 (70.19%) of them had ECOG performance scores well <2, and 79 (29.81%) patients had ECOG performance scores ≥ 2. Most subjects had positive mutation in the EGFR (46.4%), albumin level ≥3.14 (52.5%), platelet count ≥100.000 (94.3%), and neutrophil count ≥2,300 (94.7%). The 84 subjects (31.7%) of subjects had comorbidities such as diabetes mellitus (15 subjects; 5.7%), tuberculosis (36 subjects; 13.6%), and COPD (33 subjects;12.5%). However, chronic kidney failure, liver cirrhosis, and cardiac heart failure were not among the subject.

This study assessed PNI scores on all subjects. PNI scores ranged from 15.66 - 163.32 and the mean score was 39.33 ± 12.79. There were 160 people (60.4%) with PNI scores <40 and the rest (39.6%) had PNI scores ≥ 40. The purpose of the study was to assess the association between PNI scores and mortality in stage IV pulmonary adenocarcinoma patients. The subject characteristics are presented in Table 2.

Table 1. Subject Characteristics

Variables	N (%)	Mean ± SD	Median (min ; max)
Age (year old)		59.48 ± 11.24	60
< 59 years	129 (48.7)		(27 ; 84)
≥ 59 years	136 (51.3)		
Gender			
Male	170 (64.2)		
Female	95 (35.8)		
ECOG			
< 2	186 (70.19)		
≥ 2	79 (29.81)		
BMI		19.4 2 ± 3.66	19.20
< 19.42	135 (50.9)		(11.20 ; 33.30)
≥ 19.42	130 (49.1)		
Comorbidities			
Diabetes mellitus	15 (5.7)		
Tuberculosis	36 (13.6)		
COPD	33 (12.5)		
EGFR mutation			
Positive	123 (46.4)		
Negative	142 (53.6)		
Albumin level		3.14 ± 0.69	3.16
<3.14	126 (47.5)		(1.32 ; 4.61)
≥3.14	139 (52.5)		
Metastasis			
Liver	95 (35.8)		
Bone	106 (40.0)		
Brain	15 (5.7)		
Number of metastases ≤1	251 (9 4.7)		
Number of metastases >1	14 (5.3)		
Platelet count		247.11 ± 116.41	230
<100,000	15 (5.7)		(15 ; 631)
≥100,000	250 (94.3)		
The number of neutrophils		7471.40 ±	6241
<2.300	14 (5.3)	7122.01	(257 ; 88150)
≥2.300	251 (94.7)		
PNI		39.33 ± 12.79	37.83
<40	160 (60.4)		(15.66 ; 163.32)
≥40	105 (39.6)		

ECOG: Eastern Cooperative Oncology Group; BMI: Body Mass Index; COPD: Chronic Obstructive pulmonary Disease; CKD: Chronic Kidney Disease; CHF: Chronic Heart Failure; eGFR: estimated Glomerular Filtration Rate; PNI: Prognostic Nutrition Index; min: minimum; max: maximum

In the current study, 60.4% of subjects had PNI scores <40. In this group, most of them were male (61.2%) and ≥ 59 years of age (54.4%). Eighty-two (51.2%) subjects with low PNI scores had BMI <19.42. Diabetes mellitus, tuberculosis, and COPD were more prevalent in subjects with low PNI, which was found in 68 subjects (25.7%). The most common comorbidities reported in the low PNI group were tuberculosis, followed by COPD, and diabetes mellitus.

In the low PNI group, 83 subjects (51.9%) were positive for EGFR mutations and 73.8% had albumin levels <3.14. Table 26 revealed that most of the subjects in the study had platelet counts ≥ 100,000 and neutrophil counts ≥ 2,300. Only 5.7% and 5.3% of subjects had low platelet and neutrophil count, respectively. Most of them

were in the low PNI group (7.5% and 6.3%, respectively).

Metastases were also more frequent in the low PNI group. Most of the metastases were detected in bone (38.8%) followed by liver (39.4%) and brain (5.6%). As much as 5.3% of all subjects had metastases in > 1 organ.

This study assessed the effect of a low PNI score on mortality among patients with stage IV pulmonary adenocarcinoma. Further analysis was performed to identify factors that may increase the risk of mortality.

Table 2. PNI score analyses based on variables

Variables	PNI score <40 N (%)	PNI score ≥ 40 N (%)	p
Age			0.258*
≥59 y.o	73 (45.6)	56 (53.3)	
<59 y.o	87 (54.4)	49 (46.7)	
Sex			0.722*
Male	104 (65)	66 (62.9)	
Female	56 (35)	39 (37.1)	
ECOG			
≥ 2	45 (28.1)	34 (32.4)	0.459*
< 2	115 (71.9)	71 (67.6)	
BMI			
<19.42	82 (51.2)	53 (50.5)	0.902*
≥19.42	78 (48.8)	52 (49.5)	
Comorbidities			
Diabetes mellitus	8 (5)	7 (6.7)	0.894*
TB	21 (13, 1)	15 (14.3)	
COPD	20 (12.5)	13 (12.4)	
EGFR mutation			*0.028**
Positive	83 (51.9)	40 (38.1)	
Negative	77 (48.1)	65 (61.9)	
Albumin levels (g/dL)			*<0.001**
< 3.14	118 (73.8)	8 (7.6)	
≥ 3.14	42 (26.3)	97 (92.4)	
Platelet count			0.178 **
< 100,000	12 (7.5)	3 (2.9)	
≥ 100,000	148 (92.5)	102 (97.1)	
Neutrophil count			0.566 **
< 2300	10 (6.3)	4 (3.8)	
≥ 2300	150 (93.8)	101 (96.2)	
Number of metastases			0.566 **
≤ 1	150 (93.8)	101 (96.2)	
> 1	10 (6.2)	4 (3.8)	
Organ metastasis			0.481*
Liver	64 (39.4)	32 (30.5)	
Bone	62 (38.8)	44 (41.9)	
Brain	9 (5.6)	6 (5.7)	

y.o: years old; *) Chi-square test; **) Fisher exact test; significant p<0.05; ECOG: Eastern Cooperative Oncology Group; PNI: Prognostic Nutritional Index; BMI: Body Mass Index, EGFR: Epidermal Growth Factor Receptor

Table 3 shows the results of bivariate analysis between various independent variables and the outcome. Age, sex, BMI, comorbidities, metastases, platelet count, as well as neutrophil count did not significantly affect the outcome of subjects (p> 0.05). In this study, negative EGFR mutations increased the risk of mortality by 4.08 times

compared to subjects with positive EGFR mutations (p <0.001, OR (95% CI) = 4.08 (2.15 - 7.74)). ECOG ≥2 significantly increased the risk of mortality up to 2.15-fold higher than in patients with ECOG <2 (p = 0.012, OR (95% CI) = 2.15 (1, 1 7- 3.93))

PNI score significantly increased the risk of mortality. Low PNI score increased mortality risk by 6.55 times and was statistically significant (p <0.001, OR (95% CI) = 6.55 (2.84-15.11)). Age, sex, ECOG score, EGFR mutation, and liver metastasis had p <0.50 from bivariate analysis, thus these variables were considered as candidates for multivariate analysis. Multiple logistic regression with the enter method was used to find the most important variables for low PNI scores.

Table 3. Bivariate analysis of independent variables with mortality rate

Variables	Outcome (N/%)		OR (95% CI)	p
	Alive	Dead		
Age (y.o)			0.72 (0.4 -1.29)	0.263 *
≥59 years old	110 (53.1)	26 (44.8)		
<59 years old	97 (46.9)	32 (55.2)		
Sex			1.19 (0.64 -2.21)	0.579 *
Male	131 (63.3)	39 (67.2)		
Female	76 (36.6)	19 (32.8)		
ECOG			2.15 (1.17- 3.93)	0.012 *
≥ 2	54 (26.1) 153	25 (43.1)		
< 2	(73.9)	33 (56;9)		
BMI			0.88 (0.49-1.58)	0.666 *
≥19.42	103 (49.8)	27 (46.6)		
<19.42	104 (50.2)	31 (53.4)		
Comorbidities				
Diabetes mellitus	11 (5.3)	4 (6.9)	1.32 (0.41-4.31)	0.424**
Tuberculosis	32 (15.5)	4 (6.9)	0.41 (0.14-1.20)	0.093 *
COPD	29 (14.0)	4 (6.9	0.46 (0.15-1.35)	0.147 *
EGFR mutation			4.08 (2.15 - 7.74)	<0.001*
Negative	81 (39.1) 126	42 (72.4)		
Positive	(60.9)	16 (27.6)		
Albumin level			6.08 (3.04 -12.18)	<0.001 *
<3.14 g/dl	80 (38.6)	46 (79.3)		
≥3.14 g/dl	127 (61.4)	12 (20.7)		
Metastasis	196 (96.1)	55 (94.8)	0.97 (0.26-3.61)	1.000 **
1 organ	11 (5.3)	3 (5.2)		
> 1 organ				
Liver	72 (34.8)	23 (39.7)	1.23 (0.68-2.24	0.94 *
Bone	85 (41.1)	21 (36.2)	0.82 (0.45-1.49)	0.505 *
Brain	11 (5.3)	4 (6.9)	1.32 (0.40-4.31)	0.424 **
Platelet count			4.14 (0.53-32.12)	0.121 **
<100.000	14 (6.8)	1 (1.7)		
≥ 100000	193 (93.2)	57 (98.3)		
Neutrophil count			0.69 (0.21-2.27)	0.367 **
< 2300	10 (4.8)	4 (6.9)		
≥2300	197 (95.2)	54 (93.1)		
PNI			6.55 (2.84-15.11)	< 0.001*
<40	109 (52.7)	51 (87.9)		
≥40	98 (47.3)	7 (12.1)		

y.o: years old; *) Chi-square test; **)Fisher's exact test; significant p value <0.05; ECOG: Eastern Cooperative Oncology Group; PNI: Prognostic Nutritional Index; BMI: Body Mass Index; EGFR: Epidermal Growth Factor Receptor

Table 4. Multivariate analysis of PNI score

Variables	PNI score <40 (N/%)	PNI score ≥ 40 (N/%)	OR (95% CI)	p
Age (y.o)				0.186
≥59	73 (45.6)	56 (53.3)	Ref.	
<59	87 (54.4)	49 (46.7)	1.57 (0.81 -3.05).	
ECOG				0.236
≥ 2	45 (28.1)	34 (32.4)	0.64 (0.30 -1.34)	
< 2	115 (71.9)	71 (67, 6)	Ref.	
EGFR mutation				0.154
Positive	83 (51.9)	40 (38.1)	Ref.	
Negative	77 (48.1)	65 (61.9)	1.62 (0.84 - 3.14)	
Albumin level				*<0.001*
< 3.14	118 (73.8)	8 (7.6)	33.5 (14.8-75.9)	
≥ 3,14	42 (26.3)	97 (92.4)	Ref.	
Platelet count				0.601
<100,000	12 (7.5)	3 (2.9)	Ref.	
≥ 100,000	148 (92.5)	102 (97.1)	0.63 (0.11-3.57)	
Metastasis				0.489
Liver	64 (39.4)	32 (30.5)	1.29 (0.63 - 2.62)	

ECOG: Eastern Cooperative Oncology Group; PNI: Prognostic Nutritional Index; EGFR: Epidermal Growth Factor Receptor; significant p value <0.05

The results presented in Table 4 suggested that there were no variables that independently affected the PNI score except albumin level. The results of the multivariate analysis with the PNI score as a variable dependent found that albumin level <3.14 was the only variable that affected PNI score (adjusted OR = 33.5, 95% CI 14.8 - 75.9, p <0.001).

Another multivariate analysis was performed to assess the most important risk factors for mortality. Age, ECOG score, comorbidities, EGFR mutation, albumin level, platelet count, neutrophil count, liver metastasis, and brain metastasis, as well as > 1 metastases, and PNI score had p values of < 0.50, thus these variables were included in the multiple logistic regression.

The results of multivariate analysis for 6-month mortality found that ECOG, EGFR mutation, albumin level, and the PNI score had significant and independent associations with mortality. ECOG ≥2 increased the risk of 6-months mortality up to 2 folds (adjusted OR 2.262, 95% CI 1.075 - 4.757, p = 0.031). Negative EGFR mutation was associated with an increased risk of 6-months mortality up to 3-fold (adjusted OR 3.813, 95% CI 1.598-9.442, p <0.001). Meanwhile, the albumin level <3.14 was associated with an increased risk of 2-fold for 6-months mortality (adjusted OR 3.885, 95% CI 1.598 - 9.442, p = 0.003). Finally, the PNI score <40 was associated with an increased risk of 3 folds for 6-months mortality (adjusted OR 3.356, 95% CI 1.165 - 9.670, p = 0.025).

Table 5. Multivariate analyses of the outcomes

Variable	Outcome (N/%)		OR (95% CI)	p
	Alive	Dead		
Age (y.o)				0.069
< 59	97 (46.9)	32 (55.2)	Ref.	
≥ 59	110 (53.1)	26 (44.8)	0.52 (0.2 6 -1.05)	
ECOG				0.031
≥ 2	54 (26.1)	25 (43.1)	Ref.	
< 2	153 (73.9)	33 (56.9)	2.26 (1.07-4.75)	
Comorbidities				
DM	11 (5.33)	4 (6.9)	1.42 (0.31-6.44)	0.652
Tuberculosis	2 (15.52)	4 (6.9)	0.30 (0.08-1.09)	0.068
COPD	9 (14.0)	4 (6.9)	0.35 (0.10-1.28)	0.114
EGFR mutation				<0.001
Positive	126 (60.9)	16 (27.6)	Ref.	
Negative	81 (39.1)	42 (72.4)	3.81 (1.82-7.98)	
Albumin level				0.003
< 3.14	80 (38.6)	46 (79.3)	3.88 (1.59-9.44)	
≥ 3.14	127 (61.4)	12 (20.7)	Ref.	
Platelet count				0.062
< 100,000	14 (6.8)	1 (1.7)	8.05 (0.89-72.14)	
≥ 100,000	193 (93.2)	57 (98.3)	Ref	
Neutrophil count				0.595
≥ 2300	197 (95.2)	54 (93.1)	0.66 (0.14-3.08)	
< 2300	10 (4.8)	4 (6.9)	Ref.	
Metastasis				
Liver	72 (34.8)	23 (39.7)	1.62 (0.75-3.48)	0.218
Brain	11 (5.3)	4 (6.9)	1.67 (0.36-7.78)	0.510
> 1 organ	11 (5.3)	3 (5.2)	0.41 (0.08-2.18)	0.298
≤ 1 organ	196 (96.1)	55 (94.8)	Ref.	
PNI score				<0.025
≥ 40	98 (47.3)	7 (12.1)	Ref.	
< 40	109 (52.7)	51 (87.9)	3.36 (1.16-9.67)	

Ref: Reference; ECOG: Eastern Cooperative Oncology Group; PNI: Prognostic Nutritional Index; EGFR: Epidermal Growth Factor Receptor; significant p value <0.05

Discussions

Lung cancer is the most diagnosed malignancy, and its incidence has been increasing in the last three decades. Global Cancer Observatory in 2018 estimated 2.1 million new cases of lung cancers worldwide, equivalent to 11.6% of the total new cases of cancer.[10] Regarding cancer incidence rate, Indonesia is in the 8th place among Southeast Asian countries and the most common cancer among men in Indonesia was lung cancer, found in 19.4 per 100,000 with a mortality rate of 10.9 per 100,000 population.[11] The high incidence of lung cancer drove studies in various fields to improve the outcome of this disease.[12]

We performed a cohort retrospective study on 265 patients with stage IV pulmonary adenocarcinoma. Subjects consisted of 64.5% men and 35.5% women. Lung cancer is generally more common in men than women, but the incidence rate in women has been increasing, lung cancer is the fourth most common cancer in women and the second most death of cancer in women.[13] Increased incidence of lung cancer in men and women is not separated from smoking. Some observations concluded that women were more at risk than men to develop the adverse effects of carcinogens in cigarettes. Other factors such as passive smoking, old age at the onset of nicotine addiction, differences in nicotine metabolism

in women, occupational exposure, food intake, and comorbidities such as COPD also increase the risk of lung cancer in women.[14]

Most of the subjects were ≥59 years of age. Lung cancer is usually detected at an older age. Only 0.5% of lung cancer develops at <40 years of age. This condition may be due to some physiological changes that occur in old age. The thoracic cavity and diaphragm undergo structural changes which may result in reduced chest wall compliance. Old age is also associated with osteoporosis which may induce rib cage stiffness. Elderlies are also more susceptible to infection and immune response disorders. All of these factors together with decreased DNA repair will induce lung cancer and worsen the outcome.[15]

Recently, various approaches have been developed for targeted individual molecular therapies for lung cancer treatment, but the prognosis for lung cancer is still poor. Lung cancer has been associated with a high mortality rate and a low 5-year survival rate, which is less than 17%. Inadequate prognostic parameters are one of the reasons for the poor prognosis of lung cancer, thus it is critical to find accurate and applicable predictors of prognosis to improve the outcome.[12]

Prognostic Nutritional Index (PNI) was first introduced by Buzby and colleagues in 1980.[16] Various studies assess the PNI score to predict the long-term outcome in cancer patients. PNI has been adopted as a predictor of prognosis for colorectal, esophageal, gastric, bladder urinary, and ovarian cancers. Studies of PNI scores for outcome prediction in lung cancer have also been performed but the results vary.[17] Based on these facts, the current study was conducted to clarify the role of PNI score as a predictor of lung cancer prognosis, particularly in stage IV pulmonary adenocarcinoma.

PNI scores in the study ranged from 13.25 to 46.69 with the mean ± SD 31.47 ± 6.92. A meta-analysis study was performed in 2018 to assess the PNI score in lung cancer. The study found a cutoff point for PNI score based on 10 studies to be between 46.24 and 52.48.14 Cutoff point for PNI score in the current study was based on a previous study, where PNI <40 is categorized as low and PNI ≥ 40 categorized as high.[3]

The current study found that 87.2% of subjects had low PNI scores while the rest had high PNI scores. Bivariate analysis results suggested that only EGFR mutation and albumin level <3.14 were significantly associated with low PNI scores. Serum albumin initially was frequently used as an indicator of nutritional status, but further studies found that lymphocyte also plays an important role in cellular immunity against various types of cancer, thus a combination of both albumin and lymphocyte count in the form of PNI score may better reflect the outcome.[18] One of the components in the PNI score is the serum albumin level, so hypoalbuminemia may directly affect a low PNI score.

The correlation between PNI scores and EGFR mutations is unclear. No studies analyzed the association between PNI scores and EGFR mutations from a Pubmed search. EGFR mutations seem to affect PNI score indirectly through the suppression of the cellular immune system. In a study on the effects of EGFR inhibition on lung cancer cells, it was found that EGFR inhibition triggers lymphocytes T and natural killer

(NK) cell activities. The administration of low-dose erlotinib increases the tumor cell lysis and increases the effect of apoptosis.[19] It seems that EGFR mutations suppress the activity of lymphocytes and other inflammatory cells and in return suppression of lymphocyte activity will affect the decrease in PNI score.

PNI scores had a significant effect on mortality outcomes in this study. Subjects who had a PNI score <40 were at risk of 6-months mortality 3.36 times higher than subjects who had a PNI score ≥40 ($p < 0.025$, OR (95% CI) = 3.36 (1,16-9,67)). Similar results were reported from various previous studies. Li et al. (2018) explained that a low PNI score increased the risk of death by 1.72 times in SCLC type lung cancer patients. This hazard ratio was higher in NSCLC patients, which was 1.93 times. It indicated that the prognostic effect of PNI score in the NSCLC group was stronger than in the SCLC group.[17]

The mechanism that underlies the association between the PNI score and the patient outcome is complex. Carcinogenesis and tumor formation are closely related to inflammation, especially the proliferation, migration, avoidance mechanisms from the host immune system, and the chemorescence of tumor cells.[20,21] PNI scores also include albumin levels that reflect the nutritional status of cancer patients. Hypoalbuminemia has been associated with malnutrition and decreased body weight in turn increased mortality and morbidity.[21]

The importance of nutrition in the immune system has been known for a long time. Malnutrition inhibits cellular and natural immunity which further increases the host susceptibility to infection and cancer. Previous studies have found similar results that low PNI scores were associated with poor outcomes for cancer patients. The decreased PNI scores may be due to low lymphocyte count and hypoalbuminemia. Lymphocytes kill new cancer cells and a lower lymphocyte count may reflect the susceptibility of tumor immunity.[22] Various pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha are produced in the response to chronic inflammation. These factors cause hypoalbuminemia and trigger the development of cancer.[23]

ECOG score ≥2 reflects the poor functional status, including the reduced ability for self-care, quality of life, and physical activity. It is a long-term effect of cancer. Various factors may reduce a patient's functional status, one of which is cachexia and malnutrition. Cachexia has a stronger effect on functional decline than tumor location, duration, and stage. Cachexia is closely related to systemic inflammation that accompanies cancer expansion and decreased nutritional intake. Cachexia has been associated with increased neutrophils and decreased lymphocytes and increased CRP. Hypoalbuminemia is also common in patients with cachexia as the result of impaired liver function, chronic inflammation, and significant weight loss.

This study has limitations due to its retrospective cohort design. Data can only be extracted from medical records, thus reducing the completeness of the information and also the inability to control other potential confounders.

Conclusion

PNI score had a significant effect on mortality in patients with stage IV pulmonary adenocarcinoma. Subjects with PNI scores <40 were at risk of mortality three times higher than subjects with PNI score ≥40 (adjusted OR 3.356, 95% CI 1.165 - 9.670, p = 0.025). PNI scores can be considered a prognostic factor for patients with stage IV adenocarcinoma. Further studies are needed to assess whether treatments that improve PNI may also improve the outcome of patients with stage IV lung adenocarcinoma.

References

1. Jian-hui C, Iskandar EA, Cai S, Chen C, Wu H, Xu J, He Y. Significance of Onodera's prognostic nutritional index in patients with colorectal cancer: a large cohort study in a single Chinese institution. Tumor Biol. 2016;37:3277–3283.
2. Mori S, Usami N, Fukumoto K, Mizuno T, Kuroda H, Sakakura N, et al. The significance of the prognostic nutritional index in patients with completely resected non-small cell lung cancer. PloS One. 2015;10:e0136897.
3. Shimizu K, Okita R, Saisho S, Yukawa T. Prognostic nutritional index before adjuvant chemotherapy predicts chemotherapy compliance and survival among patients with non small cell lung cancer. Therapeutics and Clinical Risk Management. 2015;11:1555-1561.
4. Schlag P, Fritz T, Hölting T. Prognostic significance of nutritional status in cancer surgery. Recent Results Cancer Res. 1988;108:154–159.
5. Tong YS, Tan J, Zhou XL, Song YQ, Song YJ. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. J Transl Med. 2017;15:221
6. Sheng J, Yang Y-P, Ma Y-X, Qin T, Hu Z-H, Hong S-D, et al. Low Prognostic Nutritional Index correlates with worse survival in patients with advanced NSCLC following EGFR-TKIs. PLoS ONE. 2016;11(1): e0147226.
7. Hulley S, Cummings S, Browner W, Grady D, Newman T. 2013. Designing Clinical Research. Lippincott Williams and Wilkins; 2013.
8. Li D, Yuan X, Liu J, Li C, Li W. Prognostic value of prognostic nutritional index in lung cancer: a meta-analysis. J Thorac Dis. 2018;10(9):5298-5307. doi: 10.21037/jtd. 2018.08.51
9. Xu S, Cao S, Geng J, Wang C, Meng Q, Yu Y. High prognostic nutritional index (PNI) as a positive prognostic indicator for non-small cell lung cancer patients with bone metastasis. Clin Respir J. 2021;15(2):225-231. doi: 10.1111/crj. 13288
10. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2016;68:394–424.
11. Kementerian Kesehatan Republik Indonesia. Hari kanker sedunia. 2019 [cited 2020 Jan 28]. Available from https://www.depkes.go.id/article/view/19020100003/hari-kanker-sedunia-2019.html.
12. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines. Chest. 2017;132:29–55.
13. Ferlay J, Shin HR, Bray F. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-917.
14. Rodriguez RB, Fuentes JM. Lung cancer in women. Lung Cancer. 2012;3:79-89.
15. Li D, Yuan X, Liu J, Li C, Li W. Prognostic value of prognostic nutritional index in lung cancer: A Meta analysis. J Thorac Dis. 2018;10:5298-5307.

16. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. Am. J. Surg. 1980;139, 160–167.
17. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic review of the epidemiological literature. Nutr J. 2010;9:69. doi: 10.1186/1475-2891-9-69 PMID: 21176210.
18. Domininguez C, Tsang KY, Palena C. Short term EGFR blockade enhances immune-mediated cytotoxicity of EGFR mutant lung cancer cells: Rationale for combination therapies. Cell Death Dis. 2016;29:1-13.
19. Deme D, Telekes A.Prognostic importance of albumin in oncology. Orv Hetil. 2018;159:96-106.
20. Hoffmann TK, Dworacki G, Tsukihiro T. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. Clinical Cancer Research. 2002;8:2553–2562.
21. Ceze N, Thibault G, Goujon G. Pre-treatment lymphopenia as a prognostic biomarker in colorectal cancer patients receiving chemotherapy. Cancer Chemotherapy and Pharmacology. 2011;68:1305–1313.
22. Newcomer RJ, Wilkinson AM, Lawton MP. Focus on managed care and quality assurance: Integrating acute and chronic care. New York: Springer. 1996;p:1-36.
23. Richards CH, Roxburgh CSD, MacMillan MR. The relationships between body composition and the systemic inflammatory response in patients with primary operable colorectal cancer. PLOS ONE. 2012;7: 1-8.