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The Prognostic Significance of Pretreatment White Blood Cell and Platelet Counts for Survival Outcome in Primary Lung Cancer

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ABSTRACT
Background: In Vietnam, lung cancer ranks second among common types of cancer. Although there have been many advances in the diagnosis and treatment of lung cancer, it is still one of the deadliest types of cancer. **Objective:** We investigated the prognostic value of pretreatment white blood cell (WBC) and platelet counts of patients with lung cancer. **Methods:** This was a prospective, descriptive study with longitudinal follow-up. Data from 203 patients with stage IIIA–IV lung cancer presenting at Can Tho City Oncology Hospital between June 2020 and June 2022 were analyzed. Complete blood cell counts were obtained using standard methods. Lung cancer diagnoses and histological classifications were obtained from cancer registries. The optimal overall survival cutoff point for pretreatment WBC and platelet counts was determined using maximally selected rank statistics. **Results:** The median follow-up was 6 (interquartile range 4–8) months and the median age was 61.3 years. The number of male patients was higher than the number of female patients. Most (71.4%) patients had adenocarcinoma; 62.1% of the patients had a WBC count of > 10 × 109/L and 38.4% had a platelet count of > 400 × 109/L. The median overall survival (OS) of all patients was 8 months. The 3-month, 6-month, and 1-year OS was 88.7%, 62.4%, and 28.3%, respectively. Patients with a WBC count of <9.18 × 109/L had a higher OS than those with a count of ≥ 9.18 × 109/L (17 months versus 8 months; p < 0.001) Patients with a platelet count of < 453 × 109/L had a higher OS than those with a count of ≥ 453 × 109/L (8 months versus 7 months; p < 0.001). **Conclusion:** White blood cell and platelet count tests are routine investigations that are valuable, in combination with other factors, for predicting OS of lung cancer patients. They can help clinicians to monitor treatment response and survival.
Keywords: White blood cells, platelets, lung cancer.

1. BACKGROUND

According to Globocan 2020 estimates, lung cancer is the leading cause of cancer-related mortality in the world. In Vietnam, lung cancer ranks second among common types of cancer. Although there have been many advances in the diagnosis and treatment of lung cancer, it is still one of the deadliest types of cancer (1). The overall one-year and five-year survival rates of lung cancer are 47% and 18%, respectively, much lower than the rates of other types of cancer (2). The later the stage of the disease is, the shorter the patient's survival time. For patients with non-small-cell lung cancer, the two-year survival rate at stage I is >90% and at stage IVB it is 10% (3). Small-cell lung cancer has a worse prognosis, with a five-year survival rate of about 3.5% (4). At the time of diagnosis of small-cell lung cancer, most patients are in stages III and IV (5). Prognostic factors in lung cancer include disease stage, histopathology, physical condition, and molecular biology. EGFR mutations, ALK rearrangements, MET, BRAF mutations, and PD L1 expression are molecular biological features closely related to lung cancer treatment

and prognosis (6). However, methods of pretreatment evaluation of these molecular biological characteristics, such as PCR and NGS, are expensive and time-consuming (7). Some studies have shown that the white blood cell count is a negative prognostic factor of survival outcome of lung cancer patients (8, 9). The pretreatment platelet count is also associated with poorer survival outcomes (10, 11). In addition, nomograms that integrate factors such as white blood cell count and platelet count have been developed to predict a patient's survival time (12). However, the relationship of pretreatment white blood cell and platelet counts to lung cancer is still unclear. In addition, there is currently no cutoff value for the number of white blood cells and platelets for predicting survival of lung cancer patients.

2. OBJECTIVE

Therefore, we conducted this study to determine the relationship between the number of white blood cells and platelets and survival outcomes in lung cancer patients.

3. MATERIAL AND METHODS

Patient data

This study was approved by the institutional review board of Can Tho Oncology Hospital (Ref: 101/QĐ-BVUB). It was a prospective, observational study carried out from June 2020 to November 2022 at Can Tho City Oncology Hospital. The inclusion criteria for selecting patients were a) a diagnosis of primary lung cancer confirmed by histopathology; b) a histological grading according to WHO 2015 (13); c) disease stage IIIA–IV according to Stage 8 of TNM (14); d) having results of a pretreatment blood cell analysis test; and e) in-hospital treatment with one or more modalities such as surgery, chemotherapy, radiotherapy, targeted therapy, and palliative care. The following patients were excluded from the study: a) those with a fever of >38 °C at the time of diagnosis; b) those with signs of infection; c) those with signs of hemorrhage; d) those with lung tuberculosis; e) those with cirrhosis; and f) those using corticosteroids.

Parameters

The patient's age at the time of diagnosis, sex, histopathological type, and pretreatment white blood cell and platelet counts were obtained. The number of white blood cells and platelets was based on blood tests at the time of a confirmed diagnosis of lung cancer and before surgery, radiation therapy, or systemic therapy. Histopathology involved both non-small-cell lung cancer and small-cell lung cancer. Non-small-cell lung cancer included adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and salivary gland carcinoma. The white blood cell count was divided into three groups: reduced (< 4 × 109/L); normal (4–10 × 109/L); and increased (> 10 × 109/L). The platelet count was also divided into three groups: reduced (< 150 × 109/L); normal (150–400 × 109/L); and increased (> 400 × 109/L).

Data collection

After the lung cancer patients were diagnosed using histopathology, a total peripheral blood cell analysis was performed using an automated hematology analyzer (XN-550, Sysmex). The patients received surgery, chemotherapy, radiotherapy, targeted therapy, or immune checkpoint inhibitor therapy as prescribed by the treating doctor. The patient's survival was monitored and assessed until November 1, 2022. Overall survival was defined as the time elapsed between the date of lung cancer diagnosis and the date of death or the date of final follow-up examination.

Characteristic	n (%)
Total number	203 (100)
Age (years)	
< 65	129 (63.5)
≥ 65	74 (36.5)
Sex	
Male	144 (70.9)
Female	59 (29.1)
Disease stage	
III	28 (13.8)
IV	175 (86.2)
Histology	
Adenocarcinoma	145 (71.4)
SQCC	43 (21.2)
SMC	6 (3)
Other type	9 (4.4)
Karnofsky Performance Scale score	
60–70	90 (44.3)
80–100	113 (55.7)
Tumor location	
Left	94 (46.3)
Right	109 (53.7)
White blood cell count	
Low	2 (1)
Normal	75 (36.9)
High	126 (62.1)
Platelet count	
Low	4 (2)
Normal	121 (59.6)
High	78 (38.4)

SQCC: squamous cell carcinoma; SMC: small-cell carcinoma

Table 1. Characteristics of patients with advanced lung cancer

Statistical analysis

The data were analyzed using SPSS 16.0 and R 4.3.1 software. Descriptive statistical methods were applied to patient factors. Means and standard deviations are used to describe normally distributed continuous variables and proportions to describe binary variables. Overall survival was estimated using the Kaplan–Meier method. The log-rank test was applied to univariate analysis of overall survival. White blood cell and platelet count cutoff values related to overall survival outcomes were calculated using the maximally selected rank statistics. Hazard ratios with 95% confidence interval (CI) are presented for survival results. A p-value of < 0.005 was considered statistically significant.

4. RESULTS

Characteristics of patients

This study selected 203 patients in total. The ratio of men to women was 2.44:1. The median age was 61.27

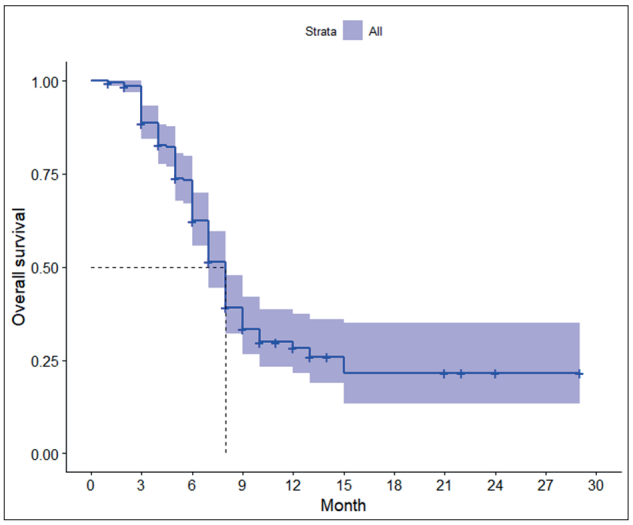

Figure 1. Overall survival of patients with lung cancer.

declined, as determined using the log-rank test (overall survival at 12 months was 50.9%, not yet reaching the median). The median overall survival of patients with an elevated platelet count was 7 months (95% Cl = 6.1–7.9 months), which was higher than that of the low platelet count group (4.5 months, 95% CL = NR) but lower than that of the average platelet count group (8 months, 95% Cl = 3–8.7 months). This difference was not statistically significant (p = 0.102). Age, sex, histological type, tumor location, and platelet count were not statistically significant factors related to overall survival in univariate analysis using Cox regression, but disease stage, physical condition, and white blood cell count at the time of diagnosis were significant (Table 1).

Multivariate analysis

Disease stage, physical state, and white blood cell count at diagnosis remained independent predictors of overall survival in the multivariate Cox regression analysis. In the assessment of their effect on overall survival, other variables like age, gender, tumor location, histopathology, and platelet count were not statistically significant (Table 2).

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥ 65/< 65years)	0.88	0.60–1.30	0.52	0.75	0.51–1.12	0.75
Sex (female/male)	1.34	0.91–1.99	0.14	1.25	0.84–1.87	0.27
Disease stage (IV/III)	17.58	4.31–71.7	<0.001	12.99	3.13–53.87	<0.001
Histopathology (aden/sqcc/smc/other)	0.97	0.82–1.16	0.77	0.93	0.78–1.10	0.39
KPS (80–100/60-70)	0.35	0.25–0.52	<0.001	0.43	0.29–0.63	<0.001
Tumor location (right/left)	1.09	0.76–1.58	0.63	0.94	0.64–1.38	0.77
WBC count (high/normal/low)	2.08	1.37–3.16	0.001	1.75	1.14–2.69	0.01
PLT count (high/normal/low)	1.41	0.98–2.02	0.063	0.92	0.63–1.35	0.68
WBC: white blood cells; PLT: platelets						

Table 2. Univariate and multivariate analyses of the effects of clinical characteristics on overall survival of patients with advanced lung cancer

years and the range was 32–89 years. The adenocarcinoma subtype accounted for the majority (71.4%) of distant metastatic disease cases (86.2%). Over half of the patients had a Karnofsky Performance Scale score of 80 or higher. Right-sided primary tumors were more prevalent. While most patients had a normal platelet count, over 60% had an elevated white blood cell count. Table 1 provides an overview of the basic traits of the patients who met the study's eligibility criteria.

Survival outcomes

The Kaplan–Meier method was used to estimate overall survival. The median follow-up period was 6 months (25%–75% interquartile range [IQR]: 4–8 months). The median overall survival was 8 months (95% CI: 7.3–8.6 months). The overall survival rates at 3, 6, and 12 months were 88.7%, 62.4%, and 28.3%, respectively. Figure 1 shows patients' overall survival.

Univariate analysis

Every variable was examined independently of the others in this initial analysis. The median overall survival time of patients with a high white blood cell count was 7 months (95% Cl = 6.3–7.7 months), which was significantly shorter (p < 0.001) than the median survival time of patients with normal white blood cell count or

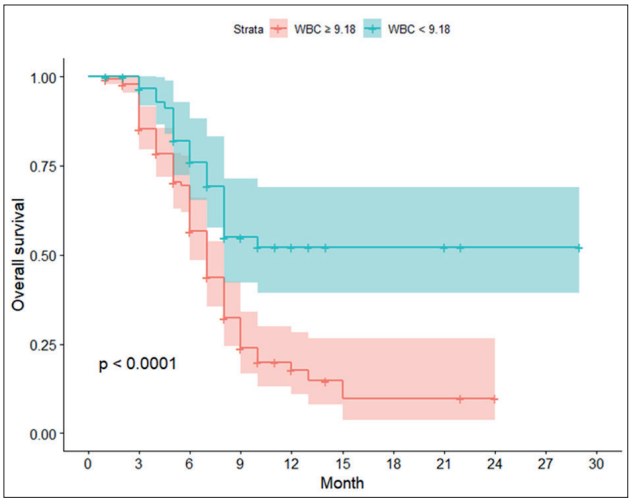

Figure 2. Surv-cutpoint function and analysis of overall survival in relation to white blood cell count (WBC)

Cutoff points for white blood cell and platelet counts

In the second analysis, the cutoff points for white

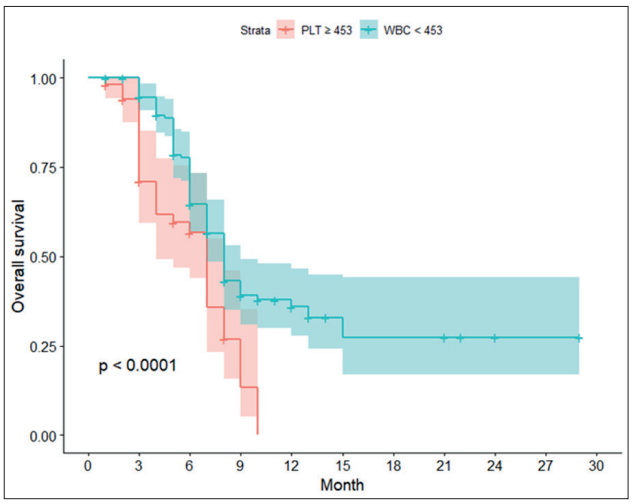

Figure 3. Surv-cutpoint function and analysis of overall survival in relation to platelet (PLT) count

Variable	Number of patients	HR (95% CI)	P-value
Disease stage			
IV	175	12.24 (2.97–50.47)	0.001
III	28		
Karnofsky Performance Scale 80–100	113	0.45 (0.31–0.65)	<0.001
60–70	90		
WBC count			
≥ 9.18 × 10⁹/L	140	1.78 (1.11–2.87)	0.017
< 9.18 × 10⁹/L	63		
PLT count			
≥ 453 × 10⁹/L	50	1.57 (1.04–2.37)	0.03
< 453 × 10⁹/L	153		

Table 3. Multivariate analysis of the white blood cell (WBC) and platelet (PLT) count cutoff points, disease stage, and Karnofsky Performance Scale (KPS) score

blood cell and platelet counts were determined using maximally selected rank statistics, which is an ideal way of predicting the survival outcome of patients with lung cancer. Figures 2 and 3 show the survival cutoff functions for white blood cell and platelet counts, which were 9.18 and 453, respectively. Following the determination of the cutoff values, we employed Cox multivariate regression to analyze white blood cell and platelet counts. Table 2 lists the variables, including disease stage and physical state, which influenced survival. Individuals who had a white blood cell count of < 9.18 × 109/L were 1.8 times more likely to die than those in the control group (HR = 1.78, 95% CI = 1.11–2.87, p = 0.017). Compared to the other group, patients with platelet counts of > 453 × 109/L showed a 1.6-fold increase in the risk of death (HR = 1.57, 95% CI = 1.04–2.37, p = 0.03). Table 3 shows that two statistically significant factors—disease stage and physical condition—independently predicted overall survival.

5. DISCUSSION

Initially, white blood cell count, disease stage, and physical condition were the only factors that were statistically significant for predicting survival in our study. However, subsequent examination of the leukocyte and platelet cutoff points showed that all four count values were statistically significant in relation to patient survival. This may be explained by the fact that the white blood cell count cutoff was 9.18 × 109/L, which was close to the lower limit (> 10 × 109/L) of the high white blood cell group. The first analysis did not yield a statistically significant result because the cutoff for the platelet count was 453 × 109/L, which was higher than the lower limit (> 400 × 109/L) of the high platelet group.

Previous studies found that leukocytosis was present in 14.5% of patients with recently diagnosed lung cancer (15) and that 20% of leukocytosis patients also had a solid malignancy (8). A higher white blood cell count prior to treatment lowers the likelihood of survival. A 10-year study of 571 lung cancer patients found that the risk of death of those with paraneoplastic leukocytosis increased 2.38-fold (HR = 2.38, 95% CI = 1.74–3.26) compared to the risk of death of those with normal leukocyte counts (16). A retrospective review of 89 patients with non-small-cell lung cancer showed that the median survival of patients with white blood cell counts of 4–10 k/µl, 8–12 k/µl, 10–20 k/µl, and 22–240 k/µl was 1 week, 7 months, and 12 months, respectively (17).

It is clear that a rise in the granulocyte colony-stimulating factor (G-CSF) is the cause of the effects of leukocytosis on lung cancer (18). Young white blood cells in the bone marrow mature more quickly when G-CSF is present (19). In a study of 227 lung cancer patients, 33 who had leukocytosis autonomously produced hematopoietic cytokines, such as interleukin-6, granulocyte-macrophage colony-stimulating factor, and G-CSF (8). In another study, white blood cell counts were 4–10, 8–12, 10–20, and 22–240 k/µl in patients with G-CSF levels of < 100 pg/ml, > 100 pg/ml, > 200 pg/ml, and > 1,000 pg/ml, respectively (17).

Preclinical models indicate that the administration of G-CSF to mice infected with non-metastatic cell lines causes these cells to become activated to metastasize distantly, which is the mechanism underlying the deleterious effects of G-CSF on survival. G-CSF injections caused a significant increase in the number of metastatic cells in mice that were previously infected with metastatic cell lines (20). High G-CSF concentrations were discovered in 66.7% of patients with adrenal metastases in a study comparing CSF type concentrations in lung cancer patients and in healthy individuals. On the other hand, 7.2% of non-metastatic patients have this rate (21). This demonstrates that in patients with lung cancer, elevated white blood cell counts are linked to elevated G-CFS, and elevated CFS is linked to stimulation of distant metastasis, leading to poor survival prognosis.

The presence of leukocytosis in lung cancer has previously been reported in the literature. A meta-analysis of 2974 patients from 20 studies found thrombocytosis in 27% of the patients. The platelet count increased by 22%, 28%, 30%, and 38% in adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma, respectively (22). A rise in platelets is linked to

poor prognosis. A meta-analysis of 40 studies involving 16,696 lung cancer patients found that a high pretreatment platelet count was associated with worse overall survival (HR = 1.54, 95% CI = 1.37–1.72) and worse disease-free survival progression/disease-free survival/event-free survival (HR = 1.62, 95% CI = 1.33–1.98) (23). Thrombocytosis was also found to be a poor prognostic factor in a meta-analysis of 14,833 patients from 37 studies, with overall reduced survival (HR = 1.033, 95% CI = 1.017–1.050), progression-free survival (HR = 1.653, 95% CI = 1.069–2.556), and disease-free survival (HR = 1.568, 95% CI = 1.276–1.928) (24).

Tumor-associated thrombocytosis is linked to humoral factors secreted from the tumor. These factors promote the production and maturation of platelets. Interleukin-6 is strongly associated with thrombocytosis in cancer (25). Previous studies have shown that tumor cells can produce interleukin-6 both in vitro and in vivo (26, 27). Platelets play numerous roles in tumor development and increase the likelihood of distant tumor metastasis (28). First, the tumor activates platelets, which adhere to the tumor and help it to avoid destruction by natural killer cells (29). Furthermore, during the invasive stage of the tumor, the platelet-derived transforming growth factor stimulates the transformation of epithelial cells to mesenchymal cells (30). Platelets also work with leukocytes and vascular endothelial cells to promote cancer cell extravasation and growth in distant organs via the adhesion molecules P-selectin and L-selectin (31). Cancer cells and platelets have a close relationship as cancer cells induce the proliferation of platelets and platelets support cancer cell invasion and distant metastasis.

The evidence presented above demonstrates that the results of our study on the prognostic value of platelet and white blood cell counts are consistent with findings of previous studies. The main strength of this investigation is that because it is a prospective study, patients were tested with the same device, limiting errors caused by differences in testing devices. However, our study has some flaws.

First, because the number of patients with small-cell lung cancer was small, no difference in survival was observed between small-cell lung cancer and non-small-cell lung cancer. However, small-cell lung cancer has a poor prognosis (4). Second, because the follow-up period was short, some patient subgroups had not yet reached median survival by the end of the study.

Third, factors such as physical condition and disease stage influence survival and may result in inconsistent cutoff points for white blood cell and platelet counts, which can change depending on population size, physical condition, and disease stage. To confirm the prognostic role of white blood cell and platelet counts, further research involving a larger number of patients with longer follow-up time, as well as the development of a nomogram that includes many factors such as the number of white blood cells and platelets, is needed.

6. CONCLUSION

Tests of white blood cell and platelet counts are routine investigations that can be used, in conjunction with other factors, to predict the prognosis of lung cancer patients and aid clinicians in monitoring treatment response and predicting overall survival.

- **Patient consent form:** The requirement for informed consent was waived.
- **Availability of data and material:** The datasets generated and/or analysed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.
- **Authors's contribution:** Study concept and design: Vo-Van Kha and Tran-Thi Huong Ly; acquisition of data: Vo-Van Kha and Tran-Thi Huong Ly; analysis and interpretation of data: Vo-Van Kha and Tran-Thi Huong Ly; drafting of the manuscript: Vo-Van Kha and Tran-Thi Huong Ly; critical revision of the manuscript: Vo-Van Kha and Tran-Thi Huong Ly; study supervision: Vo-Van Kha and Tran-Thi Huong Ly. Vo-Van Kha and Tran-Thi Huong Ly confirm the authenticity of all the raw data. All authors read and approved final version of this manuscript.
- **Conflicts of interest:** There are no conflicts of interest.
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