Original Article

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 8.8×10^9, 147.7, and 3.9, respectively. Patients with PAR $> 8.8 \times 10^9$ ($P < 0.001$), PLR > 147.7 ($P < 0.001$), and NLR > 3.9 ($P = 0.007$) were associated with poor OS. Multivariate analyses found that PAR was an independent predictor in NSCLC patients (hazard ratio [HR]: 4.604, 95% 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

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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
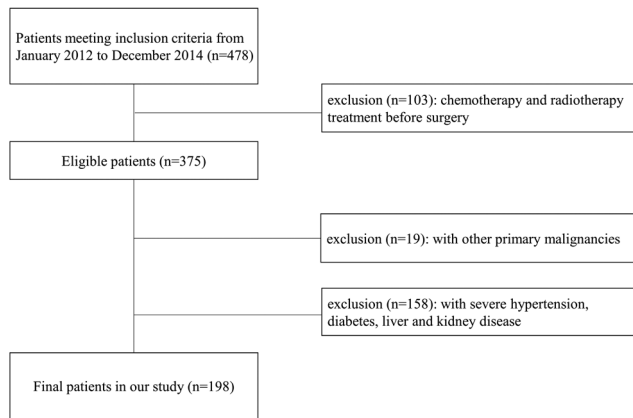
Fig. 1 Flow chart of patient selection

prognosis of NSCLC.[8,9] However, a prospective study showed that NSCLC prognosis is significantly associated with PLR, especially 1-year over survival.[10] In addition, Saito et al.[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, and 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,

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, 10^9/L	4.2 (1.73–17.2)
Lymphocyte, 10^9/L	1.59 (0.1–3.8)
Platelet, 10^9/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	
≤8.8×10^9	159 (80.3%)
>8.8×10^9	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

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.[12] The laboratory results including preoperative blood cell counts and albumin were extracted
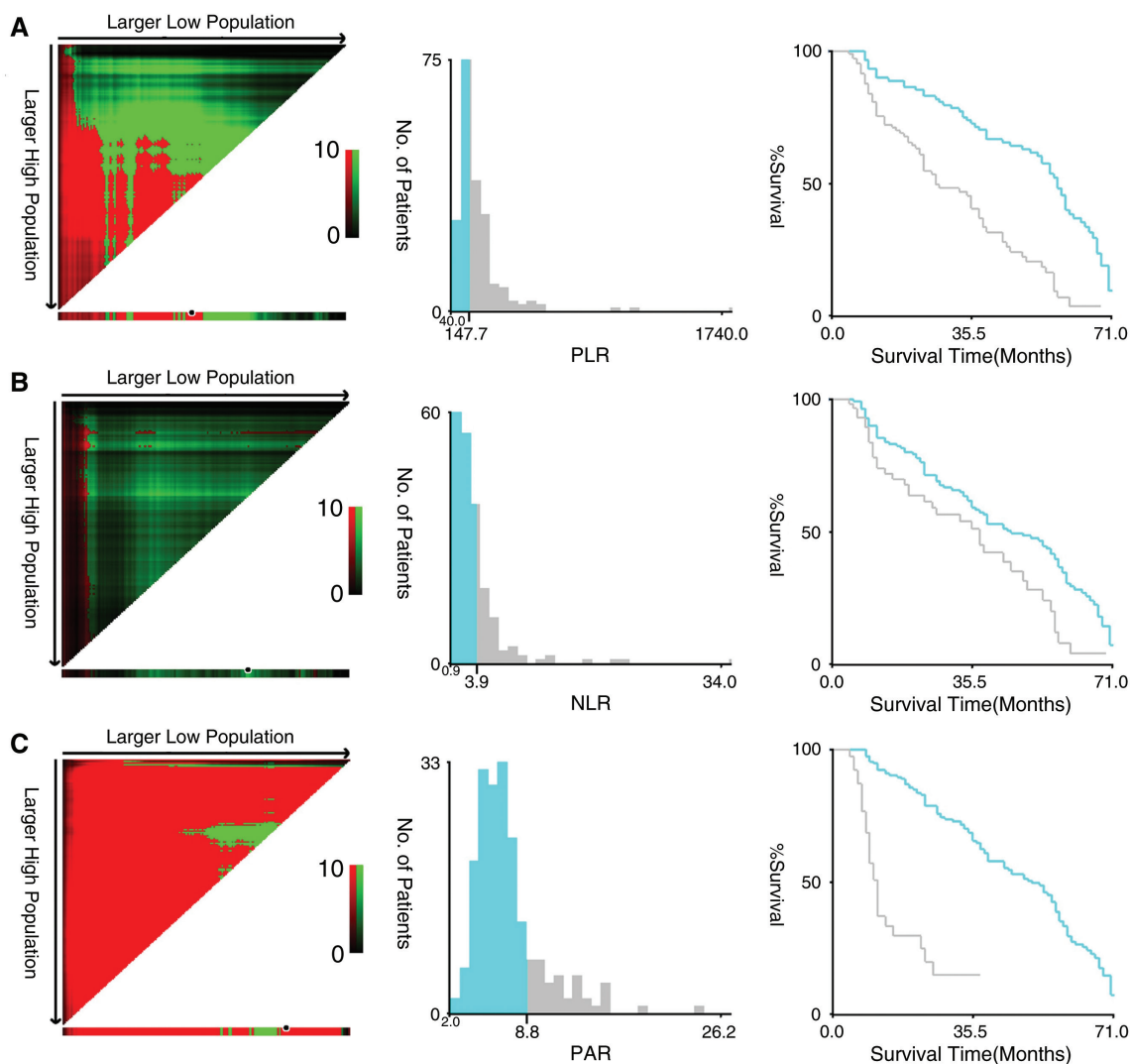
Fig. 2 X-tile analyses. The optimum cutoff points for PLR, NLR, and PAR were 147.7 (A), 3.9 (B), and 8.8×10^9 (C) according to the X-tile program. NLR: neutrophil to lymphocyte ratio; PAR: platelet to albumin ratio; PLR: platelet to lymphocyte ratio

from the medical records. PLR, NLR, and PAR were calculated. The survival information was assembled by interviewing medical record or telephoning.

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

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	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		<0.001*		0.002*
Moderate	3.216 (1.381–7.490)		4.072 (1.678–9.883)	
Poor	10.088 (0.180–1.116)		6.304 (2.316–17.159)	
Histologic type				
Adenocarcinoma		0.106		
Squamous cell carcinoma	1.212 (0.834–1.761)			
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 × 10⁹ / >8.8 × 10⁹	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

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.

Cutoff value for inflammatory markers

Using the X-tile program, the optimum cutoff points for PAR, NLR, and PLR were147.7, 3.9, and 8.8×10⁹, respectively (**Fig. 2**). According to the cutoff points, there were 90 (45.5%) and 108 (54.5%) patients in PLR ≤147.7 and PLR >147.7 groups; 139 (70.2%) and 59

(29.8%) patients in NLR ≤3.9 and NLR >3.9 groups; and 159 (80.3%) and 39 (19.7%) in PAR ≤8.8 × 10⁹ and PAR >8.8 × 10⁹groups, respectively (**Table 1**)

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 shorted 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 3   Clinicopathological features of the low and the high PAR groups

Variable	PAR ≤8.8 × 10⁹	PAR >8.8 × 10⁹	P
Age			0.789
≤60	90	23	
>60	69	16	
Gender			0.363
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

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 × 10⁹) had poor differentiation (**Table 3**). Patients with PAR >8.8 × 10⁹ had significantly worse OS compared to those with PLR ≤ 8.8 × 10⁹ (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-b.[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]
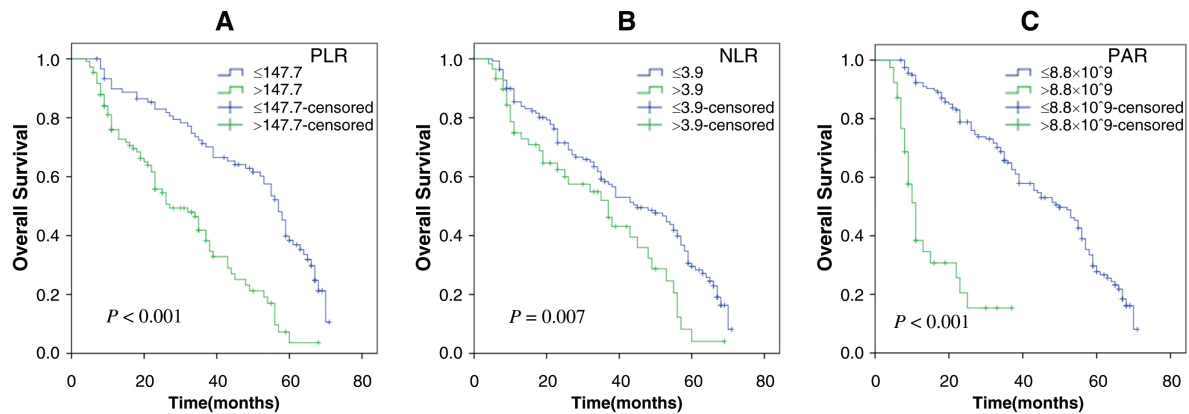
Fig. 3 Kaplan-Meier survival curves. (A) PLR >147.7 had a lower OS (P <0.001); (B) NLR >3.9 had a lower OS (P = 0.007), (C) PAR >8.8 × 10^9 had a lower OS (P <0.001). NLR: neutrophil to lymphocyte ratio; OS: overall survival; PAR: platelet to albumin ratio; PLR: platelet to lymphocyte ratio

Published studies have showed that nutrition and inflammation are associated with tumor progression.[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.[28] Decreased albumin level may aggravate the disease, leading to poor prognosis of cancer.[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.[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.

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