ORIGINAL ARTICLE

Preoperative thrombocytosis in surgically treated patients with non–small cell lung cancer

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KEY WORDS

lung cancer, non–small cell lung cancer, paraneoplastic syndrome, prognostic factors, thrombocytosis

ABSTRACT

INTRODUCTION Lung cancer is the most common cause of cancer-related death. Accurate and easy-to--use prognostic factors are necessary. Increased platelet count might be a potential prognostic factor.

OBJECTIVES We aimed to investigate the relationship between thrombocytosis and stage of lung cancer and to assess the frequency and clinical importance of thrombocytosis in this patient group.

PATIENTS AND METHODS We retrospectively analyzed hospital records of consecutive patients with non–small cell lung cancer (NSCLC) who underwent curative-intent pulmonary resections.

RESULTS Of 323 patients, 285 patients with NSCLC were selected (mean [SD] age, 66.55 [8.52] years; men, 63.86%). Squamous cell carcinoma was diagnosed in 130 patients (45.61%); adenocarcinoma, in 128 (44.91%); large cell carcinoma, in 16 (5.61%); and adenosquamous carcinoma, in 11 (3.86%). The prevalence of preoperative thrombocytosis in the whole sample was 10.18% (n = 29). Anemia was more common in patients with thrombocytosis compared with those without thrombocytosis (65.52% vs 30.08%; $P < 0.001$). Thrombocytosis was found in 22.41% of patients with stage III+IV cancer and in 3.82% of those with stage I ($P < 0.001$). Moreover, in patients with no metastases (N0, M0 according to the 7th edition of the TNM classification), thrombocytosis was more frequent in the group with stage II than in that with stage I cancer (3.85% vs 20.00%; $P = 0.002$). Thrombocytosis was also more frequent in patients with N2 than with N1 disease (9.76% vs 23.81%; $P = 0.09$).

CONCLUSIONS Thrombocytosis is often observed in patients with NSCLC and is significantly associated with the higher stage of disease.

INTRODUCTION Lung cancer is the most common cause of cancer-related death. In Poland, it is diagnosed in about 16 000 men and 6000 women every year.[1] Because of its considerable prevalence, late diagnosis, and high mortality, as well as close relationship with tobacco smoking, it is undoubtedly a serious and unresolved health-related problem. Numerous studies performed in recent decades resulted in considerable progress in diagnosis and treatment of lung cancer. Particularly, personalization of treatment, which means proper selection of therapy for specific patients, is gaining increasing importance. While planning optimal, individualized therapy, prognostic and predictive factors are crucial. They should be characterized by several features, such as simplicity and high availability, effectiveness in patient stratification, scientifically proven prognostic or predictive significance, and finally low test--related cost.

The first report of increased platelet count in a patient with cancer dates back to 1872.[2] Since then numerous studies investigating this phenomenon have been published, and baseline platelet count has been acknowledged as a prognostic factor in patients with lung cancer. The use of this simple, inexpensive, and widely available marker is an attractive option. The relationship between platelet count and the survival of patients with some of the most common types of cancer, including lung cancer, has been shown by Zhang et al.[3] Furthermore, this indicator can be used during diagnostic workup in lung cancer patients or as an indicator of lung metastasis.[4,5]

Although the issue has been investigated in several studies, it has not been fully elucidated so

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Received: April 17, 2018.
Revision accepted: June 26, 2018.
Published online: July 26, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (9): 512-517
doi:10.20452/pamw.4299

TABLE 1 Clinicopathological characteristics of the study group

Variable		All patients	Patients with thrombocytosis	Patients with normal platelet count	*P* value[c]
Total number of patients with NSCLC, n (%)		285 (100)	29 (10.18)	256 (89.82)	–
Women, n (%)		103 (36.14)	13 (44.83)	90 (35.16)	0.41
Men, n (%)		182 (63.86)	16 (55.17)	166 (64.84)	
Age, median (IQR)		66 (62.00–72.00)	64 (60.00–70.00)	67 (62.00–72.00)	0.17
Age ≥65 years, n (%)		176 (61.75)	14 (48.28)	162 (63.28)	0,17
Smoking, n (%)		179 (62.81)	20 (74.07[a])	159 (62.85[b])	0.17
COPD, n (%)		44 (15.44)	4 (14.81[a])	40 (15.81[b])	0.58
Diabetes, n (%)		49 (17.19)	3 (11.11[a])	46 (18.18[b])	0.27
Histological type, n (%)	SCC	130 (45.61)	14 (48.28)	116 (45.31)	0.97
	ADC	128 (44.91)	12 (41.38)	116 (45.31)	
	LCC	16 (5.61)	2 (6.90)	14 (5.47)	
	Adenosquamous carcinoma	11 (3.86)	1 (3.45)	10 (3.91)	
PLT, × 10^3/μl, median (IQR)		254.00 (211.00–319.00)	449.00 (423.00–546.00)	249.50 (208.00–292.00)	<0.001
Hemoglobin, g/dl, median (IQR)		13.40 (12.80–14.20)	11.30 (9.90–13.20)	13.50 (12.80–14.35)	<0.001
Anemia (hemoglobin concentration <13.5 g/dl for men, <12.0 g/dl for women), n (%)		96 (33.68)	19 (65.52)	77 (30.08)	<0.001
Neoadjuvant chemotherapy		8 (2.81)	0	8 (3.13)	–

a Missing data of 2 patients; **b** Missing data of 3 patients; **c** Patients with thrombocytosis vs patients with normal platelet count

Conversion factors to SI units: to convert hemoglobin to g/l, multiply by 10.0, platelet count to × 10^9/l, multiply by 1.0.

Abbreviations: ADC, adenocarcinoma; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LCC, large-cell carcinoma; NSCLC, non–small cell lung cancer; PLT, platelet count; SCC, squamous cell carcinoma

far. Moreover, to our knowledge, none of the studies have involved the Polish population. In our study, we aimed to investigate the relationship between thrombocytosis and stage of non–small cell lung cancer (NSCLC) and to assess the frequency and clinical importance of thrombocytosis in this patient group.

PATIENTS AND METHODS

This retrospective study was conducted in the Department of Thoracic Surgery, John Paul II Hospital, Kraków, Poland. The study group included consecutive patients with NSCLC who underwent a curative-intent pulmonary resection between September 2015 and December 2016. Data used for analysis were obtained from medical records. The following variables were recorded: patients' demographics, cancer stage, grade, histological type, and lymph node metastases, platelet count, hemoglobin concentration, comorbidities, and smoking habit.

Thrombocytosis was assessed from the last whole blood count obtained before the surgery and was defined as a platelet count higher than 400 000/μl. Preoperative hemoglobin concentrations were also measured, with anemia being defined as a hemoglobin concentration of less than 12 g/dl for women and less than 13.5 g/dl for men. The stage of lung cancer was based on the 7th edition of the TNM classification. Each patient underwent preoperative staging, including chest radiography, computed tomography, positron-emission tomography combined with computed tomography, endobronchial ultrasound, and endoscopic ultrasound. For the analysis, the final, pathological stage was used.

The approval of the ethics committee was not required due to a retrospective study design (analysis of hospital records).

Statistical analysis Statistica 12.0 software (StatSoft, Statistica 12.0, Tulsa, Oklahoma, United States) was used for statistical analysis. Continuous data were presented as mean and standard deviation (SD) or median and interquartile range (IQR), and qualitative data, as numbers and percentages. The χ^2 test and Fisher test were used to compare qualitative data, while the *t* test, Mann–Whitney test, and analysis of variance were used for quantitative data. Continuous variables were first checked for normal distribution by the Shapiro–Wilk test. For the analysis of variables with other than normal distribution, the Mann–Whitney test was used and the values were presented as median and IQR; data with normal distribution were analyzed with the *t* test. To compare more than 2 groups, the analysis of variance with proper corrections was performed. The MedCalc statistical online calculator was used for estimation diagnostic test parameters. For all tests, a *P* value less than 0.05 was considered significant. Patients with missing specific data were not included in further analysis.

RESULTS

The clinicopathologic characteristics of patients are shown in TABLE 1. The total number of patients collected between 30 June

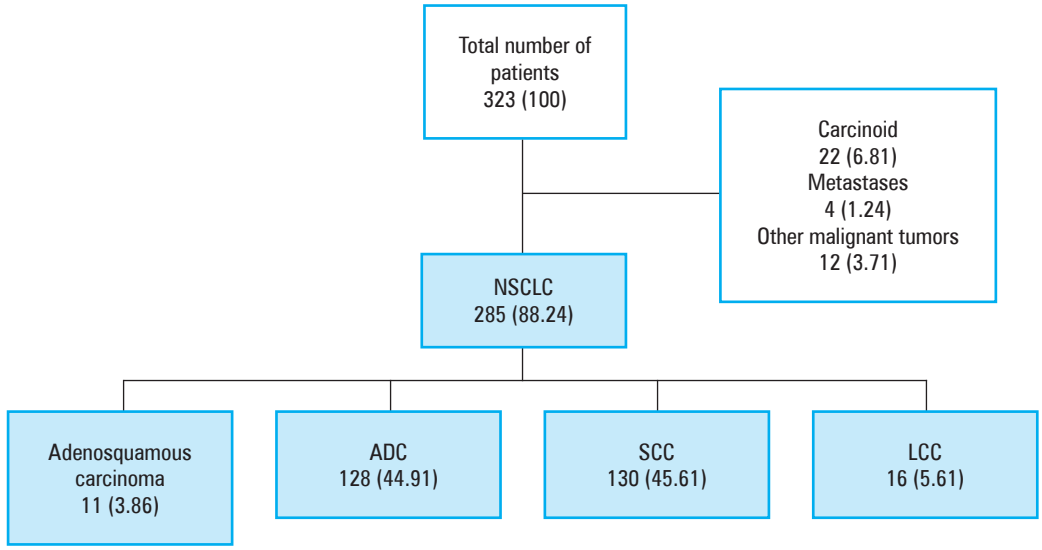

FIGURE 1 Distribution of study participants depending on the histological type of the tumor. Data are shown as number (percentage) of patients. Abbreviations: see TABLE 1

2017 and 15 November 2017 was 323. The histological types of NSCLC were squamous cell carcinoma (SCC) in 130 cases (40.2%); adenocarcinoma (ADC), in 128 (39.63%); large cell carcinoma (LCC), in 16 (4.95%); adenosquamous carcinoma, in 11 (3.41%); carcinoid, in 22 (6.81%); pulmonary metastases in 4 (1.24%); and other malignant tumors, in 12 (3.71%).

Because of different pathology, carcinoids, lung metastases, and other tumors were excluded. This resulted in a homogenous group of 285 patients with SCC, ADC, adenosquamous carcinoma, and LCC, whose data were included in the final analysis (FIGURE 1). The mean (SD) age of the study group was 66.55 (8.52) years (range, 29–88 years), and there were 182 men (63.86%). Active smoking was reported by 179 patients (62.81%); chronic obstructive pulmonary disease was observed in 44 patients (15.44%) and diabetes in 49 (17.19%). Prior neoadjuvant chemotherapy was administered in 8 patients (2.81%). The median platelet count was 254×10^3/μl (IQR, 211–319; min–max, 119.00–806×10^3/μl). Median hemoglobin concentration was 13.4 g/dl (IQR, 12.80–14.20).

The prevalence of preoperative thrombocytosis was 10.18% (29 patients). The comparison of groups with and without thrombocytosis is shown in TABLE 1. There were no differences between groups in terms of sex, age, chronic obstructive pulmonary disease, diabetes, and histological type of cancer. Preoperative anemia was significantly more common (19 [65.52%] vs 77 [30.08%]; P <0.001) as well as median hemoglobin concentrations were lower (P <0.001) in patients with thrombocytosis. There were no differences between patients with and without thrombocytosis in terms of the smoking habit. There was no relationship between histological type of cancer and smoking habit. The number (percentage) of smokers and nonsmokers was 87 (48.60%) and 41 (40.59%), respectively, in the SCC group (P = 0.20) and 75 (41.90%) and 51 (50.50%), respectively, in the ADC group (P = 0.17).

The results of analyses according to the stages of lung cancer are presented in TABLE 2. Stage distribution in the overall study group was as follows: stage IA, 98 patients (34.39%); IB, 59 (20.70%); IIA, 41 (14.39%); IIB, 29 (10.18%); IIIA, 49 (17.19%); IIIB, 1 (0.35%); and IV, 8 (2.81%). The platelet count at different stages of disease are presented in FIGURE 2. Thrombocytosis was more frequently diagnosed in the combined group of patients with III+IV stages of disease (13 [22.41]; P <0.001) than in stage I (6 [3.82]) and stage II (10 [14.29]). Similar association was observed also in the case of thrombocytosis without anemia (TABLE 2). However, there was no case of thrombocytosis without anemia in stage II. There was no difference in the prevalence of thrombocytosis between stages IIB and IIIA (6 [20.69%] vs 10 [20.41%]; P = 0.60). However, patients in group IIIA more often had thrombocytosis than patients with stage I (10 [20.41%] vs 6 [3.82%]; P <0.001) and had a higher median platelet count (276 [IQR, 242–381] vs 245 [IQR, 207–286]; P <0.001).

A separate analysis was performed in patients with no metastases (N0, M0) stage I (IA+IB) and II (IIA+IIB). In stage II, thrombocytosis was more frequent than in stage I (8 [20.00%] vs 6 [3.85%]; P = 0.002). Stage II was also characterized by a higher median platelet count (285.50×10^3/μl [IQR, 214.00–364.50] vs 245.00×10^3/μl [IQR, 206.50–287.50]; P = 0.01)

The analysis of a histological grade of the tumor showed grade I in 15 cases; grade II in 160; grade III, in 86; and grade IV, in 21. There was no association between tumor grade and thrombocytosis.

Data of patients with N0, N1, and N2 involvement are presented in TABLE 3. There were no significant differences between N0 and N1 patients in the prevalence of thrombocytosis and thrombocytosis without anemia. However, patients with N2 disease significantly more often had thrombocytosis and thrombocytosis without anemia than those with N0 disease. There was no such association in a direct comparison between N2 and N1 patients. The evaluation of thrombocytosis

TABLE 2 Relations between the stage of non–small cell lung cancer and thrombocytosis with or without anemia and the platelet count

Parameter	NSCLC stage							*P* value
	I		II		III+IV			
	IA	IB	IIA	IIB	IIIA	IIIB	IV	
Total number of patients, n	98	59	41	29	49	1	8	–
Patients with thrombocytosis, n (%)	5 (5.10)	1 (1.69)	4 (9.76)	6 (20.69)	10 (20.41)	1 (100.0)	2 (25.00)	<0.001
	6 (3.82)		10 (14.29)		13 (22.41)			<0.001
Patients with thrombocytosis without anemia, n (%)	3 (1.91)		0		7 (12.07)			<0.001
PLT, × 10^3/μl, median (IQR)	244.50 (205.00–291.00)	250.00 (208.00–286.00)	269.00 (209.00–337.00)	247.00 (221.00–347.00)	276.00 (242.00–381.00)	402.00[a]	318.00 (264.50–387.00)	<0.001
	245.00 (207.00–286.00)		269.50 (210.00–343.00)		285.00 (242.00–382.00)			<0.001
Hemoglobin, g/dl, median (IQR)	13.50 (12.80–14.50)	13.80 (13.00–14.70)	13.20 (12.60–13.90)	12.70 (11.70–14.00)	13.40 (12.10–14.10)	12.9[a]	13.30 (12.40–14.10)	0.001
	13.70 (12.90–14.60)		13.10 (12.10–13.90)		13.40 (12.20–14.10)			<0.001

a Data of a single patient

Abbreviations: OR, odds ratio; others, see **TABLE 1**

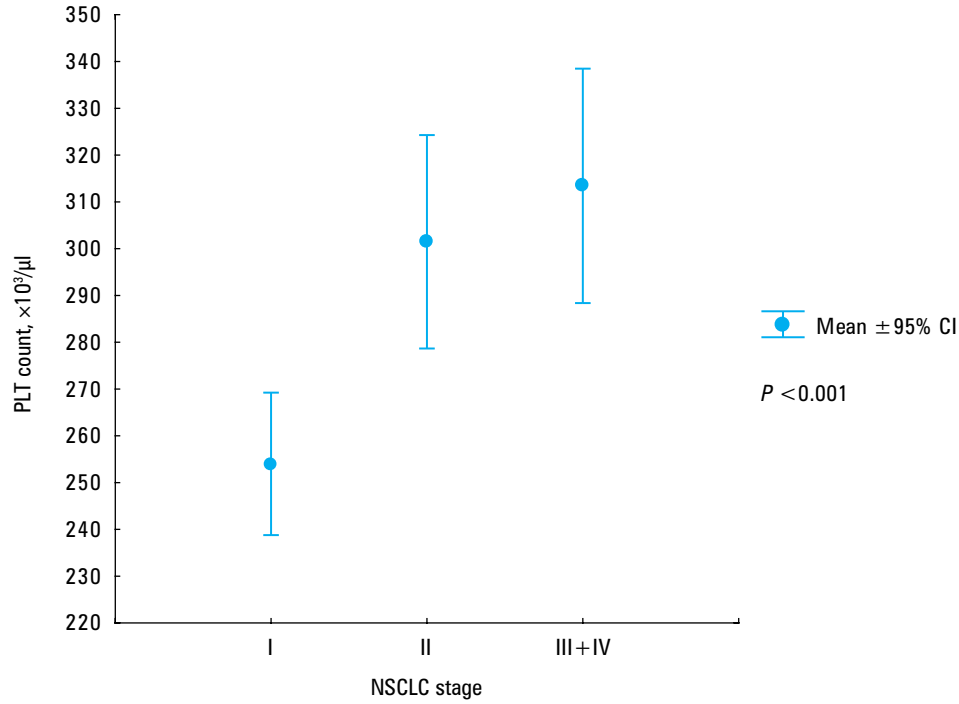

FIGURE 2 Differences in mean platelet (PLT) count depending on the stage of non–small cell lung cancer (NSCLC)

as a diagnostic test for metastases in N2 lymph nodes was characterized by a sensitivity of 23.81% (95% CI, 12.05%–39.45%), specificity of 92.18% (95%CI, 88.06%–95.23%), positive predictive value of 34.48% (20.85%–51.26%), and negative predictive value of 82.11% (95% CI, 77.15%–86.38%).

DISCUSSION Numerous studies evaluated thrombocytosis in patients with malignancy; however, only a few of them included patients with less advanced stages of lung cancer. Furthermore, none of them was performed in the Polish population.

In our group, the frequency of preoperative thrombocytosis was 10.18%, which is similar to the results obtained in previous studies on comparable groups with identical thrombocytosis cutoff values.[6,7]

The mechanism underlying increased platelet count in patients with cancer and the association of high platelet count with worse prognosis are still poorly understood. Under physiological conditions, the production of platelets in the bone marrow is mainly stimulated by thrombopoietin. In cancer, the tumor affects thrombopoiesis through some alternative factors, such as interleukin (IL) 1, IL-3, IL-6, and IL-11, fibroblast growth factor, and erythropoietin.[8] The production of so many cytokines and elevated platelet

TABLE 3 Concomitance of thrombocytosis and lymph node metastases in patients with non–small cell lung cancer

		N0	N1	*P* value (N0 vs N1)	N2	*P* value (N1 vs N2)	*P* value (N0 vs N2)
Total number of patients, n (%)		202 (70.88)	41 (14.39)	–	42 (14.74)	–	–
Patients with thrombocytosis, n (%)		15 (7.43)	4 (9.76)	0.40	10 (23.81)	0.09	0.001
Patients with thrombocytosis without anemia, n (%)		3 (1.49)	1 (2.44)	0.53	6 (14.29)	0.06	0.001
Histological type of NSCLC, n (%)	SCC	88 (43.56)	21 (51.22)	0.02	21 (50.00)	0.18	0.75
	ADC	98 (48.51)	12 (29.27)		18 (42.86)		
	Other types	16 (7.92)	8 (19.51)		3 (7.14)		

Abbreviations: see TABLES 1 and 2

count facilitate and accelerate the progression of cancer.[9] Platelets directly protect cancer cells against contact with the host's immune system, reduce the activity of natural killer cells (which are responsible for the elimination of tumor-transformed cells)[10,11], facilitate transport of cancer cells to other places in the patient's body and development of metastases,[9] and accelerate neoangiogenesis.[12] On the basis of these studies, an interplay between cancer cells and platelets has been proposed, in which platelets are involved not only in blood coagulation process. However, impaired hemostatic function and relationships with different components of the blood clotting system have been studied mainly in hematologic diseases, such as essential thrombocythemia.[13] Moreover, a method of treatment undoubtedly has an effect on hematologic changes and the immune system. For example, stereotactic ablative radiotherapy used in NSCLC may influence white blood cell count.[14] The effect of surgical procedures on thrombocytosis is not well known.

To avoid confounding factors related to different biology of cancer, we analyzed only patients with NSCLC: ADC, SCC and LCC, for which the most effective treatment modality is surgery in early stages.[15,16] However, there were some differences in the rates of the histological types, with most patients having SCC and ADC (with similar distribution). Other studies reported different rates for the various types,[6,17,18] but there is a notable trend for increased incidence of ADC.[15] We did not observe an association between an increased frequency of thrombocytosis and different histological types of lung cancer. This finding is in line with the report by Maraz et al.[17]

Smoking is recognized as the main risk factor for lung cancer. Smokers were predominant in our study group, which is in line with the results of other authors.[18] Maraz et al[17] reported a higher incidence of thrombocytosis in smokers, but this association was not confirmed in our study.

The most common hematologic abnormalities with confirmed negative prognostic value in patients with lung cancer include anemia, thrombocytosis, and leukocytosis.[6,7,19,20] Some patients in our study had coexisting anemia and thrombocytosis. To the best of our knowledge, this is the first report to show simultaneous presence of these 2 hematologic abnormalities. This may be explained by their very similar etiology in cancer patients. Anemia and thrombocytosis are types of paraneoplastic syndromes, which often indicate advanced cancer.[21]

Similarly to other authors,[22] we observed a higher frequency of thrombocytosis associated with more advanced stage of the disease. Moreover, we showed that the frequency of thrombocytosis is higher in N2 disease. In the N0M0 group, the chance of thrombocytosis was significantly higher when the primary tumor was more advanced. These observations may be clinically important. The diagnosis of thrombocytosis in a patient with lung cancer can suggest a higher stage of the disease and is a negative prognostic factor. In our group, the presence of thrombocytosis showed high specificity in the diagnosis of N2 disease.

In our study, none of the patients who underwent preoperative chemotherapy had thrombocytosis. Thrombocytopenia is a frequent adverse event of treatment with platinum-based regimens and gemcitabine.[23] It is likely that the effect of chemotherapy is a confounding factor and that the prognostic value of thrombocytosis is thus low in these patients. On the other hand, because of the small number of patients who underwent neoadjuvant chemotherapy in our study, this hypothesis should be confirmed in further research.

Similarly to Bailey et al,[4] we believe that evaluation of thrombocytosis may be a useful tool in everyday practice in oncology and thoracic surgery, although its significance is neglected. The diagnosis of this blood clotting disorder could prompt a more detailed diagnosis, particularly if found in a patient with N0, M0 tumors.

The study has several limitations, it was a retrospective study and, although the overall number of patients was relatively large, the individual subgroups were small. Another limitation is a single preoperative measurement of complete blood count, without subsequent measurements.

In conclusion, due to its low cost and wide availability, assessment of thrombocytosis may be a useful tool in preoperative screening of lung cancer patients. Thrombocytosis is associated with more advanced stage of the disease and N2 disease. In this study, thrombocytosis often coexisted with anemia. Large prospective studies are needed to further evaluate the role of thrombocytosis in lung cancer.

CONTRIBUTION STATEMENT PS conceived the concept of the study. PS, JH, and JK contributed to the design of the research. KS searched for references. PS, KS, MF, and JH were involved in data acquisition. PS analyzed the data. KS and MF interpreted the data. JK supervised data processing. All authors were involved in drafting and revising the article. All authors approved the final version of the manuscript.

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