Prognostic Value of Preoperative Blood Platelet-to-Lymphocyte Ratio in Patients Undergoing Surgery for Non-Small Cell Lung Cancer

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Abstract

Increasing evidence has suggested that the host inflammatory status is associated with prognosis of several solid tumors. Preoperative Platelet- Lymphocyte Ratio (PLR) acquired from routine blood tests, can reflect the status of systematic inflammation. In this study, we aimed to investigate effects of the pretreatment the Platelet to Lymphocyte Ratio (PLR) on the prognosis of Non-Small Cell Lung Cancer (NSCLC) patients after surgical resection.

Methods: Retrospective analysis was performed for 288 cases with histologically confirmed NSCLC that underwent curative resection from April 2009 to June 2012. All patients were classified into two groups based on the median value of PLR. The relationship between PLR and clinicopathological features was studied. Univariate and multivariate analyses were performed to assess the prognostic effect of preoperative PLR.

Results: The median value of preoperative PLR was 142 (range: 45.45 to 272.66). Based on the cut-off value of 142, all patients were divided into two groups: Low PLR ($\leq$ 142, n=145) and high PLR (142, n=143). PLR was correlated with tumor site, T stage, and clinical stage. Five-year survival rates of low and high PLR patients were 49.6% and 33.6%, respectively, which indicated a statistically significant difference (χ^2=6.554, P=0.010) between the two groups. Univariate analysis showed that smoking status, histological differentiation, clinical stage, T stage, N stage, postoperative adjuvant therapy and PLR were associated with survival (P<0.05 for all). Multivariate analysis identified N stage, postoperative adjuvant therapy, and PLR as independent prognostic factors of all the patients. In addition, stratified analysis showed that the five-year survival rate of the low PLR group was higher than that of the high PLR group with or without lymph node metastasis, and the differences were statistically significant (P=0.001 and 0.001).

Conclusion: An elevated blood preoperative PLR indicates poor prognosis in NSCLC patients. Preoperative PLR is an independent prognostic factor of NSCLC after curative resection.

Keywords: Non-small cell lung cancer; Platelet-to-lymphocyte ratio; Prognosis

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Introduction

Inflammation is a critical component of tumor progression. Inflammation can enhance tumor growth, invasion, angiogenesis, and, eventually, metastasis [1-2].

It is now becoming clear that the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an essential participant in the neoplastic process, promoting proliferation, survival and migration. (Coussens and Werb, 2002). The change of tumor related inflammatory cells also reflected to the extent of the tumor inflammatory reaction, and the high inflammation reaction has always been found to relate with poor prognosis in patients [3].

Pretreatment high neutrophil count has been reported as a poor prognostic factor for survival in patients with renal cell carcinoma gastric cancer, colorectal cancer and ovarian cancer [4-6].

To the best of our knowledge, there is no consistent conclusion of study investigating relationship between PLR and survival in patients with non-small cell lung cancer. Therefore, the aim of this study was to explore the relationships between preoperative PLR and the postoperative outcomes of patients who underwent curative surgical resection for patients with NSCLC.

Materials and Methods

Patients

We consecutively enrolled 288 patients who were diagnosed with NSCLC and underwent first line of surgery in Shandong Tumor hospital (Jinan, China) between April 2009 to June 2012. Patients were excluded if they were having the evidence of preoperative acute/chronic infection or severe bleeding, accompanied by blood system malignant tumor, with autoimmune disease or systemic infection, the death of perioperative complications from surgery.

Mean age of 288 patients was 58.1 ± 8.6 (30-78) years; 168 of 288 patients were male whereas the rest were female. 201 patients had the history of smoking. All the patients had not undergone preoperative neoadjuvant therapy.

Histopathology of NSCLC was squalors cell carcinoma in 144, adenocarcinoma in 85, large cell and other neuroendocrine carcinoma in 35, adenosquamous carcinoma in 24 patients. The postoperative clinical stage of the lung cancer was I in 148, II in 58 and III in 82 patients, which was staged according to the Tumor-Node-Metastasis (TNM) criteria (AJCC 7th edition criteria 2010-for SCLC as well as NSCLC).

Complete blood counts with automated differential counts, which included total white blood cells, neutrophils, lymphocytes, and platelets, were obtained before surgery. PLR was calculated as the ratio of the platelets to lymphocytes. Median value was used for PLR because normal distribution was absent. The patients were separated into two groups according to median value of PLR (low: ≤ 142 or high >142, respectively). The aim of this study was to analyze the clinical pathological characteristics between two groups and further analyze the influence on prognosis of patients.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc. Chicago, IL, USA). Overall Survival (OS) was defined as the time of surgry and death or the last follow-up. The chi-squared (χ^2) test was used to evaluate the relatedness between PLR and baseline clinical characteristics. The data were censored at the time of last follow-up (December 31, 2014). Univariate analysis was performed with the Kaplan-Meier method, and statistically significant differences between survival curves were assessed by the log-rank test. A Cox regression model was used to analyze independent prognostic risk factors. A P value <0.05 was considered statistically significant.

Results

Relationships between preoperative PLR and clinicopathological factors

The preoperative PLR was calculated as a simple ratio of the absolute platelet to lymphocyte count. The median PLR was 142, ranging from 43.0 to 317.8. An SPSS 19.0 analysis showed that cutoff value of 142 for PLR predicted recurrence and mortality Patients were divided in two groups as follows: Group A (PLR>142) 143 patients and group B (PLR ≤ 142) 145 patients according to the median PLR. Univariate analysis showed that tumor site (P=0.001), T stage (P=0.002), and clinical stage (P=0.010) had a statistically significant difference between the high and low PLR groups. There was no difference between patients with high PLR and those with low PLR in other clinicopathological factors (P>0.05) Table 1.

Table 1: Correlation between preoperative Platelet-to-Lymphocyte Ratio (PLR) and clinicopathological factors in NSCLC patient's n (%).

Variable	n	Preoperative PLR		χ^2	P
		≤ 142	>142		
Gender		145	143	0.667	0.414
Male	168	88	80		
Female	120	57	63		
Smoking status				1.78	0.182
Smoker	201	96	105		
Nonsmoker	87	49	38		
Age (years)				1.143	0.285
≤ 60	136	73	63		
>60	152	72	80		
Histological differentiation				2.114	0.348
Well	68	37	31		
Moderate	146	76	70		
Poorly	74	32	42		
Lesion				12.212	0.001
Central	101	65	36		
Perpheral	187	80	107		
T stage				12.381	0.002
T 1	86	30	56		
T 2	134	79	55		
T 3	58	36	32		
Clinical stag				9.126	0.01
I	148	87	61		
II	58	26	32		
III	82	32	50		
N stage				2.518	0.284
N 0	150	82	68		
N 1	37	18	19		
N 2	101	45	56		

The value of preoperative PLR to predict the prognosis of patients with NSCLC

Follow-up data were obtained from all the patients. The median length of Postoperative follow-up for surviving patients was 48 months (range: 3 to 99 months). The average OS of the 288 NSCLC patients censored at the last follow-up was 99 months. The median OS of the 145 patients with a low PLR (PLR ≤ 142) was 68 months. The median OS for the remaining 143 patients whose PLR was >142 was 38 months. Five-year survival rates of low and high PLR patients were 51.6% and 30.6%, respectively. A Kaplan-Meier survival analysis showed that the OS of the NSCLC patients whose PLR was ≤ 142 was significantly longer than that of the NSCLC patients whose platelet count was >142 (χ^2=6.554 P=0.010) (Figure 1). Univariate analysis revealed that smoking status, histological differentiation, clinical stage, T stage, N stage, postoperative adjuvant therapy and PLR were associated with survival (P<0.05), while other factors had nothing to do with the prognosis.

However, only N stage, postoperative adjuvant therapy, and PLR remained as significant prognostic indicators in the multivariate analysis (P<0.05) Table 2.

Table 2: Prognostic factors for overall survival in multivariate analysis.

Variable	HR	95% CI	p
Smoking status	1.1	0.781-1.556	0.58
N stage	1.5	1.018-2.221	0.04
Histological differentiation	1.16	0.902-1.481	0.25
PLR	1.54	1.120-2.123	0.01
Postoperative adjuvant therapy	1.6	1.181-2.176	0
T stage	0.63	0.369-1.068	0.09
Clinical stage	1	1.002-1.006	0.08
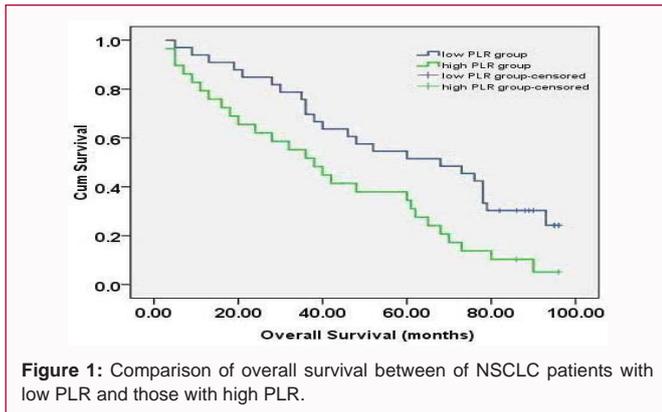
Figure 1: Comparison of overall survival between of NSCLC patients with low PLR and those with high PLR.

Figure 2: OS for patients without lymph node metastasis.

Preoperative PLR impact on the presence of lymph node metastasis of the prognosis of patients with NSCLC

According to the presence of lymph node metastasis in patients with stratified analysis, 150 patients without lymph node metastasis and 138 cases with lymph node metastasis in the study. In patients with no lymph node metastasis, the 5-year survival rate were 69.6% and 39.3% , respectively (P<0.05), and the median survival time 72 and 47 months respectively, for the low and high PLR group and the differences were statistically significant (χ^2=13.904, P=0.001) (Figure 2). In patients with lymph node metastasis, the 5-year survival rate were 71.7% and 54.3%, respectively (P<0.05), and the median survival time 45 and 27 months respectively, for the low and high PLR group and the differences were statistically significant (χ^2=11.244, P=0.001) (Figure 3).

Discussion

Lung Cancer (LC) is still the primary cause of cancer deaths worldwide, and the incidence is increasing year by year. Furthermore, despite the progress in diagnosis and treatment of these patients, the overall 5-year survival rate remains unchanged at 15% over ten years [7]. A complex tumor microenvironment is one of the important factors that affect the prognosis of patients with lung cancer. Tumour cells produce various cytokines and chemokine that attract leukocytes. The inflammatory component of a neoplasm may include a different leukocyte subtypes such as neutrophils, macrophages, and dendritic cells. All these cells produce cytokines, cytotoxic mediators such as reactive oxygen species, and soluble mediators such as tumor necrosis factor-alpha (TNF-α) and interleukins. Inflammatory cells have powerful effects on tumour development. Early in the neoplastic process, these cells are powerful tumour promoters, producing an attractive environment for tumour growth, facilitating genomic instability and promoting angiogenesis. On the other hand, inflammatory responses should also be antitumor, but cancer patients are often defective in their inflammatory responses.
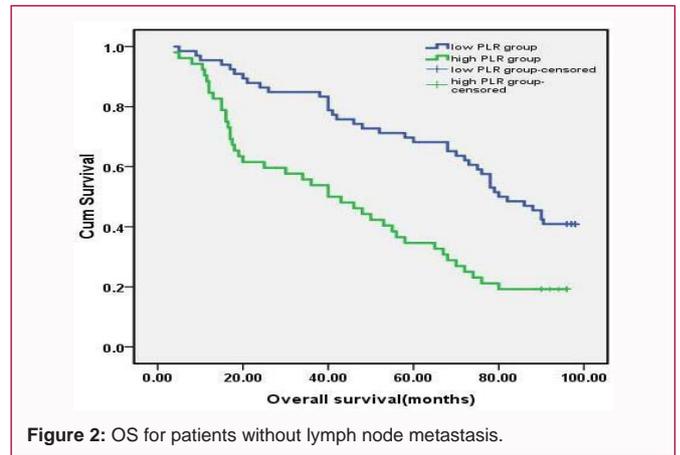
Indicators of systemic inflammatory response C-Reactive Protein (CRP) and albumin, Neutrophils and platelets, lymphocytes, macrophages, etc- have been shown to predict clinical outcomes in some solid tumors including Lung cancer. Based on the above parameters to build prognostic indicators include: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR) and Glasgow Prognostic Score (GPS). GPS had been proved to be objective and economical indicator which was independent of the tumor stage to predict survival outcome [8].

Compared to the CRP, Platelet count and lymphocyte count are repeatable, inexpensive and widely available in clinical practice, making PLR a potentially useful biomarker for predicting prognosis in NSCLC. Kwon et al. [9] reported that the colorectal cancer patients who had high PLR had the higher occurrence of lymph node metastasis.

Azab et al. [10] studies had shown that the breast cancer patients with high PLR had a higher probability of lymph node invasion and distant metastasis, high AJCC staging and the low hemoglobin. These results suggested that PLR could be a predictor some tumors. Compared with the healthy people, Kemal etc. study found that the LC patients had significantly higher NLR and PRL values compared with the healthy control group. Moreover, no relationship was observed between NLR, NLR values and TNM stages and histopathological subgroups. PLR level was helpful to early diagnosis and treatment in patients with lung cancer [11]. In addition to, Unal et al. [12] study found that the overall and disease-free survival rates were significantly associated with PLR, but was the only independent risk factors affect overall survival in patients. PLR boundary value was not the same in different studies or in different tumors, and in the GPS, PLR boundary value was defined as 150:1 [13]. Some studies chosed 152.6:1 or 194:1 as PLR boundary values according to the ROC curve or the median [12,14]. The median PLR was 142, the patients were separated into two groups according to median value of PLR (low: ≤ 142 or high >142, respectively). The study found that the high PLR group had high T staging and clinical staging, prompt high PLR group to a greater degree of malignant tumor. In the study, we found that the PLR was the risk factor affecting the prognosis of patients with NSCLC in the univariate analysis and multivariate analysis and was an independent unfavorable prognostic factor. Thus, the systemic inflammation and the immune system play an important role in the prognosis of patients with NSCLC.

PLR could reflect the relative changes of the platelet and lymphocyte count. Increased PLR can represent both Thrombocytosis

and lymphocytopenia. Thrombocytosis was reported to be associated with tumor progression and poor survival in ESCC patients [15]. Some studies also demonstrate that platelets contribute to hematogenous metastasis by means of stabilizing tumor cell arrest in the vasculature, stimulating tumor cell proliferation, promoting tumor cell extravasation, and enhancing tumor cell interaction with the extracellular matrix [16]. In addition to these mechanisms, activated platelets in the tumor environment of ovarian cancer cells have been found to increase tumor cell invasion in a dose-dependent fashion (Holmes et al., 2009).

Lymphocytopenia can also activate inhibitory immunologic mediators, such as interleukin-10 (IL-10) and Transforming Growth Factor-β (TGF-β), and results in a significant immunosuppressive effect with consequent impaired lymphocyte function [17]. These studies are consistent with our findings that preoperative PLR, a measurement of Thrombocytosis and/or lymphocytopenia, may reflect the host inflammatory status and correlate with surgical outcomes in NSCLC patients.

In Conclusion, Platelet count and lymphocyte count are repeatable, inexpensive and widely available in clinical practice, making PLR a potentially useful biomarker for predicting prognosis in NSCLC. Our study shows a significant association between the pretreatment PLR and response to prognosis in NSCLC. PLR can not only reflect the body's inflammatory and immune status, and can be used to evaluate the prognosis of patients with tumor. Thus, Preoperative PLR to assess prognosis of patients with NSCLC would provide convenient guidance for clinical practice. Our results need further study in a larger population to validate the prognostic role of PLR.

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