

ORIGINAL ARTICLE

Platelet-to-lymphocyte ratio predicts the prognosis of patients with non-small cell lung cancer treated with surgery and postoperative adjuvant chemotherapy

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Abstract

Background: Markers of preoperative tumor immunity, such as platelet-to-lymphocyte ratio (PLR), have been reported to be prognostic factors for patients with various cancers. However, the relationship between PLR and the prognosis of non-small cell lung cancer (NSCLC) patients treated with surgery and adjuvant chemotherapy as a multidisciplinary treatment is unknown.

Methods: We enrolled 327 NSCLC patients treated surgically with or without adjuvant chemotherapy (78 and 249 patients, respectively) at our hospital from 2008 to 2012. Patients had no preoperative hematological disease or infection. Preoperative PLR and clinicopathologic characteristics were recorded and their potential associations and prognostic values were assessed by Kaplan–Meier and multivariate Cox regression. The optimal cut-off value for high and low PLR was calculated from receiver operating characteristic curves.

Results: The five-year overall survival rates for patients with low and high PLR were 78% and 57% ($P < 0.01$) for all patients, and 69% and 37% ($P < 0.01$) for patients who received adjuvant chemotherapy, respectively. Similarly, the five-year disease-free survival rates for patients with low and high PLR were 66% and 62% ($P = 0.03$) for all patients, and 47% and 14% ($P < 0.01$) for patients who received adjuvant chemotherapy, respectively. Cox proportional hazard regression indicated that high PLR was an independent prognostic factor for both overall and disease-free survival in the adjuvant chemotherapy group.

Conclusion: Elevated PLR predicts poor prognosis in surgically treated NSCLC patients, especially those who receive adjuvant chemotherapy.

Introduction

Primary lung cancer has the highest cancer-related mortality rate worldwide.¹ The five-year overall survival (OS) rate for primary lung cancer is approximately 80% in patients with pathological stage I disease, but this decreases to <45% in patients with advanced lung cancer of pathological stage II or higher.² Systematic lung resection and lymph node dissection are the first methods administered as curative treatment; however, a combination of surgical and adjuvant chemotherapy is selected for advanced cancer patients with resectable cancer. Although the effectiveness of adjuvant chemotherapy is steadily improving, the

prognosis of advanced cancer patients remains poor. Therefore, there is a pressing need to identify prognostic factors for patients with primary lung cancer undergoing multidisciplinary therapy with surgery and adjuvant chemotherapy.

Numerous factors, such as tumor biomarkers or preoperative comorbidities, have been reported to be prognostic predictors of various cancers.^{3,4} In recent years, indicators such as the Glasgow prognostic score,⁵ prognostic nutritional index,⁶ neutrophil-to-lymphocyte ratio (NLR),⁷ and platelet-to-lymphocyte ratio (PLR),⁸ which reflect preoperative nutritional status, tumor immunity, potential cancer infiltration, and chronic inflammatory conditions, have

been reported to be prognostic factors for several cancers. Measurement of these indicators in patient blood is technically simple, low cost, and does not require specialized facilities. Thus, these tests are preferable compared to high-cost tumor marker assays and some radiological imaging tests.

The preoperative PLR, which is calculated by dividing the platelet count by the lymphocyte count, has been reported to be a useful prognostic factor for postoperative patients with various solid cancers.^{8,9} Relationships between PLR and chemotherapy response rates have also been reported for some cancer patients.^{10,11} However, the association between PLR and the prognosis of patients treated with surgery and adjuvant chemotherapy as multidisciplinary treatment has not been investigated. Therefore, the aim of this study was to determine the relationship between preoperative PLR values and the prognosis of patients with primary lung cancer treated with surgery and adjuvant chemotherapy.

Methods

Patients

We analyzed the medical records of 373 consecutive patients who underwent pulmonary resection at the Department of Thoracic Surgery of Osaka City University as primary treatment for pathological stage I–III non-small cell lung cancer (NSCLC) between January 2008 and December 2012. Exclusion criteria were insufficient data; preoperative inflammatory disease; hematological disease, including thromboembolism; infection; and other cancers. Ultimately, the records of 327 patients (range 20–85 years; median 67 years) who underwent curative surgery (segmentectomy, lobectomy, or pneumonectomy) were examined.

Surgery was performed through an axillary mini-thoracotomy (assisted by video) or posterolateral thoracotomy (when extended lobectomy, such as chest wall resection, pulmonary arterioplasty, or bronchoplasty, was necessary). Histological classification was performed according to the World Health Organization criteria for histological typing of lung tumors. Postoperative staging was based on the International Tumor Node Metastasis (TNM) Classification for Lung Cancer (7th edition). Patients were followed up at 1–6 month intervals postoperatively. Follow-up evaluations included physical examination, chest X-ray, and blood tests, including tumor marker analysis. Chest, brain, and abdominal computed tomography scans were performed at 3–6 month intervals. When symptoms or signs of recurrence were detected, bone scintigraphy and magnetic resonance imaging of the brain were performed. Patients with stage I adenocarcinoma

received oral fluoropyrimidine for two years, and those with stage II or III NSCLC underwent adjuvant chemotherapy. The records of 78 patients who underwent adjuvant chemotherapy (e.g. platinum, alkaloids, taxane, except oral fluoropyrimidine) were examined. The indication criteria for chemotherapy for patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1 were based on clinical judgment. When recurrence was detected, patients underwent chemotherapy, radiotherapy, or best supportive care.

The patient sample was divided into two groups: the all-patient group, which included 327 patients with NSCLC who were treated surgically; and the adjuvant chemotherapy group, which included 78 patients with NSCLC who underwent adjuvant chemotherapy after surgery.

The study was performed in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of Osaka City University (Osaka, Japan, No. 3361). Informed consent was waived because of the retrospective study design.

Platelet-to-lymphocyte ratio (PLR) evaluation

The PLR was calculated as the platelet count divided by the lymphocyte count. Using cancer-specific death as an end point for PLR, the optimal cutoff value for designation of low and high PLR was calculated by receiver operating characteristic curve analysis and was 162 for this study (data not shown).

Statistical analysis

Data analysis was performed using JMP 10 software (SAS Institute Inc., Cary, NC, USA). All demographic and baseline data were summarized using descriptive statistics. The association between PLR values and patient clinicopathologic characteristics was assessed for significance using Mann–Whitney *U*, χ^2 , or Fisher's exact tests. All *P* values are reported as two-sided, and the a priori level of significance was set at $P \leq 0.05$. Kaplan–Meier analysis was used to estimate time-to-event curves and survival rates. Univariate Cox regression analyses were performed to assess associations between clinical factors/laboratory values and OS or disease-free survival (DFS). Characteristics that demonstrated a significant association with survival by univariate analysis were entered as covariates into a multivariate proportional hazards regression model for OS and DFS. Backward elimination was performed to generate the final model. The final proportional hazards regression model was used to estimate the hazard ratio (HR) for death attributable to each covariate.

Table 1 Baseline characteristics of the total study population (n = 327)

Characteristics	Category	N	%
Gender	Male	213	65
	Female	114	35
Median age (years)		67	(20–85)
Median smoking index		800	(0–3760)
ECOG PS	0/1/2	301/21/5	92/6/2
H-J classification	1/2/3	282/36/9	87/11/3
Clinical stage	II/III	250/50/27	77/15/8
Pathological stage	II/III	212/63/52	64/19/17
Histology	Ad	241	74
	Sq	73	22
	Other	13	4
Adjuvant chemotherapy		78	24

Ad, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; H-J, Hugh-Jones; Sq, squamous cell carcinoma.

Results

Relationships between clinicopathological characteristics and PLR

A total of 327 patients with NSCLC who were treated surgically with or without adjuvant chemotherapy were included in the study. The baseline characteristics of the patients are listed in Table 1. Patient demographics, clinicopathologic characteristics, and PLRs are summarized in Table 2. In both the all-patient and adjuvant chemotherapy groups, higher PLRs were observed in patients with clinical

stage ≥ II. There was no significant difference between the high and low PLR groups in any other characteristic.

PLR and probability of survival

Figure 1a shows the Kaplan–Meier estimates for OS among all patients according to PLR. A high PLR was significantly associated with shorter OS ($P < 0.01$). The five-year OS rates for all patients in the low and high PLR groups were 78% and 57%, respectively. Figure 1b shows the same analysis for patients who received adjuvant chemotherapy. A high PLR was also significantly associated with shorter OS after five years in this group (69% and 37% for low and high PLR, respectively; $P < 0.01$).

Figure 2a shows the Kaplan–Meier estimates for DFS among all patients according to PLR. A high PLR was significantly associated with shorter five-year DFS rate (66% and 62% for low and high PLR, respectively; $P = 0.03$). The same analysis among patients who received adjuvant chemotherapy is shown in Figure 2b. Similarly, a high PLR was significantly associated with shorter DFS after five years (14% compared to 47% in the low PLR group; $P < 0.01$).

Prognostic value of PLR

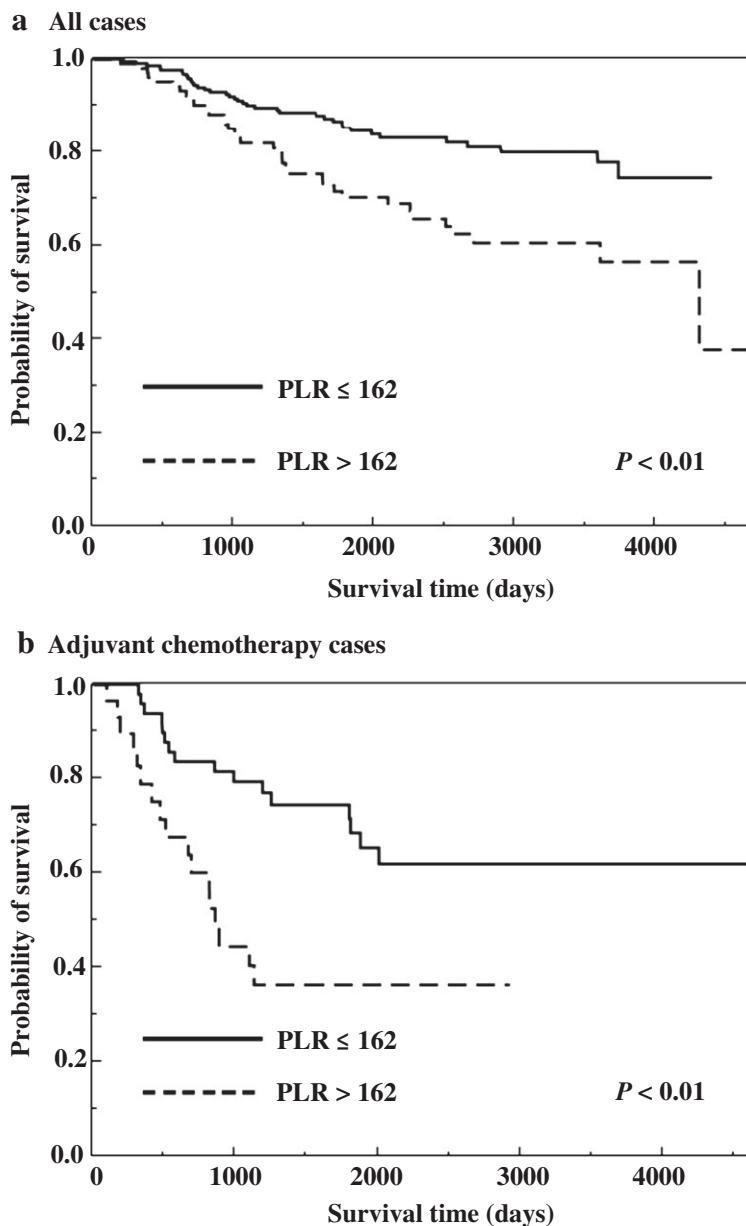
Using univariate Cox regression analysis, the following factors were significantly associated with poorer survival in the all-patient group: age > 70 years, male gender, smoking index ≥ 400, ECOG PS ≥ 2, Hugh-Jones classification

Table 2 Relationships between clinicopathologic characteristics and PLR

Variable		All cases				Adjuvant chemotherapy cases			
		Total, N	Low PLR (n = 220)	High PLR (n = 107)	P	Total, N	Low PLR (n = 45)	High PLR (n = 33)	P
Age	—	—	66.0 ± 0.7	67.6 ± 0.9	0.19	—	63.3 ± 1.3	65.1 ± 1.8	0.27
Gender	Male	213	142	71	0.56	53	31	22	0.84
	Female	114	78	36	—	25	14	11	—
Smoking Index	—	—	784 ± 53	677 ± 67	0.39	—	868 ± 109	868 ± 92	0.76
ECOG PS	0–1	322	216	106	0.55	78	45	33	—
	2~	5	4	1	—	0	0	0	—
H-J classification	1–2	318	213	105	0.52	75	43	32	0.75
	3~	9	7	2	—	3	2	1	—
Clinical stage	Stage I	250	177	73	0.02	44	31	13	<0.01
	Stage II~	77	43	34	—	34	14	20	—
	Pathological stage	Stage I	212	150	62	0.07	0	0	0
Histology	Stage II~	115	70	45	—	78	45	33	—
	Ad	241	170	71	0.05	57	36	21	0.11
Postoperative complications	Sq/other	86	50	36	—	21	9	12	—
		78	53	25	0.95	18	8	10	0.21

Ad, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; H-J, Hugh-Jones; PLR, platelet-to-lymphocyte ratio; Sq, squamous cell carcinoma.

Figure 1 Kaplan–Meier survival curves showing the relationship between platelet-to-lymphocyte ratio (PLR) and overall survival in the (a) all-patient and (b) adjuvant chemotherapy groups.



> 3, PLR > 162, clinical stage \geq II, pathological stage \geq II, and non-adenocarcinoma (Table 3). These factors were used as covariates to construct the multivariable proportional hazard model for survival. Following multivariate analysis using backward elimination the following factors were independently related to poor OS: age > 70 years (HR 2.5, $P < 0.01$), male gender (HR 3.0, $P < 0.01$), ECOG PS ≥ 2 (HR 1.1, $P = 0.01$), PLR > 162 (HR 1.9, $P < 0.01$), clinical stage \geq II (HR 1.8, $P = 0.03$), pathological stage \geq II (HR 2.5, $P < 0.01$), and non-adenocarcinoma (HR 2.0, $P < 0.01$). Using univariate Cox regression analysis, PLR > 162 and clinical stage \geq II were significantly associated with poorer survival in the adjuvant chemotherapy group. After multivariate

analysis using backward elimination, PLR > 162 was independently related to poor OS (HR 2.3, $P = 0.03$) (Table 3).

Univariate Cox regression analysis of the all-patient group showed a significant association between worse DFS and age > 70 years, male gender, ECOG PS ≥ 2 , PLR > 162, clinical stage \geq II, pathological stage \geq II, and non-adenocarcinoma. These factors were entered as covariates into the multivariable proportional hazards model for DFS. Following multivariate analysis using backward elimination, clinical stage \geq II (HR 2.3, $P < 0.01$) and pathological stage \geq II (HR 2.9, $P < 0.01$) were independently related to inferior DFS (Table 4). Among the adjuvant chemotherapy group, univariate Cox regression analysis showed that PLR > 162,

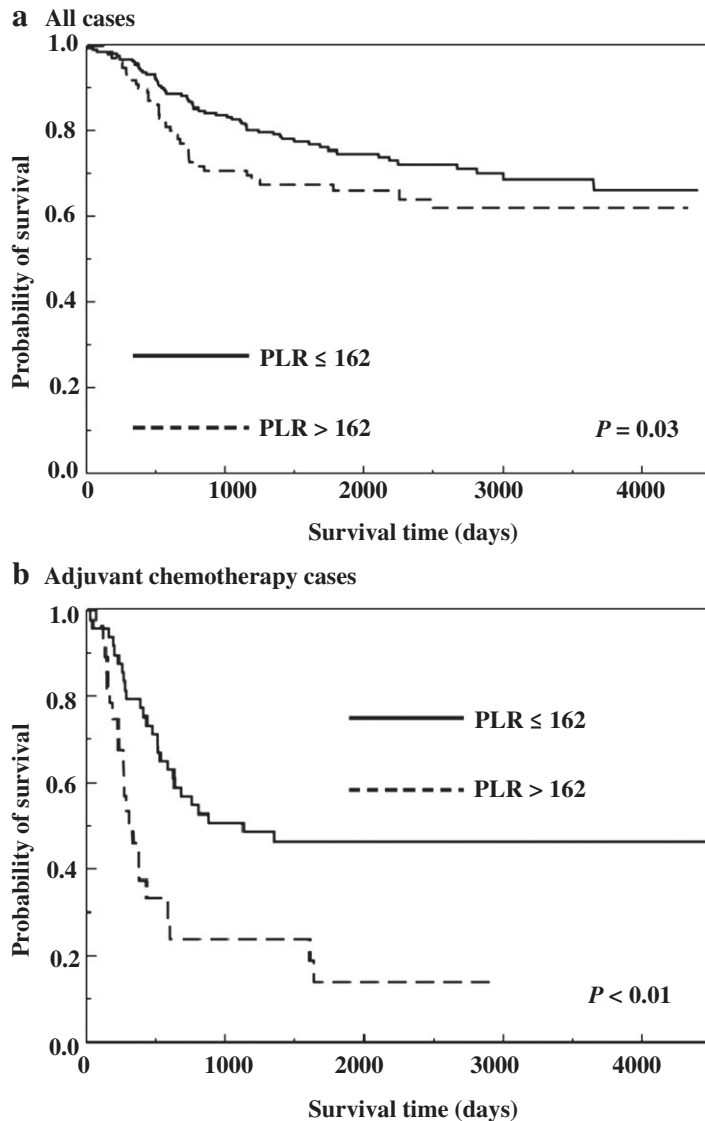


Figure 2 Kaplan–Meier survival curves showing the relationship between platelet-to-lymphocyte ratio (PLR) and disease-free survival in the (a) all-patient and (b) adjuvant chemotherapy groups.

clinical stage \geq II, and the occurrence of postoperative complications were significantly associated with poor DFS. After multivariate analysis using backward elimination, PLR > 162 was the only factor independently related to poor DFS (HR 1.9, $P = 0.04$) (Table 4).

Discussion

Primary lung cancer is a major global health problem.¹ Although the prognosis of advanced lung cancer is poor, it has gradually been improved by multidisciplinary treatment based on a combination of surgery and various adjuvant chemotherapies.^{12,13} Therefore, it is important to identify factors that predict the outcome of multidisciplinary treatments to both improve and optimize these therapies. This is the first study to report that PLR is a more prognostic

indicator for NSCLC patients treated with surgery and adjuvant chemotherapy compared to all surgical patients.

Biomarkers of inflammation, such as NLR or PLR, have been associated with the prognosis of patients with various cancers^{7,8} and have specifically been shown to be predictive markers of postoperative prognosis in gastric cancer,¹⁴ cholangiocarcinoma,¹⁵ hepatocellular carcinoma,⁸ and primary lung cancer.¹⁶ Some studies have reported that host-derived inflammation, immune response, and coagulation status play important roles in tumor growth, invasion, angiogenesis, and metastasis.¹⁷

An increase in PLR can result from a rise in platelet counts and/or a decrease in lymphocyte counts. Lymphocytes induce tumor cell apoptosis, and their abundance has been shown to be inversely proportional to tumor growth and invasion.¹⁸ A reduction in lymphocyte numbers would

Table 3 Prognostic factors associated with overall survival in univariate and multivariate analysis

Factors	All cases				Adjuvant chemotherapy cases			
	Univariate	Multivariate	HR	95% CI	Univariate	Multivariate	HR	95% CI
Age								
>70/≤70	< 0.01	< 0.01	2.5	1.6–4.0	0.06	—	—	—
Gender								
Male/female	< 0.01	< 0.01	3.0	1.4–6.8	0.41	—	—	—
Smoking index								
≥ 400/< 400	< 0.01	0.77	—	—	0.65	—	—	—
ECOG PS								
≥2/0–1	< 0.01	0.01	11	1.8–52	—	—	—	—
H-J classification								
≥3/1–2	0.02	0.42	—	—	0.73	—	—	—
PLR								
>162/≤162	< 0.01	< 0.01	1.9	1.2–3.2	< 0.01	0.03	2.3	1.1–4.6
Clinical stage								
≥ II/ I	< 0.01	0.03	1.8	1.1–3.0	0.01	0.09	—	—
Pathological stage								
≥ II/ I	< 0.01	< 0.01	2.5	1.5–4.2	—	—	—	—
Histology								
Non-ad/ad	< 0.01	< 0.01	2.0	1.2–3.6	0.08	—	—	—
Postoperative complications								
With/without	0.05	—	—	—	0.07	—	—	—

Ad, adenocarcinoma; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; H-J, Hugh-Jones; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

undoubtedly reduce the host anti-tumor immune response and promote the metastatic potential of the tumor. Several studies have also shown that low lymphocyte counts are significantly associated with poor survival in lung cancer

patients.^{19,20} Therefore, peripheral blood lymphocyte counts have been used as an important constituent marker not only in PLR but also in numerous prognostic indicators, such as NLR and the prognostic nutritional index.^{6–8}

Table 4 Prognostic factors associated with disease-free survival in univariate and multivariate analysis

Factors	All cases				Adjuvant chemotherapy cases			
	Univariate	Multivariate	HR	95% CI	Univariate	Multivariate	HR	95% CI
Age								
>70/≤70	0.03	0.06	—	—	0.34	—	—	—
Gender								
Male/female	0.02	0.25	—	—	0.91	—	—	—
Smoking index								
≥400/<400	0.13	—	—	—	0.38	—	—	—
ECOG PS								
≥ 2/0–1	0.04	0.14	—	—	—	—	—	—
H-J classification								
≥ 3/1–2	0.55	—	—	—	0.18	—	—	—
PLR								
> 162/≤ 162	0.03	0.40	—	—	< 0.01	0.04	1.9	1.0–3.4
Clinical stage								
≥ II/ I	< 0.01	< 0.01	2.3	1.4–3.7	< 0.01	0.11	—	—
Pathological stage								
≥ II/ I	< 0.01	< 0.01	2.9	1.8–4.8	—	—	—	—
Histology								
Non-ad/ad	< 0.01	0.69	—	—	0.40	—	—	—
Postoperative complications								
With/without	0.30	—	—	—	0.02	0.12	—	—

Ad, adenocarcinoma; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; H-J, Hugh-Jones; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

The elevation of platelets could promote the metastatic potential of tumor cells through several pathways.²¹ Platelets have been reported to promote the development and enlargement of tumors by non-inflammatory mechanisms, including stimulation of MM9 synthesis and production of adhesive molecules and growth factors (e.g. vascular endothelial growth factor, transforming growth factor- β , and platelet derived growth factor), which are important determinants of tumor growth and angiogenesis.²² Cancer cells in postoperative patients requiring adjuvant chemotherapy may be more persistent than those in postoperative patients with pathological stage I lung cancer. Therefore, in our study, platelets may have had a more pronounced effect on tumor growth in the adjuvant chemotherapy group compared to the all-patient group. In addition, several reports have suggested that platelets protect metastatic tumor cells from immune surveillance by killer cells, thereby nullifying the effects of immunotherapy. As they travel around the circulatory system, platelets help tumor cells to attach to the endothelium upon their arrest at metastatic sites, and thus enable metastasis.^{23,24} In order to escape immune recognition and overcome shear forces, circulating cancer cells in the bloodstream attract an entourage of platelets and use them as a cellular shield for their survival.²⁵ These protective effects of platelets on cancer cells might reduce the efficacy of several chemotherapies on lung cancer. In this study, we found that a high PLR was a better prognostic marker for patients who received adjuvant chemotherapy than for the all-patient group.

This study has some limitations. The indication criteria for adjuvant chemotherapy were based on clinical judgment; therefore, the same results might not be obtained in different facilities. Only 78 patients who received adjuvant chemotherapy were enrolled in our study, and all of the patients were from a single hospital. Our findings require validation by a large prospective multicenter study.

In conclusion, we identified a relationship between preoperative PLR and the prognosis of patients undergoing surgery for primary lung cancer. We also found that PLR was a more useful prognostic factor for postoperative patients who received adjuvant chemotherapy than for all surgical patients. Further investigation of the mechanism of action of peripheral blood cells and clarification of the relationship between PLR and individual chemotherapies may be useful for optimizing the selection of chemotherapy for patients with high PLRs. Further studies using larger patient cohorts are necessary.

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Disclosure

No authors report any conflict of interest.

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