Pretreatment Platelet Count is a Prognostic Marker in Lung Cancer: A Danish Registry-based Cohort Study

Birgitte Sandfeld-Paulsen,[1] Ninna Aggerholm-Pedersen,[2,3,4] Anne Winther-Larsen[3,5]

Abstract

To evaluated the prognostic significance of platelet count in lung cancer patients, we extracted data on 7,908 lung cancer patients diagnosed between 2009 and 2018 from Danish registries. Data showed that low and high platelet count were significantly correlated to an inferior overall survival in non–small-cell lung cancer (NSCLC) patients while low platelet count was significantly associated with inferior overall survival in small-cell lung cancer (SCLC) patients.

Background: Thrombocytosis has been associated with a poor prognosis in a wide range of malignancies. However, the results have been conflicting for lung cancer. Therefore, we evaluated the prognostic value of platelet count in a large cohort of lung cancer patients. **Patients and Methods:** All lung cancer patients diagnosed in The Central Denmark Region from 2009 to 2018 were included in the study. Data from the Danish Lung Cancer Registry were combined with data from the clinical laboratory information system on pretreatment platelet count. Platelet count was defined as low, normal, or high based on being below, within, or above the reference intervals. The prognostic value of platelet count was assessed by the Cox proportional hazard model. C-statistics were conducted to investigate if the platelet count added additional prognostic value to existing prognostic markers. **Results:** Totally, 6,758 patients with non–small-cell lung cancer (NSCLC) and 1150 patients with small-cell lung cancer (SCLC) were included. Low and high platelet count were significantly associated with decreased overall survival (OS) in NSCLC patients (low: adjusted hazard ratio (HR)=1.75 (95% confidence interval [CI]: 1.49-2.06); high: adjusted HR=1.24 (95% CI: 1.16-1.33)). In SCLC patients, only low platelet count was significantly associated with decreased OS (adjusted HR = 2.71 [95% CI: 2.02-3.65]). C-statistics showed that the prognostic models were significantly improved by the addition of platelet count for both NSCLC and SCLC patients ($P < .0001$). **Conclusion:** Low and high platelet count were adverse prognostic factors in NSCLC patients, while only low platelet count was a prognostic marker in SCLC patients.

Clinical Lung Cancer, Vol. 24, No. 2, 175–183 © 2023 The Authors. Published by Elsevier Inc.

Keywords: Biomarker, Lung cancer, Platelets, Survival, Thrombocytosis

Introduction

Regardless of the improvements in lung cancer treatment,[1] patients' prognosis remains inferior, and the disease continues to be the leading cause of cancer deaths worldwide.[2] To expand patients' survival in the future, a more optimal stratification of patients built on their prognosis is desirable. By identifying patients with an inferior prognosis, individualized treatment strategies can be initiated to improve the clinical outcome. Numerous prognostic indicators have been proposed, but so far only the tumor-node-metastasis (TNM) staging system[3] and the performance stage (PS) assessment[4] have shown valuable clinical relevance.

For several decades, studies have demonstrated a relation between platelets and cancer.[5] Besides being a well-established predictive marker for the risk of venous thrombosis in cancer patients,[6] platelets have been proposed as an important active player in tumorigenesis as several studies have indicated that platelets can affect tumor growth and metastasis.[5] In line with this, thrombocytosis has been associated with a poor prognosis in several malignancies as colorectal cancer,[7] gynecological cancers,[8,9] mesothelioma,[10] and lung cancer.[11-13] Hence, platelet count could be an inexpensive and easily obtained prognostic marker in lung

[1]Department of Clinical Biochemistry, Viborg Regional Hospital, Viborg, Denmark
[2]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[4]Department of Experimental Oncology, Aarhus University Hospital, Aarhus, Denmark
[5]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Submitted: Sep 6, 2022; Revised: Dec 3, 2022; Accepted: Dec 5, 2022; Epub: 27 December 2022

Address for correspondence: Anne Winther-Larsen, MD, PhD, Department of Clinical Biochemistry, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200, Aarhus N, Denmark
E-mail contact: Birgitte.Sandfeld@aarhus.rm.dk, ninnpede@rm.dk, anlarsen@rm.dk

https://doi.org/10.1016/j.cllc.2022.12.012

cancer. However, lung cancer data have been conflicting as the prognostic value of thrombocytosis could not be confirmed by all studies.[14-16] Although a considerable number of studies exist in the field, most studies published are based on patients with non–small-cell lung cancer (NSCLC), while only a few studies have included patients with small-cell lung cancer (SCLC). Furthermore, the published studies on SCLC and NSCLC patients have generally been conducted in patient cohorts of limited sizes. Additionally, the studies have varied extensively in the platelet cut-off value used to define thrombocytosis, which may explain the contradictory data reported. In addition, the prognostic value of thrombocytopenia remains undetermined. Given this controversy about the prognostic significance of thrombocytosis and the unexplored impact of thrombocytopenia, this study aimed to investigate the prognostic importance of the pretreatment platelet count in an extensive Danish registry-based cohort of NSCLC and SCLC patients.

Patients and Methods

Patients

The registry-based cohort has been previously thoroughly described.[17] Briefly, patients were included from the Danish Lung Cancer Registry (DLCR)[18] if they were diagnosed with lung cancer between January 2009 and June 2018 in the Central Denmark region. Information on sex, age, Eastern Cooperative Oncology Group (ECOG) PS, TNM-stage, and smoking status were retrieved for each patient at time of diagnosis from the DLCR. These data were merged with tumor characteristic data retrieved from The national Danish Pathology Data Bank[19] and with platelet count value obtained from the clinical laboratory information system.[20] The clinical laboratory information system encompasses data on all blood samples retrieved from hospitalized patients and primary care patients in the Central Denmark region. Data on mortality were obtained from the Danish Civil Registration System.[21] Merging of data on an individual level was possible owing to the unique CPR number given to all citizens in Denmark at birth and to residents at time of immigration.

The study was permitted by the Danish Patient Safety Authority (no.31-1521-400) and the Danish Data Protection Agency (no. 1-16-02-909-17). Register-based studies do not need authorization by the regional committee on health-research ethics in accordance with Danish legislation.

Platelet Count

Pretreatment platelet count was extracted for each patient if it had been performed within 90 days before the lung cancer diagnosis was registered. If multiple measurements were available in the clinical laboratory information system during the time period, the measurement closest to the date of diagnosis was selected. Patients with no available pretreatment platelet count were excluded from further analysis.

All platelet counts were analyzed on an automated hematology analyzer, either Sysmex hematology analyzer (Sysmex, Kobe, Japan) or ADVIA hematology system (Bayer Diagnostics, Tarrytown, NY), using flow cytometry.

According to the reference interval for each sex, patients were divided into 3 groups based on their pretreatment platelet count: below the reference interval = "low platelet count"; within the reference interval = "normal platelet count"; and higher than the reference interval = "high platelet count". The reference intervals estimated by Nordin et al[22] were used for the grouping (women: 165-400 $\times$ 10^9/L and men: 145-350 $\times$ 10^9/L).

Statistical Analysis

Amounts and fractions, or the median value with 5% and 95% percentiles, were used to present patient characteristics. Differences in patient characteristics between groups were analyzed by the χ^2 or the rank-sum test.

Overall survival (OS) and follow-up time were determined as the period from diagnosis until death for any reason or the last follow-up date (July 1, 2020). Any patient still alive at the end of follow-up was censored. Patients with a survival of solely one day were excluded. All patients had been followed for more than 2 years, as the most recent patients were incorporated in the study in June 2018. The primary endpoint was OS. The median OS was estimated by the Kaplan–Meier method and the median OSs between groups were compared by the log-rank test. The Cox proportional hazards model was applied to compute the crude and adjusted hazard ratios (HR). Platelet count was analyzed as both a categorical and a continuous variable, whereas sex, stage, histology, smoking, neutrophil-to-lymphocyte ratio (NLR) and PS were analyzed as categorical variables, and age was analyzed as a continuous variable. All variables were analyzed as categorical variables, except for age (continuous variable).

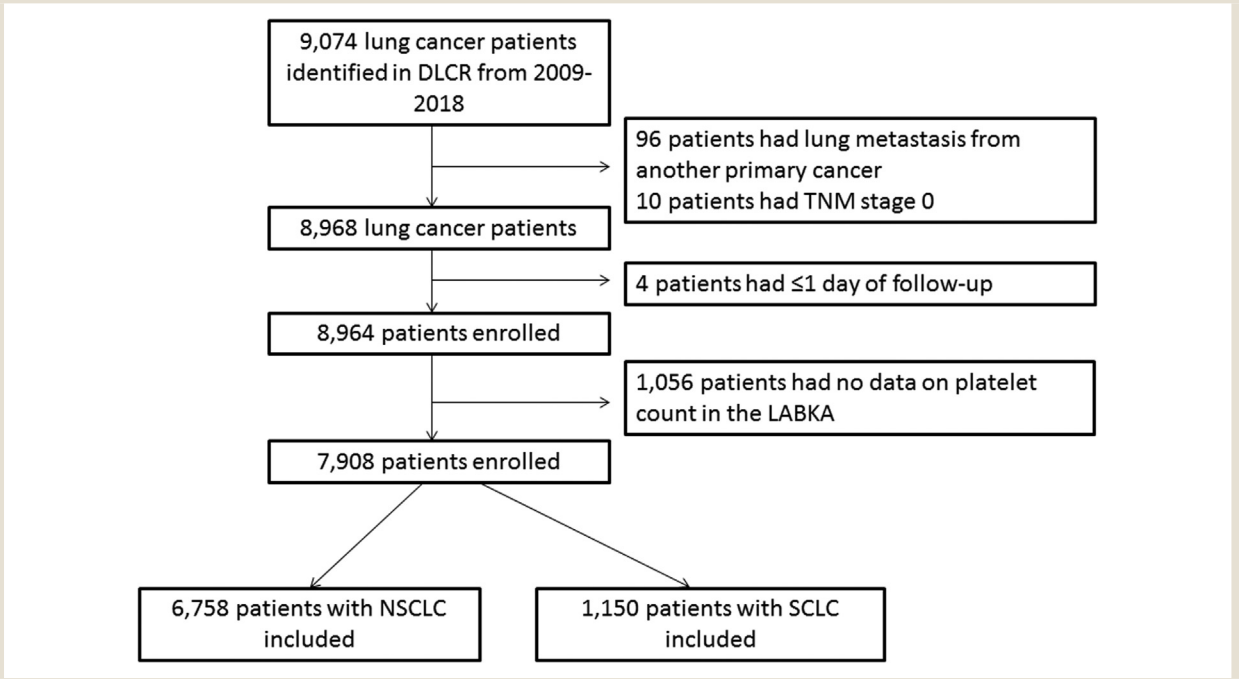
C-statistics were used to estimate whether the addition of platelet count to the well-established prognostic factors (age, sex, histology, TNM stage, PS, NLR and smoking) improved the prognostic power. NLR was included in the model as we have previously explored the role of other blood markers including hemoglobin, lymphocyte count, monocyte count, and neutrophil count, as well as NLR and platelet-to-lymphocyte ratio, and demonstrated that NLR was the superior biomarker in NSCLC as well as SCLC patients.[23-25] The following cut-points were applied for NLR: low: <3 and high: ≥ 3. Akaike's information criteria (AIC) along with Harrell's concordance index (C-index) were analyzed on models incorporating and excluding platelet count. The model with the lowest AIC was interpreted as the model with the most exact prediction of OS, and solely a difference ≥ 2 (arbitrary values) was interpreted as a real difference. For the C-index, values ranged between 0.5 and 1.0, and the value 1.0 was determined as the perfect fit. Finally, to assess whether the added value was statistically significant, likelihood-ratio tests were applied. All *P*-values were 2-sided, and a *P*-value below .05 indicated statistical significance. All statistical analyses were performed with the Stata software version 17.0 (Stata Corporation, College Station, TX).

Results

Patients

Altogether, 9074 lung cancer patients were identified in the DLCR (Figure 1). Yet, 96 patients had lung metastasis from another primary cancer, 10 patients had TNM stage 0, and 4 patients had less than 1 day of follow-up and, hence, all were excluded from further analysis. Furthermore, 1056 patients were excluded as a

Figure 1 Flow chart of inclusion and exclusion of patients. DLCR = Danish Lung Cancer Group; LABKA = clinical laboratory information system; NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer; TNM = tumor-node-metastasis.



platelet count was not available in the LABKA database. Therefore, 7908 lung cancer patients were included in the study, of whom 6758 patients had NSCLC and 1150 patients had SCLC. As shown in Supplemental Table I, the 1,056 excluded patients had a significantly higher age and higher PS than the 7908 included patients.

Patient Characteristics and Platelet Count in NSCLC Patients

The 6758 NSCLC patients had a median age of 70 years (5%-95% percentiles: 52-84). The majority of the patients were males (52%), had advanced stage of disease (III+IV: 62%), adenocarcinoma (53%), and a good PS of 0 or 1 (65%). The patients were predominantly current or former smokers (74%) (Table 1).

A platelet count above the reference interval was found in 28% of patients and a platelet count below was found in 5% of the patients (Table 1). In patients with a high platelet count, a lower age (68 years vs. 71 years, $P = .001$), a higher frequency of males (58% vs. 49%, $P < .0001$), and histology of squamous cell (28% vs. 23%, $P < .0001$) were found compared with patients with normal platelet count. Moreover, a higher frequency of stage IV patients was observed in the low and high platelet count groups compared with the normal platelet count group (49% and 51% vs. 41%, $P < .0001$) (Table 1).

Survival According to Platelet Count in NSCLC Patents

The median OS of the entire cohort of NSCLC patients was 0.94 years (95% confidence interval [CI]: 0.91-0.99). At the ultimate follow-up date, 5408 patients (80%) had died, and the median follow-up time for patients remaining alive on that day was 4.37 years (5%-95% percentiles: 2.14-10.28).

As illustrated in Figure 2A, both a low and high platelet count were significantly correlated to a decreased OS (median OS: low platelet count, 0.42 years (95% CI: 0.32-0.55); high platelet count, 0.64 years (95% CI: 0.58-0.70); normal platelet count, 1.18 years (95% CI: 1.10-1.25); $P < .0001$). Generally, the correlation was observed for all stages of lung cancer (Supplemental Figure 1). In addition to platelet count, the univariate analysis showed that sex, age, stage, histology, smoking status, and PS all were significantly associated with OS (Table 2). Thus, to assess the prognostic value of platelet count, a multivariate analysis was performed. As presented in Table 2, the platelet count stayed a prognostic predictor.

Furthermore, C-statistics were performed to evaluate if the addition of platelet count to the well-known prognostic factors (sex, age, stage, PS, histology, NLR and smoking) truly supplemented the prognostic value. As displayed in Table 3, the model was enhanced by adding platelet count and this enhancement was statistically significant ($P < .0001$).

Patient Characteristics and Platelet Count in SCLC Patients

A median age of 69 years (5%-95% percentiles: 52-83) was found in the 1150 SCLC patients (Table 4). The majority of the patients had a good PS (0+1: 60%), advanced stage (III+IV: 85%), and were current or former smokers (78%). A high platelet count was

Table 1 Patient Characteristics in all NSCLC Patients and Stratified by Pretreatment Platelet Count (N = 6758)

Characteristics	All Patients N (%)	Low Platelet Count [a] N (%)	Normal Platelet Count[a] N (%)	High Platelet Count [a] N (%)	*P*-value
Total number of patients	6758	363 (5)	4612 (68)	1883 (28)	
Age, years					
Median age (5%-95% percentiles)	70 (52-84)	72 (43-84)	71 (53-84)	68 (52-83)	.001
Sex					
Female	3271 (48)	126 (48)	2353 (51)	792 (42)	< .001
Male	3487 (52)	137 (52)	2259 (49)	1091 (58)	
Histology					
Adenocarcinoma	3610 (53)	133 (51)	2562 (55)	915 (49)	< .001
Squamous cell	1624 (24)	47 (18)	1046 (23)	531 (28)	
Other	1196 (18)	65 (25)	796 (17)	335 (18)	
Unknown	328 (5)	18 (7)	208 (5)	102 (5)	
Stage					
I	1454 (22)	62 (24)	1163 (25)	229 (12)	< .001
II	586 (9)	12 (4)	383 (8)	191 (10)	
III	1247 (18)	33 (12)	830 (18)	384 (20)	
IV	2971 (44)	128 (49)	1891 (41)	952 (51)	
Unknown	500 (7)	28 (11)	345 (8)	127 (7)	
Performance status, ECOG					
0	2305 (34)	58 (22)	1705 (37)	542 (29)	< .001
1	2127 (31)	80 (31)	1410 (31)	637 (34)	
2	813 (12)	40 (15)	519 (11)	254 (13)	
3 + 4	831 (12)	51 (19)	518 (11)	262 (14)	
Unknown	682 (10)	34 (13)	460 (10)	188 (10)	
Smoking status					
Never	312 (5)	15 (6)	246 (5)	51 (3)	< .001
Current or former	5023 (74)	169 (64)	3400 (74)	1454 (77)	
Unknown	1423 (21)	79 (30)	966 (21)	378 (20)	
Platelet level					
Median level (5%-95% percentiles)	306 (165-563)	122 (50-160)	276 (180-374)	446 (359-713)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small-cell lung cancer.
[a] Patients were divided in low (below), normal (within) and high (above) thrombocytes according to the reference interval published by Nordin et al.[22]

Figure 2 Kaplan-Meier survival curves for overall survival (OS) stratified by pretreatment platelet level being below (low), within (normal), or above (high) the reference interval in patients with non–small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), (A) OS stratified by platelet level in NSCLC. (B) OS stratified by platelet level in SCLC patients. The log-rank test was used to estimate the difference between groups.

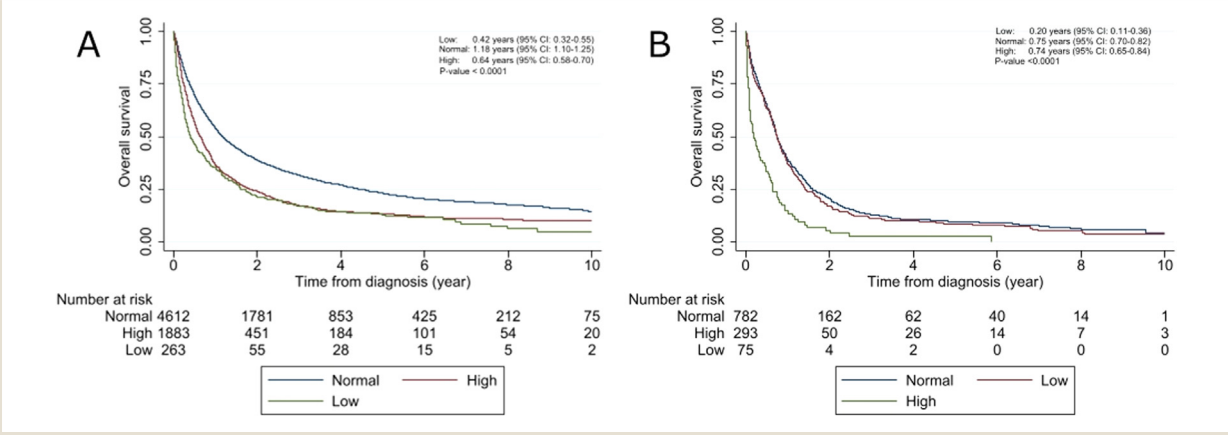


Table 2 Univariate and Multivariate Analysis of Overall Survival in NSCLC Patients (N=6758) and in SCLC Patients (N=1099)

	NSCLC		SCLC	
	HR (95% CI)	Adjusted HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
Platelet count				
Normal	1.00	1.00	1.00	1.00
Low	1.69 (1.48-1.93)	1.75 (1.49-2.06)	2.29 (1.80-2.91)	2.71 (2.02-3.65)
High	1.47 (1.39-1.56)	1.24 (1.16-1.33)	1.07 (0.93-1.23)	1.07 (0.91-1.27)
High + normal[a]	1.0001 (1.0001-1.0001)	1.0006 (1.0004-1.0009)	0.9990 (0.9990- 1.0002)	1.0003 (0.9996-1.0009)
Low + normal[a]	0.9992 (0.9987-0.9997)	0.9988 (0.9982-0.9994)	0.9962 (0.9951-0.9973)	0.9972 (0.9959-0.9985)
Age	1.02 (1.02-1.02)	1.02 (1.01-1.02)	1.04 (1.03-1.04)	1.02 (1.01-1.03)
Sex				
Female	1.0	1.00	1.0	1.00
Male	1.20 (1.13-1.26)	1.19 (1.12-1.26)	1.12 (0.99-1.26)	1.15 (1.00-1.32)
Histology				
Adenocarcinoma	1.00	1.00		
Squamous cell	0.98 (0.93-1.05)	1.08 (1.00-1.17)		
Other	1.49 (1.39-1.60)	1.26 (1.15-1.38)		
Stage				
I	1.00	1.00	1.00	1.00
II	1.55 (1.37-1.76)	1.47 (1.28-1.68)	0.98 (0.53-1.83)	1.13 (0.56-2.25)
III	3.35 (3.03-3.69)	3.39 (3.05-3.77)	3.05 (2.09-4.47)	3.36 (2.20-5.13)
IV	7.08 (6.49-7.73)	7.06 (6.40-7.78)	6.55 (4.50-9.52)	7.02 (4.63-10.67)
Smoking				
Never	1.00	1.00	1.00	1.00
Current or former	1.26 (1.10-1.44)	1.48 (1.28-1.70)	0.92 (0.48-1.78)	0.76 (0.39-1.47)
Performance status, ECOG				
0	1.00	1.00	1.00	1.00
1	1.72 (1.61-1.85)	1.42 (1.32-1.53)	1.52 (1.30-1.80)	1.25 (1.05-1.49)
2	2.90 (2.65-3.16)	2.25 (2.04-2.48)	2.86 (2.36-3.48)	2.30 (1.85-2.87)
3 + 4	4.93 (4.51-5.37)	4.00 (3.56-4.46)	4.52 (3.71-5.51)	4.83 (3.79-6.15)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer.
[a] The parameter has been evaluated as a continuous variable.

Table 3 Predictive Accuracies of the Prognostic Models

Model NSCLC	AIC	C-index
Platelet count + age + sex + stage + histology + smoking + PS + NLR	**53,537**	**0.7667**
Age + sex + stage + histology + smoking + PS + NLR	53,591	0.7648
Model SCLC		
Platelet count + age + sex + stage + histology + smoking + PS + NLR	**7991**	**0.7410**
Age + sex + stage + histology + smoking + PS + NLR	8019	0.7359

Abbreviations: AIC = Akaikes information criterion; NSCLC = non–small-cell lung cancer; NLR = neutrocyte count-to-lymphocyte ratio; SCLC = small-cell lung cancer.
AIC estimates the quality of each model relative to the other models. The values are arbitrary. The model with the minimum AIC is the model with the optimal fit of data.
C-index: Harrell's concordance index. C-index gives a measure of goodness of fit for the model. Values range between 0.5-1.0, 1.0 is the perfect fit.

found in 25% of the patients, while a low count was observed in 7% of the patients. The median age was significantly higher in patients with low platelet count than in the patients with normal or high platelet count (71 years vs. 69 years and 68 years, $P = .004$; Table 4). Moreover, a higher frequency of stage IV patients (72% vs. 59% and 55%, $P = .002$) and patients with a high PS (3+4) was seen in the low platelet count group (33% vs. 13% and 15%, $P < .0001$).

Survival According to Platelet Count in SCLC Patients

The entire cohort of SCLC patients had a median OS of 0.72 years (95% CI: 0.69-0.77). In total, 1065 patients (93%) had died on the last follow-up date. For the 85 patients still alive, the median follow-up time was 5.57 years (5%-95% percentiles: 2.41-9.79).

In contrast to the observation in NSCLC patients, only a low platelet count was significantly correlated to a decreased OS in SCLC patients as no correlation was found for a high platelet count (median OS: low platelet count, 0.20 years (95% CI: 0.11-0.36); high platelet count, 0.74 years (95% CI: 0.65-0.84); normal platelet count, 0.75 years (95% CI: 0.70-0.82); $P < .0001$; Figure 2B and Supplemental Figure 2). A multivariate analysis was performed to determine the prognostic value of low platelet count (Table 2), and the analysis showed that low platelet count continued to be a predictor of decreased OS with a HR of 2.71 (95% CI: 2.02-3.65) when adding it to a model with known prognostic factors. Again, the C-statistics revealed a significantly enhanced prognostic model by adding platelet count (Table 3, $P < .0001$).

Discussion

In this comprehensive registry-based study, we merged information from the Danish Lung Cancer Registry and the clinical laboratory information system so the prognostic value of platelet count could be assessed in a large number of patients. In 7908 patients, we observed that high platelet count was a marker of decreased survival in NSCLC patients and that low platelet count was an adverse prognostic factor in both NSCLC and SCLC patients. Furthermore, we revealed that platelet count added prognostic value to other known prognostic markers used in the clinic.

By using the reference intervals for each sex, we observed a high pretreatment platelet count in 28% of NSCLC patients and in 25% of SCLC patients. The frequency of pretreatment thrombocytosis in NSCLC patients has previously been examined in several studies. Other studies have used very different platelet cut-offs for defining thrombocytosis, and none of them have used a sex-dependent cut-off as we did. Studies applying cut-offs between 300-400 $\times 10^9$/L, as used in this study, have reported various incidences varying from around 10%[12,26] in stage I and III patients, respectively, up to 55%[11,27] demonstrated in cohorts of stage IIIB to IV and I to IIIB patients. Yet, in studies including patients with all stages of disease (I-IV), as in this study, comparable frequencies of 22%[28] and 35%[29] have been observed. In SCLC patients, the frequency of thrombocytosis was in line with a previous study of 999 SCLC patients where 23% of patients had a platelet count greater than 300 $\times 10^9$/L.[16]

A low pretreatment platelet count was much more seldom detected in our cohort and only 5% of NSCLC patients and 7% of SCLC patients had a low count. In contrast to thrombocytosis, data on the frequency of low pretreatment platelet count is scarcer in the literature. But in 823 NSCLC patients, a platelet count below 150 $\times 10^9$/L was observed in 3% of patients,[29] and in 436 SCLC patients, 3% were found to have pretreatment platelet counts between 125 and 150 $\times 10^9$/L[30] which are in accordance with the low frequencies observed in our cohort.

In NSCLC patients, we observed a significantly decreased survival in patients with high platelet count. Thereby, our data confirms previous findings of an association between high platelet count (> 300-400 $\times 10^9$/L) and short survival in NSCLC patients.[11,12,27,29] Furthermore, our data are consistent with the growing evidence indicating that platelets are functional players in several steps of tumor growth and metastasis.[5,31] Accumulating data during the last several decades have revealed that activated platelets can release growth factors that stimulate tumor growth and protect circulating tumor cells in the bloodstream from cell death as well as aid cancer cell adhesion.[5,31] Based on this, it is comprehensible that elevated platelet levels have been associated with decreased survival in cancer patients.[7-10] Taking this knowledge into account, it was unexpected that we did not find a correlation between high platelet count and survival in SCLC patients. Nevertheless, our data is in line with the largest previous study preformed in SCLC patients (N = 999) where such a correlation could not be demonstrated.[16] However, the explanation for this lack of correlation in SCLC patients is yet to be explored.

In addition, we found that low platelet count was an adverse independent prognostic factor in NSCLC patients as well as SCLC patients. As far as we know, this correlation between pretreatment thrombocytopenia and decreased survival in lung cancer has previously only been shown in one study presenting decreased survival in 12 SCLC patients with a platelet count between 125 and 150 $\times 10^9$/L compared with 422 SCLC patients with a platelet

Table 4 Patient Characteristics in all SCLC Patients and and Stratified by Pretreatment Platelet Count (N=1150)

Characteristics	All Patients N (%)	Low Platelet Count[a] N (%)	Normal Platelet Count[a] N (%)	High Platelet Count[a] N (%)	*P*-value
Total number of patients	1150	75 (7)	782 (68)	293 (25)	
Age, years					
Median age (5%-95% percentiles)	69 (52-83)	71 (55-87)	69 (52-83)	68 (53-80)	.004
Sex					
Female	575 (50)	37 (49)	402 (51)	136 (46)	.343
Male	575 (50)	38 (51)	380 (49)	157 (54)	
Stage					
I	55 (5)	2 (3)	47 (6)	6 (2)	.002
II	30 (3)	0 (0)	23 (3)	7 (2)	
III	301 (26)	11 (15)	199 (25)	91 (31)	
IV	679 (59)	54 (72)	464 (59)	161 (55)	
Unknown	85 (7)	8 (10)	49 (6)	28 (10)	
Performance status, ECOG					
0	303 (26)	5 (7)	215 (28)	83 (28)	< .001
1	389 (34)	20 (27)	275 (35)	94 (32)	
2	181 (16)	13 (17)	128 (16)	40 (14)	
3 + 4	171 (15)	25 (33)	103 (13)	43 (15)	
Unknown	106 (9)	12 (16)	61 (8)	33 (11)	
Smoking status					
Never	9 (1)	0 (0)	8 (1)	1 (0)	.433
Current or former	895 (78)	53 (71)	622 (80)	220 (75)	
Unknown	246 (21)	22 (29)	152 (19)	72 (25)	
Platelet level					
Median level (5%-95% percentiles)	292 (133-521)	110 (24-157)	267 (171-372)	444 (359-157)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; SCLC = small-cell lung cancer.
[a] Patients were divided in low (below), normal (within) and high (above) platelet count according to the reference interval published by Nordin et al.[22]

level above 150 × 10^9/L.[30] Taken the before mentioned knowledge of elevated platelets and tumorigenesis into consideration, together with data showing that thrombocytopenia in mice led to decreased tumor angiogenesis and reduced primary tumor metastasis,[32] our observation could be unexpected. However, thrombocytopenia is likely a surrogate marker for severe underlying conditions such as cancer infiltration of the bone marrow,[33] hematological diseases, or paraneoplastic autoimmune thrombocytopenia,[34] which are conditions with a poor prognosis occurring in lung cancer patients. However, these conditions occur only rarely and may not explain all thrombocytopenia cases, leaving other possible causes such as side effects of drugs, infections, and blood coagulation disorders. Unfortunately, we did not have data available to validate this suspicion. Nevertheless, despite the underlying cause of thrombocytopenia, it could be an easily-obtained and important negative prognostic marker in lung cancer patients.

This study has several strengths. As far as we know, it has evaluated platelet count in the largest number of lung cancer patients so far. As our cohort encompassed a substantially higher number of patients than previous studies (a maximum of 1120 NSCLC patients[15] and 999 SCLC patients[16]), the robustness of our data is indisputable compared to that in former studies. Furthermore, owing to the comprehensiveness of the Danish registries and the opportunity for connecting information from several registries at an individual level, it was possible to perform a population-based design with the enrollment of the entire cohort of patients diagnosed in a well-defined geographical region. Potential selection bias is thereby removed, and the generalizability of our data is increased. Regardless of the strengths of the study, there are some limitations to discuss. First, we did not have information on comorbidity or use of drugs that could affect the platelet count. Therefore, we were unable to determine if these conditions could influence our data. Second, no data on molecular genetic alteration were available in NSCLC patients. Therefore, we were incapable of adjusting for this in the analysis. Last, we found that the excluded patients had an increased median age and an increased PS than did the enrolled patients. Accordingly, a potential selections bias due to this difference cannot be ruled out.

Conclusion

We showed in an extensive group of lung cancer patients that high platelet count was an adverse prognostic factor in NSCLC patients, and that a low platelet count was an adverse prognostic marker in NSCLC patients along with SCLC patients. Additionally, we demonstrated that platelet count added extra prognostic value to the previously-established prognostic factors in NSCLC patients along with SCLC patients. Data on the prognostic value of thrombocytosis in NSCLC patients is comprehensive, and incorporating platelet count should be considered in the prognostication of these. Our finding on the prognostic value of thrombocytopenia should be validated in future studies.

Clinical Practice Points

- Thrombocytosis has been associated with increased mortality in lung cancer patients, but data has been conflicting
- This study aimed to evaluate the prognostic value of platelet count in a large group of lung cancer patients
- Data on 6758 non—small-cell lung cancer (NSCLC) patients and 1150 small-cell lung cancer (SCLC) patients were included
- Low and high platelet count were adverse prognostic factors in NSCLC patients (low: adjusted HR=1.75 and high: adjusted HR=1.24)
- Low platelet count was an adverse prognostic marker in SCLC patient (adjusted HR=2.71)
- C-statistics showed that platelet count added extra prognostic value to the previously established prognostic factors in NSCLC patients along with SCLC patient
- Data on the prognostic value of thrombocytosis in NSCLC patients is comprehensive and platelet count should be considered incorporated in the prognostication of these
- Our finding on the prognostic value of thrombocytopenia should be validated in future studies.

Disclosure

This research was funded by the Dagmar Marshall Fund [grant number: 500020, 2019] and the Einar Willumsens mindelegat [grant number: 500028, 2019]. The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.12.012.

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