ORIGINAL ARTICLE

Hematologic Paraneoplastic Syndrome in Newly Diagnosed Patients with Lung Cancer

Andika Chandra Putra[1,2*], **Steven Jonathan**[1], **Wira Winardi**[3], **Elisna Syahruddin**[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia/Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia.

[2]Faculty of Medicine, YARSI University, Jakarta, Indonesia.

[3]Department of Respiratory Medicine, Graduate School of Medicine, Juntendo University, Tokyo, Japan.

ARTICLE INFO

Article history:
Received 10 October 2022
Received in revised form
9 December 2022
Accepted 20 December 2022
Available online 30 January 2023

Keywords:
Cancer,
Hematologic paraneoplastic syndrome,
Lung cancer,
Toxicity effect.

Cite this as:
Putra AC, Jonathan S, Winardi W, *et al*. Hematologic Paraneoplastic Syndrome in Newly Diagnosed Patients with Lung Cancer. *J Respi* 2023; 9: 18–29.

ABSTRACT

Introduction: Lung cancer could have signs and symptoms generated by paraneoplastic syndromes. This study aimed to describe and analyze hematologic paraneoplastic syndrome in patients with lung cancer in Indonesia.

Methods: This was a cross-sectional analytic study conducted in Persahabatan National Respiratory Referral Hospital, Jakarta, between September 2018 and February 2019, on all newly diagnosed patients with lung cancer whose diagnosis was established and who fulfilled the inclusion and exclusion criteria.

Results: The mean age of subjects was 56.7 ± 11.4 years old. Most subjects were male, had normal nutritional status (42.6%), had a smoking history (75%), and had a moderate Brinkman Index (BI) value (52%). The most common type of histology was squamous cell carcinoma (SCC) (39.7%), with advanced stage (83.8%) and performance status <2 (94.1%). Paraneoplastic anemia was 40.4%, associated with poor nutritional status and commonly normocytic normochromic anemia. The proportion of paraneoplastic leukocytosis was 39%, associated with males and smoking history. The proportion of paraneoplastic neutrophilia was 51.5%, and it was related to males, smoking history, and SCC histology type. Paraneoplastic hypereosinophilia and thrombocytosis proportions were 2.9% and 18.4%, respectively. The proportion of paraneoplastic hypercoagulability was 91.2%, which was caused by the elevated D-dimer level.

Conclusion: The most common hematologic paraneoplastic syndromes in patients with lung cancer were hypercoagulability, neutrophilia, and anemia. The low hemoglobin (Hb) level of paraneoplastic anemia was associated with low body mass index (BMI). Male and smoking history in lung cancer patients were associated with paraneoplastic leukocytosis and/or neutrophilia.

INTRODUCTION

Lung cancer is the most frequent malignancy with the highest mortality rate worldwide.[1] Data from the World Health Organization (WHO) regarding cancer profile in Indonesia indicated that lung cancer was ranked first among the top five cancers in men and fifth in women. Symptoms and signs in patients with lung cancer can be caused by neoplastic growth of the airways, suppression or infiltration of surrounding organs or tissues, metastasis, and paraneoplastic syndromes.[2] Paraneoplastic syndromes include signs and symptoms due to tissue or organ damage at a distant location from the primary tumor and metastasis.

*Corresponding author: andika.chandra@yarsi.ac.id

Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v9-I.1.2023.18-29

A study found that 10–20% of patients with bronchogenic carcinoma, including the hematologic, neurologic, endocrine, musculoskeletal, and dermatologic systems, have paraneoplastic syndromes.[3] The hematologic paraneoplastic syndrome includes anemia, leukocytosis, neutrophilia, hypercoagulability, thrombocytosis, and hypereosinophilia.[4] Frequently, it has been difficult to confirm certain hematologic paraneoplastic syndromes. Therefore, clinicians are unsure regarding the management. To date, no data and research have been conducted on the hematologic paraneoplastic syndrome in patients with lung cancer in Indonesia. This study aimed to determine the proportion of hematologic paraneoplastic syndrome in newly diagnosed patients with lung cancer at Persahabatan National Respiratory Referral Hospital, Jakarta, and its relationship with patient characteristics.

METHODS

Study Design

This was a cross-sectional analytic study that assessed the proportion of hematologic paraneoplastic syndrome in newly diagnosed patients with lung cancer whose diagnosis had been established and its correlation with patient characteristics at Persahabatan National Respiratory Referral Hospital, Jakarta. Normal laboratory criteria and hematology paraneoplastic syndrome level were determined (Table 2).

Study Population and Sample

The study population was all patients with lung cancer who attended the thoracic oncology clinic at Persahabatan National Respiratory Referral Hospital, Jakarta, between September 2018 and February 2019. The study sample was all newly diagnosed lung cancer patients with established diagnoses who met the inclusion and exclusion criteria.

Study Procedures

The name, age, and gender of all study samples were identified. We took their medical history, including symptoms of the current illness, symptoms of infection, smoking status, Brinkman Index (BI), and past medical history. Additionally, we performed physical examinations (patients' body mass index (BMI), vital signs, and performance status (PS)) to ensure the patients met the inclusion and exclusion criteria.

Newly diagnosed patients with lung cancer whose diagnosis had been established and who had never received any therapies for lung cancer at the time of sampling were included on the condition that it was not proven that they were experiencing acute infections of the respiratory system, gastrointestinal tract, urinary tract, or central nervous system based on the history taking and physical examination. Patients who had signed a consent form before the study and underwent complete blood laboratory examinations were included in this study.

We excluded all patients with other malignancies, including patients who had received antibiotics for any indications or had received antibiotics within the last two weeks, patients who had a history of atopic/allergy or asthma, patients who had been previously diagnosed with chronic diseases, such as chronic kidney disease or other kidney disorders, chronic liver disease, blood coagulation disorders or severe malnutrition, patients who had symptoms/signs of massive acute bleeding (melena, hematemesis, acute massive hemoptysis, hematochezia, and others, except hemoptysis <250 mL); and patients who were in treatment related to the coagulation system.

RESULTS

The details of the sample of 136 subjects are shown in Figure 1. The results were grouped according to the characteristics of the subject (age, gender, BMI, smoking history, BI, histologic type, stage, and PS) and the proportion of each hematologic paraneoplastic syndrome (anemia, leukocytosis, neutrophilia, hypereosinophilia, thrombocytosis, and hypercoagulability) associated with the characteristics of the subject.

Characteristics of Study Subjects

Most of the study subjects were male, with a mean age of 56.7. The most frequent chief respiratory complaint was shortness of breath. Most of the study subjects had normal nutritional status (mean BMI 19.53 kg/m2) and a smoking history with a moderate BI value. The most common histologic type was squamous cell carcinoma (SCC). Typical carcinoid, atypical carcinoid, and non-small cell lung cancer (NSCLC) neuroendocrine carcinoma were classified as other types. There were more subjects in advanced stages and

PS <2. The characteristics of the study subjects are presented in Table 1.

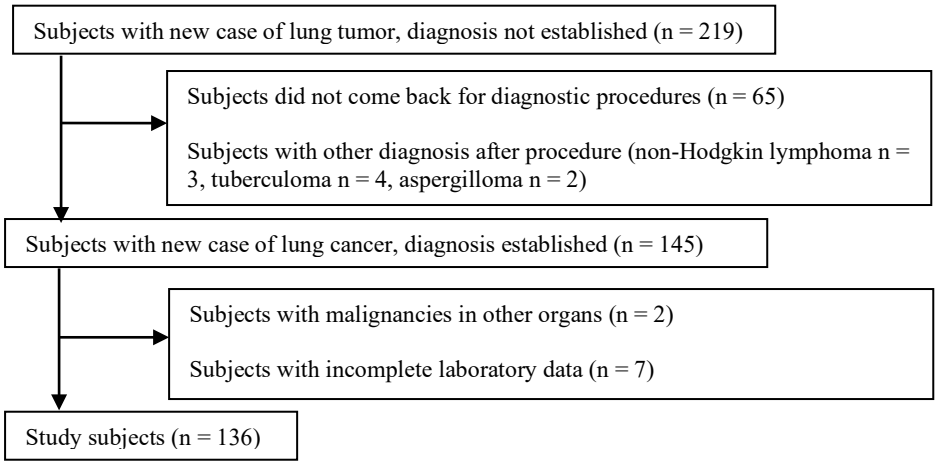

Figure 1. Study subjects sampling

Table 1. Characteristics of the study subjects

Characteristics of subjects	Number (n = 136)
Age in years old, mean ± SD	56.7 ± 11.4
Gender, n (%)	
Male	107 (78.7)
Female	29 (21.3)
BMI, kg/m^2, median (min-max)	19.53 (12.11–30.44)
BMI category, n (%)	
Low	50 (36.8)
Normal	58 (42.6)
Overweight	15 (11.0)
Obese	13 (9.6)
Chief complaint, n (%)	
Cough	32 (23.5)
Hemoptysis	15 (11.1)
Shortness of breath	38 (27.9)
Chest pain	51 (37.5)
Smoking history, n (%)	
Yes	102 (75)
No	34 (25)
BI, n (%)	
Mild	13 (12.7)
Moderate	53 (52.0)
Severe	36 (35.3)
Histologic type, n (%)	
Adenocarcinoma	51 (37.5)
SCC	54 (39.7)
Large cell carcinoma	3 (2.2)
SCLC	16 (11.8)
Others	12 (8.8)
Stage, n (%)	
I–IIIA or LD	22 (16.2)
IIIB–IV or ED (advanced)	114 (83.8)
PS, n (%)	
0–2	128 (94.1)
>2	8 (5.9)

SD = standard deviation; BMI = body mass index; BI = Brinkman Index; SCC = squamous cell carcinoma; SCLC = small cell lung carcinoma; LD = limited disease; ED = extensive disease

Proportion of Each Hematologic Paraneoplastic Syndrome

The distribution of laboratory test data is shown in Table 2. The study subjects might experience one or more hematologic paraneoplastic syndromes. Five subjects had normal laboratory results. There were three subjects with only paraneoplastic anemia, one with only paraneoplastic thrombocytosis, and 24 with only paraneoplastic hypercoagulability. There was one subject with paraneoplastic leukocytosis and neutrophilia, one with paraneoplastic hypercoagulability and thrombocytosis, and two with paraneoplastic anemia and neutrophilia. Most subjects (n=99) had paraneoplastic hypercoagulability and anemia with/without the other syndromes. The proportions listed in Figure 2 are the proportion of each hematologic paraneoplastic syndrome regardless of whether the subject had one or more hematologic paraneoplastic syndromes.

Table 2. Normal laboratory criteria and paraneoplastic syndrome distribution

Criteria	Distribution
Hb, g/dL	
Normal	
Male	13–16
Female	12–14
Anemia	
Male	<13
Female	<12
Paraneoplastic anemia	<12
Mean ± SD	12.4 ± 2.0
Leukocyte, /µL	
Normal	5,000–10,000
Leukocytosis	>10,000
Paraneoplastic leukocytosis	>12,000
Median (min-max)	10,720 (3,910–42,940)
Neutrophil	
Normal, %	52–76
Neutrophilia/granulocytosis, %	>76
Paraneoplastic neutrophilia (absolute), /µL	>8,000
Median (min-max), /µL	8,180 (2,666–37,959)
Eosinophil	
Normal, %	1–2
Eosinophilia (absolute), /µL	>500
Paraneoplastic hypereosinophilia (absolute), /µL	>1,500
Median (min-max), /µL	138 (0–6,135)
Thrombocyte, /µL	
Normal	150,000–400,000
Thrombocytosis	>400,000
Paraneoplastic thrombocytosis	>500,000
Median (min-max)	366,500 (148,000–787,000)
PT, second	
Normal	9.8–11.2
Median (min-max)	10.9 (9.4–42.6)
aPTT, second	
Normal	31–47
Median (min-max)	35.5 (11–55.1)
Fibrinogen, mg/dL	
Normal	136–384
Median (min-max)	453.9 (190–900)
D-dimer, µg/L	
Normal	0 – 500
Median (min-max)	935 (240 – 26,720)

Hb = hemoglobin; SD = standard deviation; PT = prothrombin time; aPTT = activated partial thromboplastin time; D-dimer = dimerized plasma fragment D

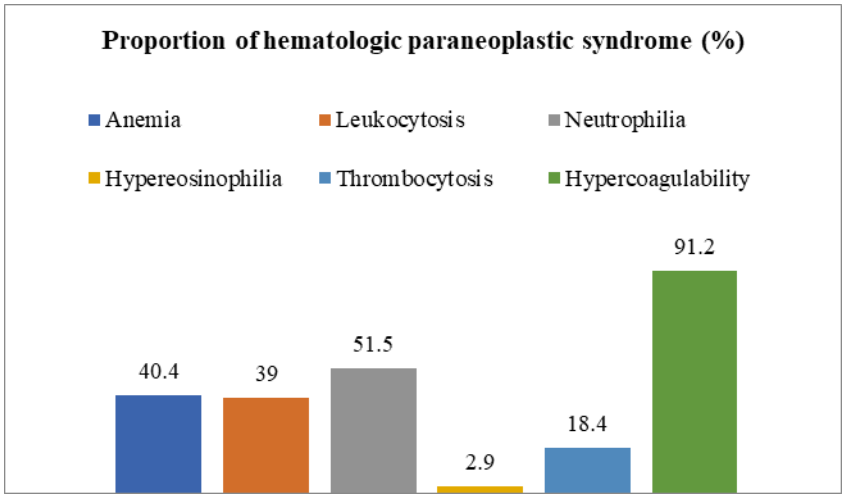

Figure 2. Proportion of each hematologic paraneoplastic syndrome

Correlation between Hematologic Paraneoplastic Syndrome and Characteristics of Study Subjects

Paraneoplastic Anemia

The most common type of anemia (50%) was normocytic normochromic anemia. Anemia in subjects was not distinguished by gender because of the same criteria for both genders. The Chi-square test showed a significant correlation between paraneoplastic anemia and BMI, as shown in Table 3.

Table 3. Correlation between patients' characteristics and paraneoplastic anemia

Characteristics of patients	Anemia	p-value*
Gender, n (%)		
Male	42 (76.4)	0.587
Female	13 (23.6)	
BMI, n (%)		
Low	29 (52.7)	
Normal	18 (32.7)	**0.002**
Overweight	7 (12.7)	
Obese	1 (1.8)	
Smoking history, n (%)		
Yes	40 (72.7)	0.614
No	15 (27.3)	
BI, n (%)		
Mild	3 (7.5)	
Moderate	22 (55)	0.443
Severe	15 (37.5)	
Histologic type, n (%)		
Adenocarcinoma	21 (38.2)	
SCC	28 (50.9)	
Large cell carcinoma	0 (0)	0.054
SCLC	3 (5.5)	
Others	3 (5.5)	
Stage, n (%)		
I–IIIA	9 (16.4)	0.961
IIIB–IV (advanced)	46 (83.6)	
PS, n (%)		
0–2	51 (92.7)	0.570
>2	4 (7.3)	

*Chi-square test. BMI = body mass index; BI = Brinkman Index; SCC = squamous cell carcinoma; SCLC = small cell lung carcinoma

Paraneoplastic Leukocytosis

There were 80 subjects with leukocytosis, of which 53 had paraneoplastic leukocytosis. The Chi-square test showed a correlation between paraneoplastic leukocytosis and gender and smoking history (listed in Table 4).

Paraneoplastic Neutrophilia

There were 70 subjects with paraneoplastic neutrophilia. Based on the Chi-square test, paraneoplastic neutrophilia was correlated with gender, smoking history, and histologic type (SCC). More detailed data is provided in Table 4.

Paraneoplastic Hypereosinophilia

Only four of the 19 subjects with eosinophilia had paraneoplastic hypereosinophilia. Fisher's exact test showed that paraneoplastic hypereosinophilia was not correlated with all the characteristics of the subjects (Table 4).

Table 4. Correlation between patients' characteristics and paraneoplastic leukocytosis, neutrophilia, and hypereosinophilia

Characteristics	Leukocytosis	p-value*	Neutrophilia	p-value*	Hypereosino-philia	p-value#
Gender, n (%)						
Male	47 (88.7)	**0.023**	62 (88.6)	**0.004**	4 (100)	0.578
Female	6 (11.3)		8 (11.4)		0 (0)	
BMI, n (%)						
Low	24 (45.3)		29 (41.4)		2 (50)	
Normal	21 (39.6)	0.359	30 (42.9)	0.358	1 (25)	0.655
Overweight	4 (7.5)		7 (10)		1 (25)	
Obese	4 (7.5)		4 (5.7)		0 (0)	
Smoking history, n (%)						
Yes	47 (88.7)	**0.003**	60 (85.7)	**0.003**	4 (100)	0.572
No	6 (11.3)		10 (14.3)		0 (0)	
BI, n (%)						
Mild	7 (14.9)		7 (11.7)		1 (25)	
Moderate	24 (51.1)	0.832	33 (55)	0.759	0 (0)	0.105
Severe	16 (34)		20 (33.3)		3 (75)	
Histologic type, n (%)						
Adenocarcinoma	23 (43.4)		27 (38.5)		0 (0)	
SCC	24 (45.3)		34 (48.5)		3 (75)	
Large cell carcinoma	1 (1.9)	0.148	1 (1.4)	**0.035**	0 (0)	0.419
SCLC	3 (5.7)		6 (8.6)		1 (25)	
Others	2 (3.8)		2 (3)		0 (0)	
Stage, n (%)						
I–IIIA	9 (17)	0,839	11 (15.7)	0.880	1 (25)	0.511
IIIB–IV (advanced)	44 (83)		59 (84.3)		3 (75)	
PS, n (%)						
0–2	49 (92.5)	0,510	65 (92.9)	0.520	4 (100)	1.00
>2	4 (7.5)		5 (7.1)		0 (0)	

*Chi-square test; #Fisher's exact test. BMI = body mass index; BI = Brinkman Index; SCC = squamous cell carcinoma; SCLC = small cell lung carcinoma

Paraneoplastic Thrombocytosis

There were 25 subjects with paraneoplastic thrombocytosis among the 49 subjects with thrombocytosis. The Chi-square test revealed that paraneoplastic thrombocytosis was not correlated with all the patients' characteristics (Table 5).

Paraneoplastic Hypercoagulability

Although the hemostasis test showed abnormal results in 124 subjects, none had signs of bleeding. Elevated D-dimer level was the most frequent finding (75%). Paraneoplastic hypercoagulability was not statistically correlated with all the patients' characteristics, as shown in Table 5.

Table 5. Correlation between patients' characteristics and paraneoplastic thrombocytosis and hypercoagulability

Characteristics of patients	Thrombocytosis	p-value*	Hypercoagulability	p-value*
Gender, n (%)				
Male	21 (84)	0.472	99 (79.8)	0.287
Female	4 (16)		25 (20.2)	
BMI, n (%)				
Low	11 (44)	0.594	48 (38.7)	0.062
Normal	11 (44)		54 (43.5)	
Overweight	1 (4)		12 (9.7)	
Obese	2 (8)		10 (8.1)	
Smoking history, n (%)				
Yes	20 (80)	0.523	95 (76.6)	0.163
No	5 (20)		29 (23.4)	
BI, n (%)				
Mild	3 (15)	0.485	12 (12.6)	0.472
Moderate	8 (40)		48 (50.5)	
Severe	9 (45)		35 (36.8)	
Histologic type, n (%)				
Adenocarcinoma	12 (48)	0.624	47 (37.9)	0.480
SCC	8 (32)		50 (40.3)	
Large cell carcinoma	1 (4)		2 (1.6)	
SCLC	3 (12)		15 (12.1)	
Others	1 (4)		10 (8.1)	
Stage, n (%)				
I–IIIA	7 (28)	0.076	18 (14.5)	0.091
IIIB–IV (advanced)	18 (72)		106 (85.5)	
PS, n (%)				
0–2	23 (92)	0.618	116 (93.5)	0.364
>2	2 (8)		8 (6.5)	

*Chi-square test. BMI = body mass index; BI = Brinkman Index; SCC = squamous cell carcinoma; SCLC = small cell lung carcinoma

DISCUSSION

Gender

Based on data from Global Cancer Observatory (GLOBOCAN) 2018, lung cancer accounts for the highest number of new cases in men and the third-highest among women in Indonesia. In this study, there were more male subjects (78.7%) than female subjects (21.3%). Consistent with the data from GLOBOCAN 2018, the incidence of lung cancer in Indonesia and the world is higher for men than for women.[5] Similar results were obtained by Nakamura, *et al*. (2017) in Japan (male 64.2% vs. female 35.8%) and Dewi (2018) at Persahabatan National Respiratory Referral Hospital, Jakarta (male 77.4% vs. female 22.6%).[6,7] Jusuf, *et al*. (2017) stated that the number of male patients with lung cancer was three times that of female patients.[1] Additionally, more men than women had a smoking history.

Age

The mean age of the study subjects was 56.7 ± 11.4 years old. This is similar to the mean age in a study conducted by Dewi (2018) at Persahabatan National Respiratory Referral Hospital, Jakarta (54.68 ± 10.59 years old).[7] However, in a study by Novariani (2015) at Persahabatan National Respiratory Referral Hospital, Jakarta, the median age of patients with lung cancer was 56 years old (ranging from 20 to 86 years old).[8] A higher median was obtained by Nakamura, *et al*. (2017) in Japan (67.5 ± 9.6 years old for men and 65.9 ± 9.8 years old for women).[6] This difference might be influenced by the difference in the age of starting smoking. The age of starting smoking in Indonesia was lower than in other countries, according to data from the Global Youth Tobacco Survey (GYTS) 2014 in Indonesia.[9] Approximately 26% of children aged 10–11 years old and 43% of children aged 12–13 in Indonesia had tried smoking. One study found that the proportion of smokers aged <14 years old was about 30% in America and 0.1% in Japan, whereas the proportion of smokers aged 15–17 years old was 38.5% in America and 21% in Japan. Factors that reduced the lung cancer risk in Japanese residents were low alcohol consumption and more effective use of cigarette filters.

Chief Respiratory Complaints

The most common chief respiratory complaints among the subjects in this study that caused them to seek medical care were shortness of breath (37.5%), chest

pain (27.9%), cough (23.5%), and hemoptysis (11.1%). This is similar to the result of a study conducted by Athey, *et al.*[10] All these results are consistent with the frequency of lung cancer symptoms, namely, shortness of breath with a frequency of 3–60%, chest pain with 20–49%, cough with 8–75%, and coughing up blood with 6–35%.[3]

Nutritional Status

The majority of subjects had normal BMI (42.65%). A similar result was obtained by Nakamura, *et al*. (2017) in Japan (72.3%).[6] Conversely, Dewi (2018) found a different outcome in a study conducted at Persahabatan National Respiratory Referral Hospital, Jakarta, as low BMI was the dominant factor in patients with lung cancer (45.2%).[7] Sanikini, *et al*. (2018) used the BMI criteria for Europe and found that normal BMI constituted the highest proportion.[11] Poor nutritional status was not associated with lung cancer risk.

Smoking History

In this study, almost 75% of subjects had a smoking history, and 25% did not have a smoking history. Dewi (2018) found that 74.2% of patients with lung cancer in Persahabatan National Respiratory Referral Hospital, Jakarta, had a smoking history.[7] Similar result was obtained by Nakamura, *et al*. (2017) in Japan (73.5%).[6] Smokers had a 20 times higher relative risk (RR) of lung cancer than non-smokers, while ex-smokers had a nine times higher RR, and secondhand cigarette smoke exposure had a 1.3 times higher RR.[12]

Brinkman Index (BI)

In this study, there were more subjects with moderate (52%) and severe (35.3%) BI than mild BI (12.7%). Similar results were found in a study conducted by Novariani (2015) at Persahabatan National Respiratory Referral Hospital, Jakarta.[8] In Japan, Fukumoto, *et al*. (2015) found that more of the study subjects were smokers with ≥20 pack-years (83.4%).[13] These criteria were still in the range of moderate to severe BI.

Lung Cancer Histologic Type

The most common histologic type of lung cancer found was SSC (39.7%), followed by adenocarcinoma (37.5%). The dominance of SSC was related to the number of male subjects and smokers. Similar results were obtained by Zhang, *et al*. (2018) and Kong, *et al*. (2014) in China.[14,15] Baburao, *et al*. (2015) in Bangalore identified the dominance of SSC.[16] Data from Sembiring, *et al*. (2017) on the percentage of lung cancer histologic type at Persahabatan National Respiratory Referral Hospital, Jakarta, indicated that adenocarcinoma (64%) was the most common.[17] Dewi (2018) obtained a similar result (60%).[7]

Lung Cancer Stage

Among the study subjects, 16.18% were in the early/limited stage, and the remaining 83.82% were in the advanced stage. Similar findings were obtained in the studies conducted by Dewi and Novariani at Persahabatan National Respiratory Referral Hospital, Jakarta.[7,8] These findings are consistent with data from the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia/Persahabatan National Respiratory Referral Hospital, Jakarta, indicating that more patients with lung cancer who sought medical assistance were already in advanced stages.[17] In Japan, Nakamura, *et al*. (2017) found that 80.6% of patients were diagnosed in the early stage.[6] This was enabled with a good early lung cancer detection system.[18,19]

Performance Status (PS)

Only 5.9% of the subjects had PS 3, and the majority (94.1%) had PS 0–2. On the Karnofsky scale, 90–100 is equivalent to PS 0.[20] The reason for this result could be that the sampling of research subjects was only performed in the thoracic oncology clinic that allowed patients with PS 0–2 to seek medical advice. Dewi (2018) found that most hospitalized patients with lung cancer who had pneumonia had PS >2.[7]

Paraneoplastic Anemia

The proportion of paraneoplastic anemia in this study was 40.4%, with an average Hb of 12.4 g/dL, and the most common type was normocytic normochromic anemia (50%). Souilah, *et al*. (2018) reported that the proportion of anemia was about 33.7%, with a mean Hb of 12.4 g/dL.[21] A higher proportion was obtained by Baburao, *et al*. (2015) in Bangalore (61.5%).[16] About 53% of subjects with paraneoplastic anemia had malnutrition. In this study, paraneoplastic anemia significantly correlated with BMI (poor nutritional status). Zabłocka-Słowińska, *et al*. (2017) found that the Hb levels of newly diagnosed patients with lung cancer were significantly lower under malnutrition.[22]

Furthermore, Bacha, *et al*. (2018) found that among patients with NSCLC in Tunisia, cancer-related anemia was correlated with malnutrition.[23] Additionally, Macciò, *et al*. (2015) found that in patients with cancer in various organs, Hb levels were positively correlated with BMI and inversely correlated with tumor stage and PS.[24] However, in this study, paraneoplastic anemia was not associated with PS since there were more subjects with PS <2 (the correlation with PS 3 or 4 could not be evaluated).

Paraneoplastic Leukocytosis

The proportion of paraneoplastic leukocytosis in this study was 39%. Baburao, *et al*. (2015) obtained a similar result in Bangalore with 36.5%.[16] The sampling method in this study was the same as that of Baburao, *et al*., who screened samples according to clinical criteria (medical history taking and physical examination). Paraneoplastic leukocytosis was more commonly found in SSC but not statistically significant. This is similar to the result of this study.

This study screened subjects with infection with clinical criteria and then excluded them. Dewi (2018) found increased leukocyte levels that did not differ significantly among patients with lung cancer with/without pneumonia.[7] The study found that procalcitonin (PCT) could predict pneumonia in patients with lung cancer with a cutoff point of 0.65 µg/L. However, the sensitivity and specificity were low (<80%). This study did not use PCT since there was no consensus on the cutoff point for diagnosing infection in patients with cancer (many studies have suggested different cutoff points).[25] Increased PCT predicted sepsis, bacteremia, and metastasis in malignancies. Nevertheless, Scheinpflug, *et al*. (2015) stated that PCT could not distinguish infection and non-infection in NSCLC.[26] Furthermore, Avrillon, *et al*. (2015) noted that 40% of patients with lung cancer had false positive PCT results of >0.5 µg/L.[27] Increased PCT can also be induced by trauma, major surgery, cardiogenic shock, metastasis, or neuroendocrine natures of the malignancy. For these reasons, PCT could not be the standard marker of infection in patients with solid tumor.[28]

According to the Chi-square test, in this study, paraneoplastic leukocytosis was related to gender and smoking history. Higuchi, *et al*. (2016) found that an increase in leukocytes (neutrophils, lymphocytes, monocytes, and eosinophils) was associated with young age, male, and smoking habits.[29] Other studies supported the correlation between leukocytosis and smoking odd ratio (OR 6.6) and male (OR 1.6). Smoking habits led to a 20–30% increase in leukocytes. In this condition, neutrophil levels increased significantly compared to other leukocyte counts.

Paraneoplastic Neutrophilia

In this study, the proportion of paraneoplastic neutrophilia was 51.5%. It has been reported that neutrophilia was found in 30% of patients with solid tumor and 40% of patients with lung cancer.[30] According to the Chi-square test, paraneoplastic neutrophilia was related to gender, smoking history, and histologic type. Higuchi, *et al*. (2016) reported that neutrophilia was correlated with males (OR 1.6) and smoking (OR 3.9).[29] Alveolar macrophages exposed to cigarette smoke produced cytokines stimulating granulocyte monoclonal-colony stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (G-CSF). Smoking also induced sequestration and activation of neutrophils in pulmonary capillaries. In this study, paraneoplastic neutrophilia was more commonly found in the SCC type. In lung cancer with large cell carcinoma, SCC, and poorly differentiated adenocarcinoma, cancer cells generated Interleukin-6 (IL-6), which caused the production of G-CSF (stimulating neutrophil formation).

Paraneoplastic Hypereosinophilia

In this study, the proportion of eosinophilia was 14%, and the proportion of paraneoplastic hypereosinophilia was 2.9%. It has been reported that eosinophilia appeared in 3% of patients with lung cancer.[30] Eosinophilia was found in 19.8% of newly diagnosed patients with lung cancer in Bangalore, India.[16] Hypereosinophilia was found in various types of NSCLC in case reports. However, paraneoplastic hypereosinophilia was very rare and found in only eight adenocarcinoma cases, five large cell carcinoma cases, and two SCC cases. All these case reports involved male patients, most of whom smoked and were in advanced stages.[31] Four subjects with paraneoplastic hypereosinophilia in this study were males who had a smoking history, had the histologic type of SCC (three subjects) and SCLC (one subject), and most of them (three subjects) were in the advanced stage. This study had no significant correlation between paraneoplastic hypereosinophilia and patient characteristics.

Paraneoplastic Thrombocytosis

The proportion of paraneoplastic thrombocytosis in this study was 18.4%. Similar results were obtained in the study by Baburao, *et al*. (2015) in India (14.6%).[16] This might be due to the similarity in the data collection method, which was during the first evaluation and not throughout the course of the disease. Some studies indicated that these proportions ranged between 13–32% or 40%.[30,32] The Chi-square test showed that paraneoplastic thrombocytosis did not significantly correlate with all the characteristics tested in this study.

Boddu, *et al*. (2016) found that the proportion of paraneoplastic thrombocytosis was 4.6%, which was associated with the lung cancer stage.[33] It was suspected that inflammatory cytokines that affected thrombocytosis also played a role in tumor progression and metastasis. Thrombocytosis was thought to be associated with tumor spread in lung cancer and other malignancies. This was not found in this study, as paraneoplastic thrombocytosis was not correlated with stage or histologic type. Thrombocytosis was also correlated with low survival and poor prognosis of lung cancer. This was not found in this study since most subjects had PS <2.

Paraneoplastic Hypercoagulability

Although no clinical manifestations of coagulation or bleeding disorders were found in any subjects, one or more abnormalities of hemostasis function were found in most subjects (91.2%), with elevated D-dimer level being the most common. It has been reported that coagulation disorders were found in 50% of patients with cancer and 90% in cases of metastasis. Another study found that coagulation disorders were not correlated with histologic type. Only D-dimer level was correlated with advanced stage (metastasis and poor prognosis). In this study, there was no correlation between paraneoplastic hypercoagulability and histologic type. Elevated D-dimer levels were considered the most representative of hypercoagulability conditions since they were the marker of ongoing coagulation activation.

Another study found a significant correlation between elevated D-dimer levels in patients with lung cancer and stage and PS but not with histologic type. In this study, most subjects with paraneoplastic hypercoagulability (elevated D-dimer level) were already in advanced stages/with metastasis (86%), even though they were not associated. The D-dimer analysis did not find a correlation with stage, histologic type, or PS. Paraneoplastic hypercoagulability in the study subjects did not significantly correlate with all the subjects' characteristics.

Hypercoagulability puts patients with cancer at risk of developing venous thromboembolism (VTE). Zhang, *et al*. (2018) found a high incidence of VTE in newly diagnosed patients with lung cancer in the form of deep vein thrombosis (DVT) or pulmonary embolism.[14] This risk increased with the administration of chemotherapy/radiotherapy. The type of adenocarcinoma had a three times greater risk of VTE 3 than SCC. Almost all the subjects in this study were at risk of VTE. However, the risk was not investigated further. Anticoagulant administration in patients with lung cancer with hypercoagulability was recommended, although not indicated. A meta-analysis by Zhang, *et al*. (2018) highlighted that anticoagulant (heparin) had beneficial effects for 1–2 years of survival, especially in patients with SCLC.[14] Khorana, *et al*. (2016) recommended using Khorana scores as a risk assessment tool for determining the risk of VTE and the administration of thromboprophylaxis according to the risk among hospitalized patients with cancer to reduce the incidence of VTE.[34]

CONCLUSION

The most common hematologic paraneoplastic syndromes found in patients with lung cancer were hypercoagulability, neutrophilia, and anemia. The low Hb level of paraneoplastic anemia was correlated with low BMI. Male and smoking history in lung cancer were associated with paraneoplastic leukocytosis and/or neutrophilia. In the future, further research is needed to assess the correlation between hematologic paraneoplastic syndrome and the prognosis of patients with lung cancer.

Acknowledgments
None declared.

Conflict of Interests
The authors declared there is no conflict of interest.

Funding
This study was self-funded by the main author.

Authors' Contributions
Conceiving the research idea: ACP and SJ. Data collecting: SJ. Supervising: ACP and ES. Analyzing the

data and writing the manuscript: ACP, SJ, and WW. All authors provided critical feedback and contributed to the final manuscript.

REFERENCES

1. Jusuf A, Yahya W, Hermansyah E. Epidemiologi Kanker Paru. In: Jusuf A (ed) *Dasar-Dasar Diagnosis Kanker Paru*. Jakarta: UI Press, 2017, pp. 1–9.
2. Jusuf A, Hudoyo A, Andriani R, *et al*. Diagnosis Kanker Paru. In: Jusuf A (ed) *Dasar-Dasar Diagnosis Kanker Paru*. Jakarta: UI Press, 2017, pp. 127–168.
3. Silvestri GA, Pastis NJ, Tanner NT, *et al*. Clinical Aspects of Lung Cancer. In: Broaddus VC, Mason RJ, Murray JF, et al. (eds) *Murray & Nadel's Textbook of Respiratory Medicine*. Elsevier Saunders, pp. 940–964.
4. Paraschiv B, Diaconu CC, Toma CL, *et al*. Paraneoplastic Syndromes: The Way to an Early Diagnosis of Lung Cancer. *Pneumologia* 2015; 64: 14–19. [PubMed]
5. International Agency for Research on Cancer. *Fact Sheets by Population, Incidence, Mortality, and 5-Year Prevalence: Both Sexes: Indonesia*. Geneva, http://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf (2018).
6. Nakamura K, Ukawa S, Okada E, *et al*. Characteristics and Prognosis of Japanese Male and Female Lung Cancer Patients: The BioBank Japan Project. *J Epidemiol* 2017; 27: S49–S57. [PubMed]
7. Dewi AP. *Kadar Procalcitonin pada Pasien Kanker Paru dengan Pneumonia*. Universitas Indonesia, https://lib.ui.ac.id/detail?id=20481531&lokasi=lokal (2018).
8. Novariani R. *Proporsi Kanker Paru dengan Riwayat Kanker pada Keluarga*. Universitas Indonesia, https://lib.ui.ac.id/detail?id=20417080&lokasi=lokal (2015).
9. (WHO) WHO. *Global Youth Tobacco Survey (GYTS) Indonesia Report, 2014*. New Delhi, https://apps.who.int/iris/handle/10665/205148 (2015).
10. Athey VL, Walters SJ, Rogers TK. Symptoms at Lung Cancer Diagnosis are Associated with Major Differences in Prognosis. *Thorax* 2018; 73: 1177–1181. [PubMed]
11. Sanikini H, Yuan J-M, Butler LM, *et al*. Body Mass Index and Lung Cancer Risk: A Pooled Analysis based on Nested Case-Control Studies from Four Cohort Studies. *BMC Cancer* 2018; 18: 220. [PubMed]
12. Latimer KM, Mott TF. Lung Cancer: Diagnosis, Treatment Principles, and Screening. *Am Fam Physician* 2015; 91: 250–256. [PubMed]
13. Fukumoto K, Ito H, Matsuo K, *et al*. Cigarette Smoke Inhalation and Risk of Lung Cancer: A Case-Control Study in a Large Japanese Population. *Eur J Cancer Prev* 2015; 24: 195–200. [PubMed]
14. Zhang X, Wu L, Xu Y, *et al*. Trends in the Incidence Rate of Lung Cancer by Histological Type and Gender in Sichuan, China, 1995-2015: A Single-Center Retrospective Study. *Thorac Cancer* 2018; 9: 532–541. [PubMed]
15. Kong J, Xu F, He M, *et al*. The Incidence of Lung Cancer by Histological Type: A Population-Based Study in Tianjin, China during 1981-2005. *Respirology* 2014; 19: 1222–1228. [PubMed]
16. Baburao A, Narayanswamy H. Clinico-Pathological Profile and Haematological Abnormalities Associated with Lung Cancer in Bangalore, India. *Asian Pac J Cancer Prev* 2015; 16: 8235–8238. [PubMed]
17. Sembiring R, Hidajat H, Jusuf A, *et al*. Klasifikasi Histologis Kanker Paru. In: Jusuf A (ed) *Dasar-Dasar Diagnosis Kanker Paru*. Jakarta: UI Press, 2017, pp. 89–101.
18. Sagawa M, Sugawara T, Ishibashi N, *et al*. Efficacy of Low-Dose Computed Tomography Screening for Lung Cancer: The Current State of Evidence of Mortality Reduction. *Surg Today* 2017; 47: 783–788. [PubMed]
19. Nawa T, Fukui K, Nakayama T, *et al*. A Population-Based Cohort Study to Evaluate the Effectiveness of Lung Cancer Screening Using Low-Dose CT in Hitachi City, Japan. *Jpn J Clin Oncol* 2019; 49: 130–136. [PubMed]
20. Jusuf A, Wibawanto A, Icksan A, *et al*. *Kanker Paru Jenis Karsinoma bukan Sel Kecil: Pedoman Diagnosis dan Penatalaksanaan di Indonesia*. Jakarta, 2016.
21. Souilah S, Dermech N, Benbetka Y, *et al*. *Anemia during Lung Cancer*. 2018. Epub ahead of print 15 September 2018.
22. Zabłocka-Słowińska KA, Kosacka M, Porębska I, *et al*. The Usefulness of Routinely Used Malnutrition Screening Tools in Predicting Anemia in Lung Cancer Patients. *Adv Clin Exp Med* 2017; 26: 1383–1389. [PubMed]
23. Bacha S, Mejdoub El Fehri S, Habibech S, et al. Impact of Malnutrition in Advanced Non-Small

Cell Lung Cancer. *Tunis Med* 2018; 96: 59–63. [PubMed]
24. Macciò A, Madeddu C, Gramignano G, *et al*. The Role of Inflammation, Iron, and Nutritional Status in Cancer-Related Anemia: Results of a Large, Prospective, Observational Study. *Haematologica* 2015; 100: 124–132. [PubMed]
25. Sbrana A, Torchio M, Comolli G, *et al*. Use of Procalcitonin in Clinical Oncology: A Literature Review. *New Microbiol* 2016; 39: 174–180. [PubMed]
26. Scheinpflug K, Schalk E, Grabert E, *et al*. Procalcitonin is Not Useful to Discriminate between Infectious and Non-Infectious CRP Elevation in Patients with Non-Small Cell Lung Cancer. *Infection Control and Hospital Epidemiology* 2015; 36: 1117–1118. [PubMed]
27. Avrillon V, Locatelli-Sanchez M, Folliet L, *et al*. Lung Cancer May Increase Serum Procalcitonin Level. *Infect Disord Drug Targets* 2015; 15: 57–63. [PubMed]
28. Durnaś B, Wątek M, Wollny T, *et al*. Utility of Blood Procalcitonin Concentration in the Management of Cancer Patients with Infections. *Onco Targets Ther* 2016; 9: 469–475. [PubMed]
29. Higuchi T, Omata F, Tsuchihashi K, *et al*. Current Cigarette Smoking is a Reversible Cause of Elevated White Blood Cell Count: Cross-Sectional and Longitudinal Studies. *Prev Med Reports* 2016; 4: 417–422. [PubMed]
30. Jameson JL, Longo DL. Paraneoplastic Syndromes: Endocrinologic/Hematologic. In: Jameson JL, Fauci AS, Kasper DL, et al. (eds) *Harrison's Principles of Internal Medicine, 20e*. New York, NY: McGraw-Hill Education, http://accessmedicine.mhmedical.com/content.aspx?aid=1160012181 (2018).
31. Abughanimeh O, Tahboub M, Abu Ghanimeh M. Metastatic Lung Adenocarcinoma Presenting with Hypereosinophilia. *Cureus* 2018; 10: e2866. [PubMed]
32. Pastis NJ, Tanner NT, Silvestri GA. Extrapulmonary Syndromes Associated with Lung Tumors. In: Grippi MA, Elias JA, Fishman JA, et al. (eds) *Fishman's Pulmonary Diseases and Disorders*. New York, NY: McGraw-Hill Education, http://accessmedicine.mhmedical.com/content.aspx?aid=1122367942 (2015).
33. Boddu P, Villlines D, Aklilu M. Paraneoplastic Leukocytosis and Thrombocytosis as Prognostic Biomarkers in Non-Small Cell Lung Cancer. *Zhongguo Fei Ai Za Zhi* 2016; 19: 725–730. [PubMed]
34. Khorana AA, Carrier M, Garcia DA, *et al*. Guidance for the Prevention and Treatment of Cancer-Associated Venous Thromboembolism. *J Thromb Thrombolysis* 2016; 41: 81–91. [PubMed]