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Prognostic Significance of Initial Platelet Counts and Fibrinogen Level in Advanced Non-Small Cell Lung Cancer

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Thrombocytosis and coagulation systems activation are commonly associated with disease progression and are suggested poor prognostic factors in patients with malignancies. This study aimed to investigate the prevalence and prognostic significance of thrombocytosis and elevated fibrinogen levels in patients with advanced non-small cell lung cancer (NSCLC). Initial platelet counts and fibrinogen levels were reviewed in 854 patients with histologically proven NSCLC. Thrombocytosis was defined as platelet counts > 450 × 10^9/L. A serum fibrinogen level > 4.5 g/L was considered high. At the time of diagnosis, initial platelet counts and serum fibrinogen levels were evaluated before treatment. Clinicopathologic data including histological type, tumor, node, metastasis (TNM) stage, performance status, treatment method, and survival time were evaluated. Initial thrombocytosis was found in 6.9% of patients, and elevated fibrinogen levels were found in 55.1% of patients. Patients with thrombocytosis had a significantly poorer prognosis than patients with normal platelet counts ($P < 0.001$). In multivariate survival analysis, thrombocytosis was an independent prognostic factor ($P < 0.001$). An elevated serum fibrinogen level was associated with poor prognosis ($P < 0.001$). In conclusion, initial thrombocytosis and a high fibrinogen level are independent factors for predicting poor prognosis in patients with advanced NSCLC.

Keywords: Carcinoma Non-Small Cell Lung; Prognosis; Thrombocytosis; Fibrinogen

INTRODUCTION

Thrombocytosis and activation of the coagulation system are observed in patients with various malignancies (1, 2), these features have prognostic significance in patients with lung cancer (3). The mechanism of this phenomenon is not completely understood. However, there is evidence that the tumor cells secrete humoral factors that may lead to thrombocytosis and activation of the coagulation system (4).

Most previous studies have associated thrombocytosis and elevated fibrinogen levels with poor prognosis in patients with lung cancer (2, 3). However, most of these studies included many resectable non-small cell lung cancer (NSCLC) and small cell lung cancer cases (3, 5).

The purpose of the current study was to investigate the prognostic value of pretreatment thrombocytosis and elevated fibrinogen levels in patients with advanced NSCLC.

MATERIALS AND METHODS

Patients

This retrospective clinical study included 950 consecutive patients with advanced NSCLC who were treated at a tertiary referral university hospital between January 2007 and December 2009. Excluded from the study were subjects with operable NSCLC, double primary cancer (n = 67), concomitant myeloproliferative disorders or hematologic disorder (n = 5), follow up loss (n = 3) and conditions known to be associated with reactive thrombocytosis (inflammatory diseases, autoimmune disorders) (n = 1). Furthermore, patients without available data on platelet counts levels and the death date (n = 20) were excluded. In the analysis of high fibrinogen levels and survival, 75 patients without available data on the fibrinogen level and 35 patients with chronic liver disease were excluded.

Medical records of 854 patients were reviewed. The patient cohort included 558 men and 296 women, with a median age of 66.3 yr (range 65.5-67.0 yr).

The pathological diagnosis of primary lung cancer was in accordance with the World Health Organization classification of lung tumors. Accordingly, there were 384 adenocarcinomas, 203 squamous cell carcinomas, 6 large cell carcinomas, and 261 unclassified NSCLC. All patients were classified according to the 2010 American Joint Committee on Cancer Staging system.

Pretreatment clinical evaluation was based on physical examination, the Eastern Co-operative Oncology group (ECOG) performance status, and underlying disease. Chemotherapy and radiotherapy history were also reviewed. Further investigations included radiography, bronchoscopy, computed tomog-

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raphy of the chest and abdomen, positron emission tomography, and magnetic resonance imaging of the brain. The survival duration was evaluated from the date of histological diagnosis to death.

Study design

Thrombocytosis was defined as a platelet count of at least 450 × 10^9 platelets/L and a high serum fibrinogen level of at least 4.5 g/L. Platelet counts and fibrinogen levels were measured at the first visit to our hospital.

Platelet counts and fibrinogen levels following either chemotherapy or radiotherapy were not included in this study because of the possible effects of treatment on platelet levels and the coagulation system. Other variables, including sex, age, ECOG performance status, underlying disease, such as chronic liver disease, clinical stage, chemotherapy, radiotherapy, and duration of survival, were evaluated.

Statistical analysis

Comparison between the two groups was analyzed using chi-square test and Fisher's exact test. Survival curves were calculated using the Kaplan-Meier method. The survival curves were compared using the log-rank test, whereas multivariate survival analyses were performed using the Cox's proportional hazards regression model. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) package for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

This research was carried out after receiving approval from the institutional review board of Seoul National University Hospital (No. H-1104-021-357). Informed consent was waived by the board.

Table 1. Study population of patients described by histological type and TNM stage

Types or stages	Patients	
	No.	%
Histological diagnosis	854	
Squamous cell carcinoma	384	44.9
Adenocarcinoma	203	23.8
Large cell carcinoma	6	0.7
Unclassified NSCLC	261	30.6
TNM stage		
IIIa	66	7.7
IIIb	131	15.4
IV	657	76.9

NSCLC, non-small cell lung cancer; TNM, tumor, node, metastasis.

RESULTS

Thrombocytosis and baseline characteristics

The distributions of stage and histological type in the study population are listed in Table 1. The relationships between thrombocytosis and baseline characteristics are shown in Table 2. No significant differences in platelet count were noted according to age, sex, underlying disease, performance status, or smoking history.

Frequency of thrombocytosis and a high fibrinogen level in patients with advanced NSCLC

Fifty-nine of 854 (7%) advanced NSCLC patients had thrombocytosis and 416 of 754 (55.2%) patients had a high fibrinogen level. Platelet counts and fibrinogen levels did not differ according to TNM stage (Table 3).

Thrombocytosis, high fibrinogen level and survival

The influence of thrombocytosis on survival was analyzed among 854 patients with advanced NSCLC (Fig. 1A). Patients with thrombocytosis had a poor survival rate ($P < 0.001$), with a median duration of survival of 340.5 days (95% confidence interval [CI], 251.7-429.1) than those with normal platelet counts, whose median survival was 565.9 days (95% CI, 527.6-604.3).

In addition, a trend towards short survival was seen in patients

Table 2. Thrombocytosis and baseline characteristics in study populations

Parameters	Platelet count (× 10^9/L)		
	≤ 450	> 450	*P* value
No. (%)	795/854 (93.0%)	59/854 (7.0%)	
Age	66.4	63.9	0.10
Sex (M)	518/795	40/59	0.68
DM	97/795	9/59	0.49
HTN	238/795	16/59	0.64
Tuberculosis	82/795	7/59	0.70
CLD	35/795	1/59	0.31
ECOG (0-2)	753/795	54/59	0.24
Stage (IV)	611/795	45/59	0.91
Smoking (PY)	18.6	24	0.23
Chemotherapy	576/795	42/59	0.83
Radiotherapy	293/795	17/59	0.75

DM, diabetes mellitus; HTN, hypertension; CLD, chronic liver disease; ECOG, Eastern Cooperative Oncology Group; PY, pack-year.

Table 3. Platelet counts and fibrinogen levels at diagnosis according to TNM stage

TNM stage	Platelet > 450 × 10^9/L No. (%)	Median value (× 10^9/L)	95% CI (× 10^9/L)	Fibrinogen > 4.5 g/L No. (%)	Median value (g/L)	95% CI (g/L)
IIIa	5/66 (7.5)	288.9	273.1-305.1	31/59 (52.5)	4.98	4.70-5.27
IIIb	8/131(7.2)	291.1	267.5-316.1	67/124 (54.0)	4.98	4.70-5.27
IV	46/657(7.0)	286.0	278.4-292.7	318/571 (55.7)	4.91	4.77-5.04

TNM, tumor, node, metastasis; CI, confidence interval.

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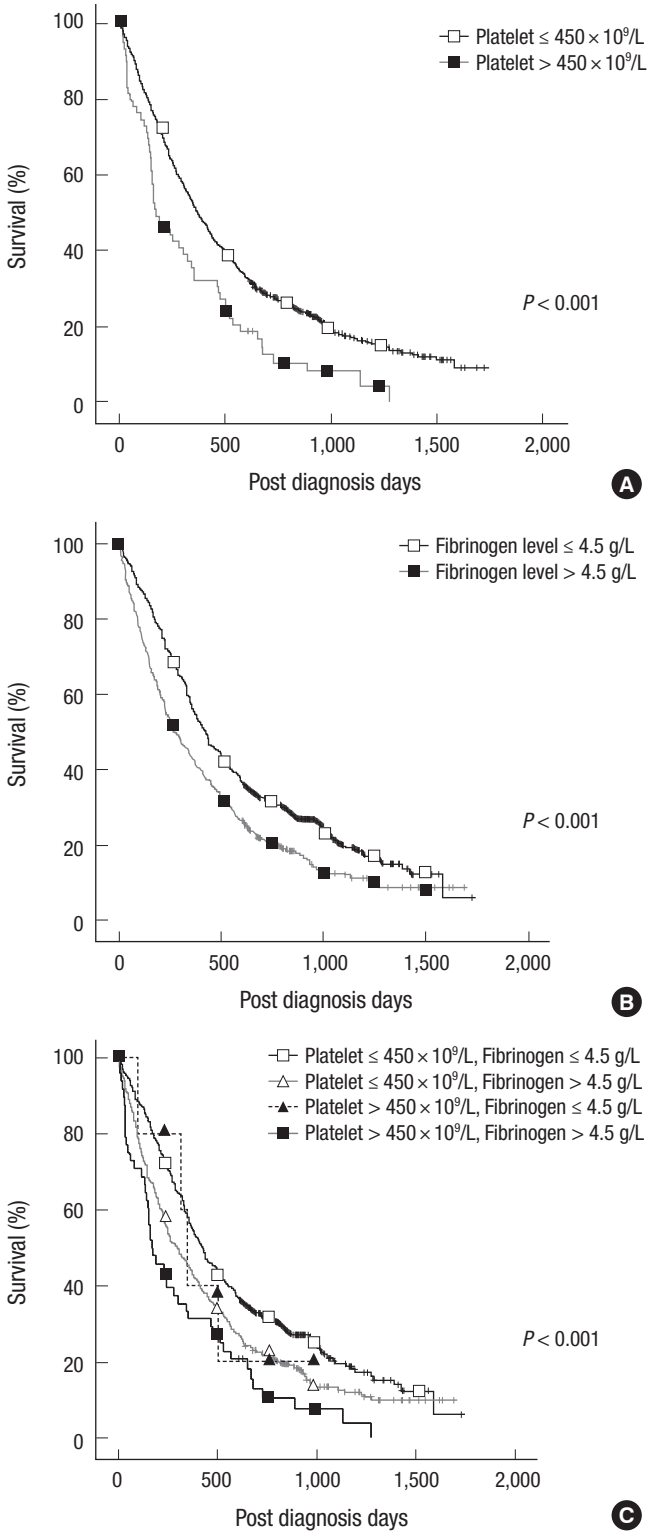

Fig. 1. Survival of lung cancer patients after diagnosis (Kaplan-Meier analysis). (**A**) Stratified to normal and elevated platelet count. (**B**) Stratified to normal and elevated fibrinogen level. (**C**) Stratified to normal and elevated platelet count and fibrinogen level.

with a high fibrinogen level ($P < 0.001$), where the median duration of survival was 469.7 days (95% CI, 421.6-517.8) as compared with 622.3 days (95% CI, 562.4-682.3) in patients with a normal fibrinogen level (Fig. 1B). Survival duration was significantly shorter among patients with both thrombocytosis and a high fibrinogen level (median survival time, 333 days; 95% CI, 223.0-433.0) than among those without this finding (median survival time, 623.4 days; 95% CI, 563.0-683.8, $P < 0.001$) (Fig. 1C). Survival of patients with thrombocytosis alone was 487.5 days (95% CI, 435.1-540.0) and that of the patients with an elevated fibrinogen level alone was 454.8 days (95% CI, 192.3-717.3).

In the multivariate model, the Cox proportional hazards model revealed that thrombocytosis ($P = 0.004$), the fibrinogen level ($P < 0.001$), sex, age, ECOG performance status, and chemotherapy had independent prognostic significance (Table 4). Administration of radiotherapy did not exhibit any statistical significance.

Table 4. Multivariate analysis of prognostic factors by Cox proportional hazard model

Variables	HR	95% CI	*P* value
Platelet counts			
≤ 450 × 10^9 · L^{-1}	1		
> 450 × 10^9 · L^{-1}	1.51	1.14-2.00	0.004
Fibrinogen			
≤ 4.5 g/L	1		
> 4.5 g/L	1.34	1.13-1.58	< 0.001
TNM stage			
IIIa	1		
IIIb	1.02	0.72-1.45	0.913
IV	1.98	1.45-2.69	< 0.001
ECOG PS			
0-2	1		
3-4	2.02	1.47-2.77	< 0.001
Sex			
Male	1		
Female	1.55	1.30-1.84	< 0.001
Histology			
Adenocarcimona	1		
Squamous cell carcinoma	0.80	0.67-0.96	0.016
Large cell carcinoma	0.96	0.78-1.18	0.693
Unclassified NSCLC	1.73	0.77-3.90	0.189
Chemotherapy			
Yes	1		
No	2.22	1.85-2.66	< 0.001
Radiotherapy			
Yes	1		
No	1.03	0.89-1.21	0.677
Age			
≤ 70 yr	1		
> 70 yr	1.26	1.07-1.47	0.005

HR, hazard ratio; CI, confidence interval; TNM, Tumor, Node, Metastasis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, Non-Small Cell Lung Cancer.

DISCUSSION

The purpose of this study was to determine the prevalence of thrombocytosis and coagulation system activation and to evaluate their associations with the prognosis of patients with advanced NSCLC. The prevalence of thrombocytosis in patients

with pancreatic (6), gastric (7), and colon cancers (8) is well known. In patients with lung cancer, the reported frequencies of thrombocytosis and coagulation system activation vary between 4.5% and 41% (9-11). The frequency of thrombocytosis (7%) in our study was lower than that in previous studies. In addition, the frequency of an elevated fibrinogen level (55.2%) was higher than reported previously.

Most studies have shown that thrombocytosis and activation of the coagulation system occur in early stage operable lung cancers (5, 12). Maraz et al. (13) showed increaed thrombocytosis with advanced lung cancer. In contrast, to previous findings, we could not find a correlation between clinical stage and thrombocytosis and the fibrinogen level (3, 14). Our results suggest that thrombocytosis and activation of the coagulation system does not depend on tumor burden or clinical stage, but may instead represent individual tumor characteristics. The pathophysiological mechanisms of thrombocytosis and a high fibrinogen level in cancer patients are related to tumor-derived humoral factors such as interleukin (IL)-6, IL-1, and macrophage colony-stimulating factor (15-17). Tumor cells have been shown to release IL-6, which stimulates megakaryocytopoiesis (18). Adherence of platelets to tumor cells in peripheral blood may prolong the survival of tumor cells and enable them to adhere to the vessel wall (19). In addition, platelet-derived endothelial cell growth factor induces angiogenesis in vitro and in vivo (20). Fibrinogen is deposited around solid tumors and they may act as an extracellular matrix (21). Thus, individual tumor characteristics may influence thrombocytosis and activation of fibrinogen level and cancer metastasis.

Survival rates of patients with either thrombocytosis or activation of the coagulation system were similar. The formation of platelet-fibrin-tumor cell aggregates may cause endothelial adhesion and metastatic potential. Platelet-fibrin-tumor cell aggregates may protect tumor cells in the blood stream and may promote adherence to the vessel wall (22). A statistical analysis of our study may support this view because the patients with both thrombocytosis and activation of the coagulation system had poorer prognosis than those with either thrombocytosis or activation of the coagulation system.

We have demonstrated that patients with both thrombocytosis and activation of coagulation system showed poor prognosis in patients with advanced NSCLC. Elevated levels of platelet counts and fibrinogen are significant prognostic factors in lung cancer (23, 24). Pedersen and Milman (3) showed that a reduced duration of survival in patients with lung cancer was associated with a higher platelet count. In this study, performance status was not included in the multivariate model unlike our study. Jones et al. (23) revealed that an elevated fibrinogen level was correlated with increasing tumor size, an advanced pathological T stage in lung cancer patients. Ferrigno et al. (25) found that a high fibrinogen level was associated with poorer survival. However, the study included a small sample size of 343 patients. In other study, platelet levels did not have a significant effect on survival (26). In contrast, our results indicated that initial thrombocytosis and an elevated fibrinogen level was associated with poor prognosis in a large study population of 854 patients with NSCLC, and thus, thrombocytosis and an elevated fibrinogen level may have independent prognostic value for these patients. TNM stage, performance status, sex, histology, age, chemotherapy, or radiotherapy were included in the survival analysis. TNM stage, performance status, sex, age, chemotherapy was associated with survival among advanced NSCLC patients. Survival was not associated with histology. Histology of unclassified NSCLC could not be evaluated in this retrospective study.

Our study has a couple of limitations. First, this study was performed retrospectively. Despite the strict enrollment criteria used, we were unable to completely exclude conditions that might cause hematologic changes in advanced NSCLC. Second, even though the purpose of this study was to evaluate the prognostic significance of initial platelet and fibrinogen levels, follow-up changes in platelet and fibrinogen levels in advanced NSCLC patients after treatment were not examined in this study. Third, we transcribed into unclassified NSCLC if it was not sorted by subtype in the pathology report. It is the limitation of the retrospective study, too.

In conclusion, our study findings showed that the frequencies of thrombocytosis and a high fibrinogen level were 7.0% and 55.2%, respectively, at the time of advanced NSCLC diagnosis. Patients with both initial thrombocytosis and a high fibrinogen level had shorter survival than those with neither of these. The survival duration of patients without thrombocytosis or a high fibrinogen level was approximately twice as long as that of patients with both thrombocytosis and a high fibrinogen level. Finally, and importantly, both the initial platelet counts and the fibrinogen level are independent prognostic factors in patients with advanced NSCLC.

DISCLOSURE

The authors have no conflicts of interest to declare.

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