Preoperative Platelet to Albumin Ratio Predicts Outcome of Patients with Non-Small-Cell Lung Cancer

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Objective: The purpose of this study was to evaluate the predictive power of the platelet to albumin ratio (PAR) on survival outcomes of patients with non-small-cell lung cancer (NSCLC).

Patients and Methods: In all, 198 patients with NSCLC were recruited. The X-tile software was performed to identify the optimal cutoff values for PAR, platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR). The Kaplan–Meier method, univariate and multivariate analyses Cox regression were used to analyze the prognostic factors for overall survival (OS).

Results: In all, 198 patients were enrolled, containing 146 (73.7%) men and 52 (26.3%) women. The optimal cutoff values for PAR, PLR, and NLR were \(8.8 \times 10^9\), 147.7, and 3.9, respectively. Patients with \(\text{PAR} > 8.8 \times 10^9\) \((P < 0.001)\), \(\text{PLR} > 147.7\) \((P < 0.001)\), and \(\text{NLR} > 3.9\) \((P = 0.007)\) were associated with poor OS. Multivariate analyses found that PAR was an independent predictor in NSCLC patients \(\text{hazard ratio [HR]}: 4.604, 95\% \text{confidence interval [CI]}: 2.557–8.290, P < 0.001\).

Conclusion: Preoperative PAR is a useful and potential prognostic biomarker in NSCLC patients who have received primary resection.

Keywords: non-small-cell lung cancer, prognosis, platelet, albumin, platelet to albumin ratio

Introduction

Lung cancer is one of the most common cancer with a leading mortality over the world. Lung cancer is divided into two categories, non-small-cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and NSCLC accounts for 83% of lung cancer.\(^{1,2}\) Although with similar staging and histological classification, the survival outcomes of patients were significantly different. The treatment of NSCLC has been improved, but the prognosis is still dissatisfactory.\(^{3}\) Some novel biomarkers have been identified as potential predictors of NSCLC prognosis.\(^{4,5}\) However, these markers are rarely used in the clinic. Therefore, an effective method with clinically significant to forecast the prognosis of NSCLC patients is urgently needed.

The systemic inflammatory response plays a vital role in the cancer progression and promotion of metastatic spread.\(^{6,7}\) Therefore, distinct and novel serum biomarkers of inflammation from clinical laboratory test have been the subject of studies. Platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and platelet to albumin ratio (PAR) are indicators as clinical markers responding the inflammatory state. Some studies have found high PLR and NLR levels are related to the poor
Platelet to Albumin Ratio Predicts NSCLC prognosis of NSCLC.\textsuperscript{8,9} However, a prospective study showed that NSCLC prognosis is significantly associated with PLR, especially 1-year over survival.\textsuperscript{10} In addition, Saito et al.\textsuperscript{11} found that PAR is an independent risk factor in patients with cholangiocarcinoma. Therefore, these inflammation indicators are still unclear in NSCLC prognosis, and they are not more effective in clinical practice. This study aimed to explore the clinical significance of inflammatory markers of NSCLC and their relationship with the overall survival (OS).

Materials and Methods

Patients

The patients with NSCLC who have underwent radical operation of lung cancer from January 2012 to December 2014, in the First Affiliated Hospital of Zhengzhou University were evaluated in this study. The inclusion criteria were as follows: (1) confirmed as NSCLC with histopathological method; (2) blood tests taken 2 weeks before surgery; and (3) available follow-up data. The patients who had received chemotherapy and radiotherapy treatment before surgery and combined with other primary malignancies, severe hypertension, diabetes, liver and kidney disease were excluded. In all, 198 NSCLC patients were ultimately enrolled in this research (Fig. 1). This study was approved by the research ethics committee of the First Affiliated Hospital of Zhengzhou University. This research was consistent with the standards of the Declaration of Helsinki.

Follow-up and clinical data collection

Clinical data including patients’ age, gender, smoking history, type of resection, histopathology, tumor, node, metastasis (TNM) staging, and differentiation were collected from the retrospective electronic medical records. TNM staging was based on the 7th edition of the TNM classification.\textsuperscript{12} The laboratory results including preoperative blood cell counts and albumin were extracted.

| Table 1 Clinical characteristics and levels of inflammatory markers of patients |
|---------------------------------------------------|-----------------|
| Parameter | Number (%)/median (range) |
| Age | |
| ≤60 | 113 (57.1%) |
| >60 | 85 (42.9%) |
| Gender | |
| Male | 146 (73.7%) |
| Female | 52 (26.3%) |
| Smoking history | |
| Yes | 129 (65.2%) |
| No | 69 (34.8%) |
| Resection type | |
| Lobectomy | 134 (67.7%) |
| Segmentectomy | 47 (23.7%) |
| Pneumonectomy | 17 (8.6%) |
| Surgical options | |
| Thoracotomy | 122 (61.6%) |
| VATS | 76 (38.4%) |
| Differentiation | |
| Well | 13 (6.6%) |
| Moderate | 102 (51.5%) |
| Poor | 83 (41.9%) |
| Histologic type | |
| Adenocarcinoma | 126 (63.6%) |
| Squamous cell carcinoma | 60 (30.3%) |
| Others | 12 (6.1%) |
| TNM stage | |
| I | 36 (18.2%) |
| IIA | 80 (40.4%) |
| IIB | 21 (10.6%) |
| IIIA | 42 (21.2%) |
| IIIB | 6 (3.0%) |
| IV | 13 (6.6%) |
| Albumin (g/L) | 38.8 (8.96–52.10) |
| Neutrophil, 10\textsuperscript{9}/L | 4.2 (1.73–17.2) |
| Lymphocyte, 10\textsuperscript{9}/L | 1.59 (0.1–3.8) |
| Platelet, 10\textsuperscript{9}/L | 238.5 (80–551) |
| PLR | |
| ≤147.7 | 90 (45.5%) |
| >147.7 | 108 (54.5%) |
| NLR | |
| ≤3.9 | 139 (70.2%) |
| >3.9 | 59 (29.8%) |
| PAR | |
| ≤8.8 × 10\textsuperscript{9} | 159 (80.3%) |
| >8.8 × 10\textsuperscript{9} | 39 (19.7%) |

NLR: neutrophil to lymphocyte ratio; PAR: platelet to albumin ratio; PLR: platelet to lymphocyte ratio; TNM: tumor, node, metastasis; VATS: video-assisted thoracoscopic surgery

Fig. 1 Flow chart of patient selection
Statistical analysis

The optimal cutoff points of PLR, NLR, and PAR were calculated to by the X-tile 3.6.0. The clinicopathologic characteristics were evaluated by descriptive analysis. The clinicopathological characteristics grouped by PAR were compared by the chi-squared tests or Fisher’s exact tests. The Kaplan–Meier method was utilized to estimate survival time with log-rank tests. The prognostic factors of survival were identified with univariate and multivariate analyses cox proportional hazards regression models. The multivariate cox analysis was based on the factors with significantly prognostic values in the univariate cox analysis. All statistical analyses were conducted using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). P value <0.05 was considered significant.

Results

Patient characteristics

Table 1 describes the clinical characteristics and levels inflammatory markers of 198 patients in the study. All patients consisted of 146 (73.7%) men and 52 (26.3%) women. The median age of patients was 59 years (range: 18–83 years) and there were 85 patients older than 60 years. In all, 129 patients (65.2%) had smoking history. 134 patients (67.7%) underwent
lobectomy, 47 patients (23.7%) underwent segmentectomy, and 17 patients (8.6%) underwent pneumonectomy. According to the differentiation, 83 patients (41.9%) had poor differentiation, whereas 102 patients (51.5%) had moderate differentiation and 13 (6.6%) patients had high differentiation. More than half (n = 122, 61.6%) underwent thoracotomy, the other patients (n = 76, 38.4%) underwent video-assisted thoracoscopic surgery. Based on 7th AJCC cancer staging manual, 36 of the tumors (18.2%) were stage I, 80 (40.4%) stage IIA, 21 (10.6%) stage IIB, 42 (21.2%) stage IIIA, 6 (3.0%) stage IIIB, and 13 (6.6%) stage IV. Squamous cell carcinoma and adenocarcinoma accounted for 30.3% and 63.6%, respectively.

The median of follow-up duration of all enrolled NSCLC was 43 months, ranging from 3 to 72 months. The relationship between OS and three indicators, PAR, PLR, and NLR, was analyzed using Kaplan–Meier method analysis, respectively (Fig. 3). The Kaplan–Meier method analysis manifested that higher PAR, PLR, and NLR were significantly associated with shorter survival time (P < 0.001; P < 0.001; P = 0.007, respectively). Table 2 shows the association between clinic pathological variables and OS. Univariate analyses showed significant prognostic factors of poor survival containing age (P = 0.026), TNM stage (P = 0.016), tumor differentiation (P < 0.001), PLR (P < 0.001), NLR (P = 0.009), and PAR (P < 0.001). In multivariate analysis, independent risk factors of poor patient survival consisted of age (hazard ratio [HR] 1.842, 95% confidence

### Table 2 Univariate and multivariate Cox proportional hazards regression models for overall survival in patients with non-small-cell lung cancer

| Parameter               | Univariate analysis | Multivariate analysis |
|-------------------------|--------------------|-----------------------|
|                         | HR (95% CI)        | P value               |
| Age                     |                    |                       |
| ≤60 / >60               | 1.488 (1.049–2.109) | 0.026*                |
|                         |                    | 1.842 (1.285–2.641)   | 0.001*                |
| Gender                  |                    |                       |
| Male/Female             | 1.152 (0.791–1.678) | 0.462                 |
| Smoking history         |                    |                       |
| Yes/No                  | 0.950 (0.663–1.361) | 0.780                 |
| Surgical options        |                    |                       |
| Thoracotomy/VATS        | 1.235 (0.865–1.764) | 0.245                 |
| Differentiation         |                    |                       |
| Well                    |                    |                       |
| Moderate                | 3.216 (1.381–7.490) | <0.001*               |
| Poor                    | 10.088 (0.180–1.116) | 6.304 (2.316–17.159)  |
| Histologic type         |                    |                       |
| Adenocarcinoma          | 1.212 (0.834–1.761) | 0.106                 |
| Squamous cell carcinoma |                    |                       |
| Others                  | 0.449 (0.180–1.116) |                       |
| TNM stage               |                    |                       |
| I,II/III,IV             | 1.566 (1.087–2.258) | 0.016*                |
|                         | 1.536 (1.022–2.308) | 0.039*                |
| PLR                     |                    |                       |
| ≤147.7 / >147.7         | 2.837 (1.942–4.147) | <0.001*               |
|                         | 1.474 (0.888–2.448) | 0.134                 |
| NLR                     |                    |                       |
| ≤3.9 / >3.9             | 1.686 (1.140–2.494) | 0.009*                |
|                         | 0.917 (0.588–1.428) | 0.700                 |
| PAR                     |                    |                       |
| ≤8.8 × 10^9 / >8.8 × 10^9 | 6.949 (4.210–11.469) | <0.001*               |
|                         | 4.604 (2.557–8.290) | <0.001*               |

CI: confidence interval; HR: hazard ratio; NLR: neutrophil to lymphocyte ratio; PAR: platelet to albumin ratio; PLR: platelet to lymphocyte ratio; TNM: tumor, node, metastasis; VATS: video-assisted thoracoscopic surgery

### Prognostic analysis

The median of follow-up duration of all enrolled NSCLC was 43 months, ranging from 3 to 72 months. The relationship between OS and three indicators, PAR, PLR, and NLR, was analyzed using Kaplan–Meier method analysis, respectively (Fig. 3). The Kaplan–Meier method analysis manifested that higher PAR, PLR, and NLR were significantly associated with shorter survival time (P < 0.001; P < 0.001; P = 0.007, respectively). Table 2 shows the association between clinic pathological variables and OS. Univariate analyses showed significant prognostic factors of poor survival containing age (P = 0.026), TNM stage (P = 0.016), tumor differentiation (P < 0.001), PLR (P < 0.001), NLR (P = 0.009), and PAR (P < 0.001). In multivariate analysis, independent risk factors of poor patient survival consisted of age (hazard ratio [HR] 1.842, 95% confidence
interval [CI] 1.285–2.641, \( P = 0.001 \), TNM stage (I, II vs III, IV HR: 1.536, 95% CI: 1.022–2.308, \( P = 0.039 \)), tumor differentiation (\( P = 0.002 \)), and PAR (HR: 4.604, 95% CI: 2.557–8.290, \( P < 0.001 \)). The higher PAR group (\( > 8.8 \times 10^9 \)) had poor differentiation (Table 3). Patients with PAR >\( 8.8 \times 10^9 \) had significantly worse OS compared to those with PLR \( \leq 8.8 \times 10^9 \) (\( P < 0.001 \)) (Fig. 3C). Therefore, this research indicated that PAR was a superior and independent prognosis predictor for NSCLC.

**Discussion**

Previous studies have demonstrated that PLR, NLR, and albumin are novel inflammatory predictors of patients with NSCLC.\(^9,10,13\) However, recent studies have questioned the prognostic effect of inflammatory markers on cancer. Dutta et al.\(^14\) found that PLR could not accurately predict the prognosis of gastric cancer. The researchers discovered that the change of NLR was not an important predictor of lung cancer.\(^15\) Furthermore, the current study only found that PAR has an effective prognostic effect in cholangiocarcinoma.\(^11\) Therefore, the prognostic value of these inflammatory markers of NSCLC is still unclear and further study is needed. In this study, preoperative PAR was an independent and significantly prognostic factor for NSCLC who have undergone surgical resection, whereas PLR and NLR were not.

The underlying mechanism of inflammation affecting cancer prognosis is not clear, but it could be associated with inflammatory response and tumor microenvironment changing. Platelet counts are critical indicator of inflammatory response. Numerous studies have demonstrated that platelets can influence cancer progression, and thrombocytosis is an important factor for poor prognosis.\(^16–19\) The possible explanation is that platelets are stimulated by diverse cytokines secreted by tumors in patients with high platelet counts, containing vascular endothelial growth factor receptor (VEGFR), thrombospondin-1, and transforming growth factor-\( \beta \).\(^20–22\) Growth factors such as VEGFR directly affect tumor cell proliferation.\(^23,24\) Platelet-derived growth factor (PDGF) in platelet a-granules also stimulates cancer cell growth and angiogenesis.\(^25\)

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**Table 3  Clinicopathological features of the low and the high PAR groups**

| Variable         | PAR \( \leq 8.8 \times 10^9 \) | PAR \( > 8.8 \times 10^9 \) | \( P \) |
|------------------|-------------------------------|-----------------------------|-------|
| Age              | 90                            | 23                          | 0.789 |
| \( \leq 60 \)    | 69                            | 16                          | 0.363 |
| Gender           |                               |                             |       |
| Male             | 115                           | 31                          |       |
| Female           | 44                            | 8                           |       |
| Smoking history  |                               |                             | 0.825 |
| Yes              | 103                           | 26                          |       |
| No               | 56                            | 13                          |       |
| Resection type   |                               |                             | 0.194 |
| Lobectomy        | 112                           | 22                          |       |
| Segmentectomy    | 35                            | 12                          |       |
| Pneumonectomy    | 12                            | 5                           |       |
| Surgical options |                               |                             | 0.139 |
| Thoracotomy      | 102                           | 20                          |       |
| VATS             | 57                            | 19                          |       |
| Differentiation  |                               |                             | <0.001* |
| Well/ Moderate   | 115                           | 0                           |       |
| Poor             | 44                            | 39                          |       |
| Histologic type  |                               |                             | 0.729 |
| Adenocarcinoma   | 100                           | 26                          |       |
| Squamous cell carcinoma | 48            | 12                          |       |
| Others           | 11                            | 1                           |       |
| TNM stage        |                               |                             | 0.054 |
| I, II            | 115                           | 22                          |       |
| III, IV          | 44                            | 17                          |       |

PAR: platelet to albumin ratio; TNM: tumor, node, metastasis; VATS: video-assisted thoracoscopic surgery.
Published studies have showed that nutrition and inflammation are associated with tumor progression.\textsuperscript{26,27} Albumin is considered as a sensitive marker in the evaluation of nutrition. Since malignant cells can cause malnutrition and systemic inflammatory response, the synthesis of albumin in cancer patients is inhibited and serum albumin levels drop sharply.\textsuperscript{28} Decreased albumin level may aggravate the disease, leading to poor prognosis of cancer.\textsuperscript{29} Furthermore, the systemic inflammation reduces albumin synthesis by cytokines, and hypoalbuminemia plays a major role in reducing the immune response and promoting cancer progression.\textsuperscript{30}

In summary, because PAR was the combination of the platelet count and albumin, it was found a strong prognostic factor of NSCLC after primary resection in this study. In addition, platelets count and serum albumin are easily available and low cost. However, the present study has some limitations. It is a retrospective research with small sample size. And we need to recruit more NSCLC patients and conduct prospective studies.

**Conclusion**

Our study demonstrates that PAR is a useful prognostic biomarker of NSCLC undergoing complete surgical resection; thus it can be used to guide individualized treatment and evaluate prognosis of NSCLC.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

**References**

1. Petersen I, Warth A. Lung cancer: developments, concepts, and specific aspects of the new WHO classification. J Cancer Res Clin Oncol 2016; 142: 895–904.
2. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66: 271–89.
3. Vijayvergia N, Shah PC, Denlinger CS. Survivorship in non-small cell lung cancer: challenges faced and steps forward. J Natl Compr Canc Netw 2015; 13: 1151–61.
4. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2010; 28: 744–52.
5. O’Byrne KJ, Gatzemeier U, Bondarenko I, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol 2011; 12: 795–805.
6. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene 2008; 27: 5904–12.
7. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 2004; 4: 71–8.
8. Yu Y, Qian L, Cui J. Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: A meta-analysis of 7,219 patients. Mol Clin Oncol 2017; 7: 498–506.
9. Zhao QT, Yuan Z, Zhang H, et al. Prognostic role of platelet to lymphocyte ratio in non-small cell lung cancers: A meta-analysis including 3,720 patients. Int J Cancer 2016; 139: 164–70.
10. Lan H, Zhou L, Chi D, et al. Preoperative platelet to lymphocyte and neutrophil to lymphocyte ratios are independent prognostic factors for patients undergoing
11) Saito N, Shirai Y, Horiuchi T, et al. Preoperative platelet to albumin ratio predicts outcome of patients with cholangiocarcinoma. Anticancer Res 2018; 38: 987–92.

12) Vallières E, Shepherd FA, Crowley J, et al. The IASLC lung cancer staging project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2009; 4: 1049–59.

13) Zhu J, Lian L, Qin H, et al. Prognostic evaluation of patients with resectable lung cancer using systemic inflammatory response parameters. Oncol Lett 2019; 17: 2244–56.

14) Dutta S, Crumley AB, Fullarton GM, et al. Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative resection of gastric cancer. Am J Surg 2012; 204: 294–9.

15) Sanchez-Salcedo P, de-Torres JP, Martinez-Urbistondo D, et al. The neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers for lung cancer development. Lung Cancer 2016; 97: 28–34.

16) Kawai K, Kitayama J, Tsuno NH, et al. Thrombocytosis before pre-operative chemoradiotherapy predicts poor response and shorter local recurrence-free survival in rectal cancer. Int J Colorectal Dis 2013; 28: 527–35.

17) Cakar B, Karaoglanoglu M, Sayici Y, et al. The prognostic value of thrombocytosis in newly diagnosed lung cancer patients: a retrospective analysis. J BUON 2011; 16: 677–81.

18) Hwang SG, Kim KM, Cheong JH, et al. Impact of pretreatment thrombocytosis on blood-borne metastasis and prognosis of gastric cancer. Eur J Surg Oncol 2012; 38: 562–7.

19) Baranyai Z, Jósa V, Tóth A, et al. Paraneoplastic thrombocytosis in gastrointestinal cancer. Platelets 2016; 27: 269–75.

20) Gasic GJ, Gasic TB, Stewart CC. Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci USA 1968; 61: 46–52.

21) Dubernard V, Arbeille BB, Lemesle MB, et al. Evidence for an alpha-granular pool of the cytoskeletal protein alpha-actinin in human platelets that redistributes with the adhesive glycoprotein thrombospondin-1 during the exocytotic process. Arterioscler Thromb Vasc Biol 1997; 17: 2293–305.

22) Qian X, Tuszynski GP. Expression of thrombospondin-1 in cancer: a role in tumor progression. Proc Soc Exp Biol Med 1996; 212: 199–207.

23) Goubren HA, Burnouf T, Radosevic M, et al. The platelet-cancer loop. Eur J Intern Med 2013; 24: 393–400.

24) Nash GF, Turner LF, Scully MF, et al. Platelets and cancer. Lancet Oncol 2002; 3: 425–30.

25) Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its involvement in disease. Mayo Clin Proc 2006; 81: 1241–57.

26) Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860–7.

27) Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883–99.

28) Yeun JY, Kaysen GA. Factors influencing serum albumin in dialysis patients. Am J Kidney Dis 1998; 32: S118–25.

29) Lis CG, Gupta D, Lammersfeld CA, et al. Role of nutritional status in predicting quality of life outcomes in cancer—a systematic review of the epidemiological literature. Nutr J 2012; 11: 27.

30) Lin MY, Liu WY, Tolan AM, et al. Preoperative serum albumin but not prealbumin is an excellent predictor of postoperative complications and mortality in patients with gastrointestinal cancer. Am Surg 2011; 77: 1286–9.