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Procalcitonin Level in Non-Small Cell Lung Cancer Patients among Indonesian Population

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Abstract

BACKGROUND: Serum Procalcitonin (PCT) is a biomarker that is frequently used to diagnose an infection. In some cases of thoracic malignancy, procalcitonin level appears to increase. However, the role of procalcitonin to diagnose malignancy is not certain yet, and the causes have not been known.

AIM: This study aimed to investigate procalcitonin levels in non-small cell lung cancer patients.

METHODS: This was an observational study with a cross-sectional design. All lung cancer patients did not diagnose based on cytology/histopathology results with no evidence nor were signs and symptoms of infection recruited through consecutive sampling. The subtypes of lung cancer include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, staged III and IV. The procalcitonin levels were analysed from blood using immunofluorescent assay. Data were then analysed with the Chi-Square test by Epi Info™ 7 programs in which p-value < 0.05 was considered statistically significant.

RESULTS: A total of 68 lung cancer patients fulfilled the criteria of this study, 55 men (80.9%) and 13 women (19.1%). The highest percentage of cytology/histopathology type found was adenocarcinoma (80.9%), and 60.3% of those were diagnosed in stage IV. An increased procalcitonin level (greater than 0.01 ng/mL) occurred in 80.9% of Non-Small Cell Lung Cancer (NSCLC) patients. It appears that the higher the stage of lung cancer, the lower procalcitonin levels would be, although it was not statistically significant. There was no association between lung cancer subtype with procalcitonin levels.

CONCLUSION: An increased level of procalcitonin may be an indication not only for infection but also for Non-Small Cell Lung Cancer.

Introduction

Procalcitonin (PCT) is a derivate of calcitonin hormones. It is produced primarily in the liver by macrophages (Kupffer cells) or neuroendocrine cells which are involved in systemic reactions in response to endotoxin circulation and inflammatory cytokine produced during bacterial or fungal infections [1], [2] [3]. The plasma level is associated with the severity of the infection [4]. In healthy individuals, PCT levels are very low (< 0.1 ng/ml). Procalcitonin has shown the importance of distinguishing the diagnosis of cancer patients with clinical symptoms of fever and increased levels of CRP [5], [6]. On the other hand, recent studies showed PCT concentrations at the right level with sepsis in patients with an advanced stage of cancer [7]. This raises doubts about the role of procalcitonin in diagnosing infections in cancer patients.

Patients with malignant diagnoses have a high risk of developing infections which are non-specific clinical signs and the sign of several different clinical outcomes, such as drug reactions, actual

infections, or paraneoplastic syndromes commonly known as 'neoplastic fever' [7]. The PCT values rise rapidly at 2-4 hours from the bacterial infection onset. PCT has a half-life of 22-24 hours; therefore, this concentration can be halved when the infection is cured [8]. Although PCT in patients with oncology neutropenia fever has been investigated in several studies, recent meta-analysis studies failed to define its role. Also, Shomalli et al., [9] studied the role of PCT as a biomarker to distinguish fever due to infection and non-infectious fever in non-neutropenia patients with solid tumours and hematologic malignancy. They also argued that the increase in PCT levels and C-Reactive Protein could also increase in malignancy. Several malignancies usually show false positive for PCT.

Information about the values and characteristics of PCT are limited to lung cancer incidence [10]. Based on the above description, this study aimed to investigate the procalcitonin levels in non-small cell lung cancer patients.

Material and Methods

This was an observational study with a cross-sectional design to investigate the characteristics of procalcitonin levels in non-small cell lung cancer patients among Indonesia population. The study was conducted in Adam Malik General Hospital for 3 months. Data were collected through the medical records of Adam Malik General Hospital from November 2016 to June 2017.

Subjects were recruited through consecutive sampling based on cytology/histopathology result. Patients diagnosed with tumour mediastinum and lung tumour metastasis were excluded from this study. Smoking status was also recorded. Patients categorised as active smokers if they have a smoking history of ≥ 100 cigarettes throughout their lives [11], passive smoker (a person who inhales cigarette smoke from a smoker). Type of cigarettes includes clove cigarettes (kretek) and filter (white) cigarettes. The Brinkman Index value was obtained from the multiplication of the average number of cigarettes smoked a day and multiplied by the duration of smoking (years). The value of Brinkman Index (IB) is mild if 0-199, moderate if 200-599, and severe if > 600 [12].

First, 4 ml of peripheral venous blood were taken and then inserted into the EDTA tube. Next, the serum was isolated. The procalcitonin values were determined by immunofluorescence using BRAHMS procalcitonin sensitive Kryptor automated system (Thermo Scientific, Brahms, Henningsdorf, Germany) [10]. The values of serum procalcitonin were determined, in which levels above 0.01 ng/ml was considered high [10].

To assess the relationship between gender, age, and the Brinkman index with procalcitonin levels in non-small cell lung cancer patients, the Chi-Square test was performed. While the procalcitonin levels based on the cytologic/histopathologic subtypes cancer stage were analysed with Mann-Whitney and Kruskal Wallis test, data were analysed using Epi Info™ 7 programs in which p-value of < 0.05 was considered statistically significant.

Results

Based on the characteristics of the subjects, it was found that the highest number of gender in lung cancer incidence was male (80.9%). The average age dominant with lung cancer was 40–60 years (51.5%). All subjects were smokers and mostly categorised as heavy smoker based on Brinkman index (75%). The most common subtype of lung cancer was adenocarcinoma type (80.9%). The data can be seen in Table 1.

Table 1: Demographic characteristics of the study subjects

Characteristics		n	%
Gender	Male	55	80.9
	Female	13	19.1
Age	Under 40 years-old	3	4.4
	40-60 years-old	35	51.5
	Over 60 years old	30	44.1
Smoking status	Active smoker	68	100.0
	Non smoker	0	0.0
Type of cigarettes	Clove cigarettes (kretek)	44	64.7
	Filter cigarettes (white)	24	35.3
Brinkman Index	Severe	51	75.0
	Moderate	14	20.6
	Mild	3	4.4
Cytology/histopathology	Adenocarcinoma	55	80.9
	Squamous Cell Carcinoma	12	17.6
	Large Cell Carcinoma	1	1.5
pTNM	I	8	11.8
	II	10	14.7
	III	9	13.2
	IV	41	60.3
Procalcitonin levels	Increased (> 0.01 ng/ml)	55	80.9
	Normal (≤ 0.01 ng/ml)	13	19.1

The association between procalcitonin levels and gender, age and Brinkman index on Non-Small Cell Lung Cancer patients were displayed in table 2.

Table 2: The association between demographic factors and the levels of procalcitonin

Variables		Procalcitonin level				*p-value*
		Increased		Normal		
		n	%	n	%	
Sex	Male	44	80.0	11	84.6	0.702[a]
	Female	11	20.0	2	15.4	
Age	Under 40 years-old	2	3.6	1	7.7	0.53[a]
	40-60 years-old	30	54.5	5	38.5	
	Over 60 years old	23	41.8	7	53.8	
Brinkman Index	Severe	40	72.7	11	84.6	0.38[a]
	Moderate	13	23.6	1	7.7	
	Mild	2	3.6	1	7.7	
Total		55	100.0	13	100.0	

a) Chi-Square test.

Table 3 showed that there was no difference in the levels of procalcitonin between adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. It appears that the higher the stage of lung cancer, the lower procalcitonin levels would be. However, this correlation was not observed in stage IV cancer patients, and thus it was not statistically significant.

Table 3: The comparison of procalcitonin levels based on tumour diagnosis

Variables		n	Procalcitonin levels		*p value*
			mean ± SD	median (min-max)	
Cytology/ histopathology	Adenocarcinoma	(n = 55)	1.02 ± 2.06	0.34 (0.02 - 11.9)	0.206 [a]
	Squamous Cell Carcinoma and large cell	(n = 13)	0.91 ± 1.24	0.48 (0.14 - 4.2)	
Stage	I	(n = 8)	1.21 ± 2.23	0.44 (0.02 - 6.71)	0.12 [b]
	II	(n = 10)	0.84 ± 0.45	0.90 (0.14 - 1.47)	
	III	(n = 9)	0.63 ± 1.04	0.17 (0.04 - 2.86)	
	IV	(n = 41)	1.07 ± 2.24	0.25 (0.02 - 11.9)	

a) Mann-Whitney test; b) Kruskal Wallis test.

Generally, it can be concluded that there was no effect of the cancer cell types nor cancer stage on serum procalcitonin levels.

Discussion

The sample of this research was 68 cases of lung cancer patients who have been diagnosed definitively (cytology/histopathology). Based on the gender of the subjects, there were 55 male patients (80.9%) whereas there were 13 female patients (19.1%). The same situation was also reflected in other parts of the world. Aareleid conducted epidemiological studies of lung cancer from 1985 to 2014. According to that study, 18,399 cases (80.3%) were male patients whereas 4491 cases (19.7%) were female patients [13]. In Indonesia, specifically in Adam Malik General Hospital, Medan, the highest number of patients based on gender was male with 85.62% compared to a female with 24 patients (24.37%) [3].

In this study, the number of patients between the age of 40-60 years were predominant with 36 patients (51.4%), followed by the age group of over 60 years with 30 patients (42.9%). An epidemiological study conducted by Ridge in 2015 also suggested that about 60% of lung cancer cases were suffered by patients aged 50-60 years old [14]. In his study, he also stated that the prevention of cigarettes was a top priority for public health. Globally, cigarettes are one of the biggest death factors with a 1:10 ratio in adults and a mortality rate of about 5 million people per year [14]. Similarly, a study conducted by Soeroso in 2018 showed that 60% of lung cancer cases suffered by patients aged 55-64 years [15], [16].

Brinkman index is used to assess the severity level of smoking. The Brinkman index in this study found that 75.7% of subjects were heavy smokers, 20% were moderate smokers, and the other 4.3% were light smokers. A similar result was also found by Soeroso et al., [15], [16] in which 52.9% of their research participants were categorised as heavy smokers. Also, this study was to evaluated nicotine dependence based on the Fagerstrom Tolerance Questionnaire (mFTQ), and the results showed that 65% of Fagerstrom scores were very high. Epidemiologic studies suggest that smoking is the leading cause of lung cancer. Smokers are 22 times more likely to die of lung cancer than nonsmokers [1]. Smoking has a role in lung cancer at various levels. Smoking can cause mutations of genes that leads cell to be oncogenic. One of the mutations is a p53 mutation found in more than 53% in smokers [2]. Furthermore, smoking can also influence adverse effects during therapy, either chemotherapy or radiotherapy [2].

Lung cancer is one of the leading causes of death around the world, particularly in Indonesia. In 2014, WHO stated that the mortality rate due to lung cancer reached 21.8% for men and 9.1% for a woman in Indonesia [17]**.** The most common type of cancer found in this study was adenocarcinoma (80.9%). Although previous studies found that squamous cell carcinoma as the most common type found, new paradigm depicted that adenocarcinoma was the most common type of cancer. This is probably because the type of cigarettes favoured by Indonesians is clove cigarettes. This study found that the most common type of lung cancer found in Batak tribe in Indonesia was adenocarcinoma (92.9%), and the most consumed cigarette type was clove cigarettes. Clove cigarettes contain clove that will make smokers suck in more deeply; thus, smokes containing carcinogenic substances eventually enter the peripheral respiratory tract [16], [18]. Syahruddin et al., [19] found that the EGFR mutations rate among Indonesian population reached 57.1% common mutations (exon 19 ins/dels, L858r) and about 29% uncommon mutations (G719X, exon 20 ins, T790M, L861Q).

In this study, most of the patients have entered the stage IV of cancer (60%), and the patients in stage III were 14.3%. This is slightly different from the results found by Soeroso in 2010-2012 in which most of the cases were in stage III with 56 cases (33.54%) from a total of 167 patients [3]. However, there is a trend found that lung cancer is generally diagnosed when it has entered an advanced stage. There are some factors that may cause late diagnosis. One of them is the absence of accurate screening to date [4].

The results showed that serum procalcitonin based on histopathology (adenocarcinoma, squamous cell, and large cell) in this study did not show a significant difference in the Kruskal-Wallis test ($p > 0.05$). This study also showed that the values of procalcitonin increased in 55 samples (80.9%). This contrasts with Avrillon's findings that 42% of 89 samples experienced an increase in procalcitonin

levels [10]. Procalcitonin is not a substance commonly used as a diagnostic tool for cancer, but recent research conducted by Vincenzi et al., [5] showed an increased in procalcitonin levels with cancerous conditions. The study also stated that during an advanced stage of cancer, the production of inflammatory cytokines is more active than usual leading to procalcitoninemia conditions [5].

Ghillani et al., [20] found an increased level of procalcitonin compared with healthy subjects by 17.5%, 53%, and 29% respectively in patients with squamous cell cancer, large cell, and adenocarcinoma. Non-cancer patients had low procalcitonin levels in average compared with patients with stage I-III cancer (0.029 ng/mL vs 0.127 ng/mL, $p < 0.0001$) or the stage IV disease (0.029 ng/mL vs 0.190 ng/mL, $p < 0.0001$). Cancer patients who have accelerated developmental stage have a higher mean of PCT than those in the low stages (0.190 ng/mL vs 0.127 ng/mL, $p = .004$) [21]. However, the patients in severe stages had an increase in the PCT values baseline compared with the patients in low stages (0.47 vs 0.27 ng/mL), $p = 0.017$) [9]. The PCT values were higher in the patients with small cell lung cancer than adenocarcinoma (0.33 ng/mL vs 0.07 ng/mL, $p < 0.001$). Furthermore, the PCT levels were significantly higher in the patients with liver metastasis (0.37 vs 0.09 ng/mL, $p < 0.001$) [22]. Another study showed an increase in PCT associated with metastatic stage cancer in 43 patients with solid tumour and 15 healthy control subjects; the highest level was found in metastatic cancer [23]. Also, it was found that procalcitonin levels were high in colorectal cancer. Keramidaris et al., [6] studied the relationship between bacterial translocation and cancer condition and found PCT positive in the majority of their samples (55.3%), higher procalcitonin levels were also found in metastatic patients than no metastasis ($p = 0.01$).

One of the limitations of this study was incomplete medical records data, especially data of lung cancer patients undergoing distant metastasis. Therefore, the relationship between procalcitonin levels and lung cancer patients undergoing metastasis cannot be assessed. Also, this study did not conduct C-reactive protein examination in all lung cancer patients due to health insurance limitations in Indonesia.

In conclusion, an increased level of procalcitonin was observed in most patients with Non-Small Cell Lung Cancer. It appears that the higher the stage of lung cancer, the lower procalcitonin levels would be, although it was not statistically significant. There was no association between lung cancer subtype with procalcitonin levels.

An increased level of procalcitonin may raise a suspicion for Non-Small Cell Lung Cancer, particularly if no evidence of infection was found.

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