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

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Abstract

Background: More and more evidence showed that the host inflammatory status is associated with prognosis of several solid tumors. The status of systematic inflammation could be reflected by preoperative Platelet–Lymphocyte Ratio (PLR) which acquired from routine blood tests. In this study, we aimed to evaluate effects of the pretreatment the Platelet to Lymphocyte Ratio (PLR) on the prognosis of Non-Small Cell Lung Cancer (NSCLC) patients underwent 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 (≤ 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 predictive factor of NSCLC who receive curative resection.

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

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Introduction

Inflammation has been recognized to play a pivotal role in tumor progression. Inflammation promotes 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 is associated with poor prognosis in patients [3]. The Platelet-to-Lymphocyte Ratio (PLR) has been widely used predict the outcome of treatment of patients with various malignancies, such as gastric cancer, colorectal cancer and ovarian cancer [4-6]. However, the combination of PLR and prognosis in patients with non-small cell lung cancer who received curative resection therapy is rarely reported. In this study, we aimed to elucidate the relationships between preoperative PLR and the postoperative outcomes of NSCLC patients who underwent curative surgical resection.

Materials and Methods

Patients

Data from 288 patients who were diagnosed with NSCLC and underwent first line of surgery

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				1.780	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	0.010
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		

in Shandong Tumor Hospital (Jinan, China) between April 2009 to June 2012. The following criteria was excluded: existing 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. A 168 males (58.3%) and 120 females were enrolled in this study. Mean age was 58.1 ± 8.6 (30-78) years. 201 patients had the history of smoking. All the patients had not underwent preoperative neoadjuvant therapy. Histopathology of NSCLC was squamous cell carcinoma in 144, adenocarcinoma in 85, large cell and other neuroendocrine carcinoma in 35, adenosquamous carcinoma in 24 patients. According to the Tumor–Node–Metastasis (TNM) criteria (AJCC 7th edition criteria 2010-for SCLC as well as NSCLC), the postoperative clinical and tumor staging were defined, stage I 148, stage II 58 and stage III 82. Before surgery, Clinical and radiological data were retrieved and analyzed. White blood cell count, neutrophils, lymphocytes, and platelets, AFP, alanine transaminase et al were included. PLR was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes. Median value was used for PLR because normal distribution was absent. According to median value of PLR, the patients were separated into two groups (low: ≤142 or high >142, respectively). In total, there were 143 patients with high PLR (PLR>142) group, and another 145 patients with low PLR (PLR ≤ 142) group, respectively.

Postoperative follow-up

Patients were followed up by hospitalization or phone calls. The median follow-up duration was 48 months (range: 3.0~99.0 months). The deadline of follow-up data was December 31, 2014. Overall Survival (OS) was calculated from the time of surgery and death or the last follow-up.

Statistical analysis

All statistical analysis was performed using SPSS version 21.0 software (SPSS, Inc. Chicago, IL, USA). The categorical variables were compared by the chi-squared test. Univariate and multivariate analyses were performed using a logistic regression model. Survival analysis was performed using Kaplan-Meier method and log-rank test. Factors affecting OS were determined by univariate and multivariate Cox proportional hazards regression analyses. 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. In univariate analysis, there were significantly positive correlations between tumor site (P=0.001), T stage (P=0.002), and clinical stage (P=0.010) in the high and low PLR groups. While, other clinicopathological factors there were no difference between patients with high PLR and those with low PLR (P>0.05) (Table 1).

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

The median OS of the 288 NSCLC patients was 49 months. Kaplan-Meier survival analysis showed that patients with PLR ≤ 142 also had better long-term survival than patients with PLR>142 (68 months *vs.* 38 months), (χ2=6.554, P=0.010) (Figure 1). The estimated 5-year OS rate for low and high PLR patients was 51.6% and 30.6%, respectively. In univariate analysis, smoking status, histological differentiation, clinical stage, T stage, N stage, postoperative adjuvant therapy and PLR affecting survival (P<0.05), while other factors had nothing to do with the prognosis. In multivariate analysis, only N stage, postoperative adjuvant therapy, and PLR were independent risk factors affecting the prognosis of patients (P<0.05) (Table 2).

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

In multivariate analysis, lymph node metastasis showed a better distinguishing power for predicting the prognosis of patients. In our study, 150 patients without lymph node metastasis and 138 cases with lymph node metastasis. Significant differences was discovered in patients with lymph node metastasis, the 5-year survival rate with low PLR and high PLR patients were 71.7% and 54.3%, respectively (P<0.05),while the median survival time 72 and 47 months respectively, (χ^2=13.904, P=0.001) (Figure 2). In patients with lymph

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

Variable	HR	95% CI	*p*
Smoking status	1.103	0.781–1.556	0.578
N stage	1.504	1.018–2.221	0.040
Histological differentiation	1.156	0.902-1.481	0.251
PLR	1.542	1.120-2.123	0.008
Postoperative adjuvant therapy	1.603	1.181-2.176	0.002
T stage	0.628	0.369–1.068	0.086
Clinical stage	1.004	1.002–1.006	0.08

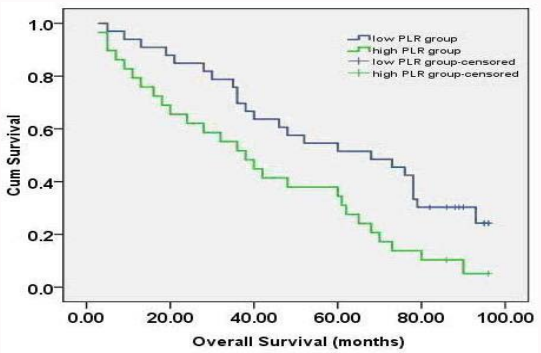

Figure 1: Comparison of overall survival between of NSCLC patients with low PLR and those with high PLR.

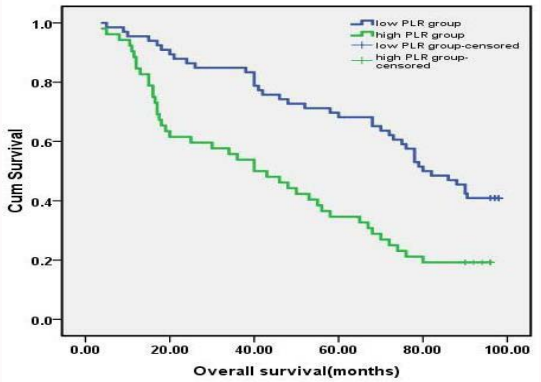

Figure 2: OS for patients without lymph node metastasis.

node metastasis, the 5-year survival rate were 69.6% and 39.3%, respectively (P<0.05), and the median survival time 45 and 27 months respectively, for the low and high PLR group and the differences had statistically significant (χ2=11.244, P=0.001) (Figure 3).

Discussion

Lung Cancer (LC) is the highest incidence and mortality malignant tumor, and the incidence is increasing year by year. Furthermore, in the past ten years, despite the progress in diagnosis and treatment of these patients, the overall 5-year survival rate hovers around 15% [7]. Accumulated evidence shows that inflammatory processes in the tumor microenvironment was associated with the prognosis of patients with lung cancer. Many studies have confirmed that tumor is the result of the interaction between its own characteristics and systemic inflammatory reaction, which leads to cell injury, oxidative stress and the increase of prostaglandin, which leads to gene mutation and promotes the occurrence and development of tumor. C-Reactive Protein (CRP), albumin, neutrophils, platelets, lymphocytes,

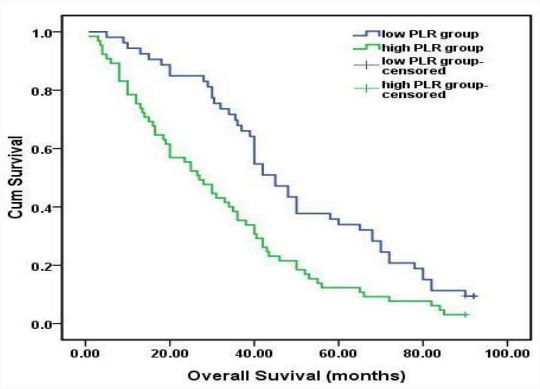

Figure 3: OS for patients with lymph node metastasis.

macrophages et al were the commonly used components of inflammatory system [8]. Based on the above parameters to build prognostic indicators include: Platelet-to-Lymphocyte Ratio (PLR, Neutrophil-to-Lymphocyte Ratio (NLR), 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. Compared to the CRP, Platelet count and lymphocyte count had become a potentially useful biomarker for predicting prognosis in NSCLC with the advantage of inexpensive and widely available in clinical practice. Kwon etc reported that the colorectal cancer patients who had high PLR had the higher occurrence of lymph node metastasis [9]. Azab Studies had shown that the probability of lymph node invasion, distant metastasis, high AJCC stage and low hypo hemoglobin in patients with breast cancer was positively correlated with high PLR [10]. These results suggested that PLR could be a predictor some tumors. Compared with the healthy people, Kemal study found that the LC patients had significantly higher NLR and PLR values. The level of PLR was beneficial to the early diagnosis and treatment of patients with lung cancer, but there were no clinicopathological features related to PLR [11]. In addition to, Unal [12] study found that PLR was a risk factor for the overall and disease-free with lung cancer, 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 choose 152.6:1 or 194:1 as PLR boundary values according to the ROC curve or the median [14]. In this study, the median of PLR 142 was used as the cutoff point to divide patients into low PLR group and high PLR group (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 affects the prognosis of patients with NSCLC. PLR could reflect the relative changes of the platelet and lymphocyte count, the increase of PLR reflects the relative increase of platelet count or the relative decrease of lymphocyte count, which can was also associated with the prognosis of tumor patients. Malignant tumors are often associated with increased platelets, which secrete some growth factors Platelet-Derived Growth Factors (PDGF), PF4, TGF-β, Vascular Endothelial Growth Factor (VEGF), etc. These growth factors can stimulate the proliferation of tumor cells, adhesion with other cells, and then promote the growth

and metastasis of tumor. Some pro-inflammatory cytokines, such as IL-1, IL-6, can promote megakaryocyte proliferation and further lead to thrombocytopenia. Hypothrombinemia has been considered to be an important indicator affecting the prognosis of many tumors. At the same time, platelet-derived angiogenic mediators released in tumor micro vessels during platelet aggregation and degranulation may also be an important determinant of tumor growth. On the other hand, lymphocytes play an important role in immune surveillance against tumor development. Lymphocytes can be specifically recognized and activate anti-tumor immunity directly or indirectly. The decrease of lymphocytes provides a favorable environment for tumor invasion and metastasis.

Conclusion

Peripheral blood cell count is a simple and economical test method, which is widely used in hospitals. PLR can not only reflect the inflammation and immune status of the body, but also can be used to evaluate the prognosis of tumor patients. Therefore, the use of preoperative peripheral blood PLR determination to evaluate the prognosis of patients with NSCLC will provide convenient and rapid guidance for clinical practice. For its more in-depth application value and reference value, our results need clinical confirmation of multicenter and large sample size.

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