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RESEARCH ARTICLE

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Pretreatment platelet-to-lymphocyte ratio is associated with the response to first-line chemotherapy and survival in patients with metastatic gastric cancer

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Background: Several studies have shown that platelet-to-lymphocyte ratio (PLR) is a prognostic factor for various cancers. However, there is no study about the role of PLR in predicting response to first-line chemotherapy of metastatic gastric cancer. Therefore, this study aimed to establish whether PLR is associated with the response to first-line chemotherapy and survival in patients with metastatic gastric cancer.

Methods: We enrolled 273 patients diagnosed with metastatic gastric cancer. The best cut-off value of PLR to predict chemotherapeutic response was chosen by receiver operating characteristic (ROC) curve analysis. Prognostic significance was determined using the log-rank test and multivariate Cox regression analysis.

Results: Based on the cut-off value of PLR, patients were divided into a low PLR group and high PLR group. In logistic regression analysis, the low PLR group had a significantly higher disease control rate than the high PLR group had (91.3 vs 76.1%, *P*=.002), and PLR was an independent risk factor for response to first-line chemotherapy (odds ratio [OR]: 3.256; 95% confidence interval [CI]: 1.521-6.969; *P*=.002). The low PLR group had significantly longer overall survival (OS) than the high PLR group had (13.4 vs 9.2 months; *P*=.020). Multivariate survival analysis showed that PLR was significantly associated with OS [hazard ratio (HR): 1.002; 95% CI: 1.000-1.003; *P*=.020].

Conclusions: Pre-treatment PLR is associated with the response rate to first-line chemotherapy and survival outcomes in patients with metastatic gastric cancer.

KEYWORDS
chemotherapy, gastric cancer, platelet-to-lymphocyte ratio, tumor response

1 | INTRODUCTION

Gastric cancer is one of the most common malignancies worldwide, and almost half of the total occurs in Eastern Asia (mainly in China).[1] Although diagnosis and treatment have improved greatly, two-thirds of gastric cancer patients are diagnosed with metastatic disease.[2] At present, the major treatment options for metastatic gastric cancer include chemotherapy and targeted therapy. However, the response rate to first-line treatment is only 27%-54%.[3-5] Therefore, it is important to find biomarkers that can distinguish patients who might benefit from potentially efficacious treatment. Human epidermal growth factor receptor (HER) 2 is the only molecular biomarker currently in clinical use to tailor patients to targeted therapy with trastuzumab.[5] However, chemotherapeutic drugs still have no consistent and recognized biomarkers.

It is reported that some clinical variables have the potential to influence therapeutic effects in gastric cancer. These variables fit broadly into three categories: patient- and tumor-related characteristics and host reaction to the tumor. The patient-related factors include performance status (PS) and complications, and the tumor-related factors include tumor differentiation, size and localization.[6,7] The host-related factors are usually systemic inflammatory response. More recently, there has been a growing interest in systemic inflammatory response, which is thought

to have an important role in tumor development and growth through several mechanisms.[8] The tumor, host-derived stromal tissues containing host inflammatory cells, and blood vessels that have a complex microenvironmental host-tumor relationship may lead to tumor growth, progression, and metastasis.[9] On the basis of these findings, a variety of inflammatory markers have been investigated. Among these inflammatory parameters, the lymphocyte response has an effect on suppression of cancer progression.[10] Platelets might be involved in the inflammatory reaction by releasing growth factors or increasing angiogenesis.[9,10]

Thus, the platelet-to-lymphocyte ratio (PLR) might provide more information in clinical practice. In recent studies, peripheral PLR has been shown as a prognostic indicator in several types of cancer, including non-small lung cancer, gastric cancer, colorectal cancer, ovarian clear cell carcinoma, prostate cancer and pancreatic cancer.[11-16] Studies of the role of PLR in gastric cancer had some limitations that need to be taken into account. First, most of them only selected patients with resectable early-stage rather than metastatic gastric cancer.[16,17] Second, even in patients with metastatic gastric cancer, chemotherapy was not considered or mentioned.[18,19] Nevertheless, chemotherapy regimen should be considered as an important confounding factor. Third, almost all the studies focused on the correlation between PLR and survival outcomes such as overall survival (OS), cancer-special survival or progression-free survival.[16,17]

There are no reports on the relationship between PLR and chemotherapeutic response in metastatic gastric cancer. Therefore, the objective of this study was to explore whether pre-treatment PLR is associated with the response to first-line chemotherapy and survival in patients with metastatic gastric cancer.

2 | MATERIALS AND METHODS

2.1 | Patients

Between May 2005 and December 2013, 335 patients received first-line palliative chemotherapy for metastatic gastric cancer at the First Hospital of China Medical University. The criteria for patient inclusion were: (1) age ≥18 years; (2) histologically confirmed diagnosis of gastric cancer; (3) presence of evaluable disease or measurable lesions; (4) at least two cycles of chemotherapy and treatment response evaluation after two cycles; (5) Eastern Cooperative Oncology Group (ECOG) PS ≤2; (6) clinicopathological data available at the beginning of chemotherapy; and (7) no prior anti-tumor treatment in ~6 months, such as radiotherapy or chemotherapy. Patients with esophageal cancer, squamous cell carcinoma, or gastroesophageal junction tumors were excluded. Finally, 273 patients met the inclusion criteria. This study was approved by the Ethical Standards Committee of the First Hospital of China Medical University. Written informed consent was obtained from each participant before enrollment.

All patients underwent laboratory tests and chest and abdominal pelvic computed tomography. History taking and physical examination revealed no systemic infection and fever before patients started the first cycle of chemotherapy. OS was counted from the time of metastasis to the time of death or last follow-up visit, which was 27 July 2014.

2.2 | Measurement of PLR

Venous blood was sampled before the first cycle of chemotherapy and collected in EDTA-containing tubes. Baseline PLR was calculated as the platelet count divided by the lymphocyte count.

2.3 | Treatment and response evaluation

All the patients received standardized palliative first-line chemotherapy after diagnosis. The most commonly used chemotherapy regimen was oxaliplatin-based regimen (n=130, 47.6%), followed by taxane-based (n=80, 29.3%), platinum-based and 5-flurouracil single drug regimen. The oxaliplatin-based regimen was oxaliplatin and fluoropyrimidine (5-flurouracil, capecitabine or S-1). The taxane-based regimens included paclitaxel or docetaxel and fluoropyrimidine (capecitabine or S-1) and DCF(docetaxel,cisplatin, and 5-fluorourancil). The platinum-based regimens were XP (capecitabine plus cisplatin) and FP (5-fluorourancil plus cisplatin). The 5-flurouracil single drug regimen was capecitabine or S-1. The chemotherapy regimen was decided at the discretion of the physicians.

Tumor response to treatment was assessed after two cycles of chemotherapy, based on the rules established by the Response Evaluation Criteria in Solid Tumors (RECIST).[20] The responses were: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Disease control was defined as CR, PR or SD.

2.4 | Statistical analysis

Receiver operator characteristic (ROC) analysis was conducted to reveal an association between PLR and tumor response after two cycles

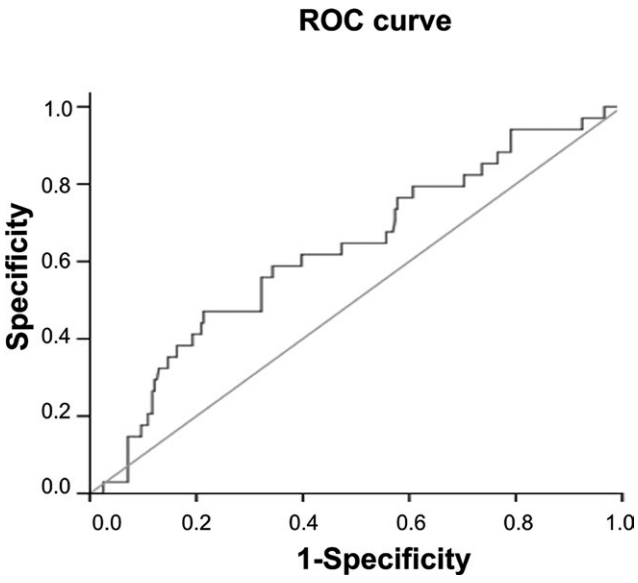

FIGURE 1 Receiver operating characteristic curve for the platelet-to-lymphocyte ratio and the response to first-line chemotherapy for patients with metastatic advanced gastric cancer

TABLE 1 Baseline characteristics of patients

Variables	Total (n=273)	Low PLR group (n=206)	High PLR group (n=67)	*P* value
Age	56.68±10.731	57.29±10.565	54.82±11.097	.157
Gender				
Male	186 (68.1%)	146 (70.9%)	40 (45.6%)	.088
Female	87 (31.9%)	60 (29.1%)	27 (40.3%)	
ECOG				
0	61 (22.3%)	48 (23.2%)	13 (19.4%)	.229
1	201 (73.6%)	152 (73.8%)	45 (73.1%)	
2	11 (4.0%)	6 (2.9%)	5 (7.5%)	
Chemotherpaeutic regimen				
Oxaliplatin-based	130 (47.6%)	94 (45.6%)	36 (53.7%)	.285
Taxane-based	80 (29.3%)	63 (30.6%)	17 (25.4%)	
Platinum-based	33 (12.1%)	23 (11.2%)	10 (14.9%)	
5-Fu single drug	30 (11%)	26 (12.6%)	4 (6.0%)	
Lung metastasis				
No	257 (94.1%)	194 (94.2%)	63 (94.0%)	.965
Yes	16 (5.9%)	12 (5.8%)	4 (6.0%)	
Peritoneum metastasis				
No	207 (75.8%)	158 (76.7%)	49 (73.1%)	.554
Yes	66 (24.2%)	48 (23.3%)	18 (26.9%)	
Liver metastasis				
No	203 (74.4%)	156 (75.7%)	47 (70.1%)	.364
Yes	70 (25.6%)	50 (24.3%)	20 (29.9%)	
Differentiation				
Well	17 (6.2%)	11 (5.3%)	6 (9.0%)	.420
Moderate	48 (17.6%)	41 (19.9%)	7 (10.4%)	
Poor	121 (44.3%)	89 (43.2%)	32 (47.8%)	
Signet ring	35 (12.8%)	26 (12.6%)	9 (13.4%)	
No data	52 (19.0%)	39 (18.9%)	13 (19.4%)	
White blood cell count, 10^9/L	6.45±2.172	6.41±2.083	6.59±2.436	.755
Neutrophil count, 10^9/L	4.03±1.920	3.82±1.823	4.67±2.075	.002
Lymophocyte count, 10^9/L	1.74±0.651	1.88±0.639	1.28±0.446	<.001
Hemoglobin, g/L	111.64±20.541	116.19±18.770	97.67±19.544	<.001
Platelet count, 10^9/L	255.67±102.449	225.88±75.996	347.25±118.458	<.001

PLR, platelet-to-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group.
Variables are expressed as mean±SD or n (%).

of first-line chemotherapy. The independent *t* test and χ^2 test were used to evaluate the relatedness between PLR and baseline clinical characteristics. A logistic regression model was used to analyze the independent risk indicators for the response to first-line chemotherapy. Survival data were analyzed using the Kaplan-Meier method. Comparison of survival curves was performed using log-rank analysis. A multivariate prognostic model was performed for all variables that were significantly associated with OS at $P \leq .05$ in the univariate analysis. $P < .05$ was considered statistically significant and all *P* values corresponded to two-sided significance tests. All statistical analyses were performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics and grouping of PLR

There were 273 patients included in this study. The median age was 57 years and 186 (68.1%) patients were male. Two hundred and sixteen patients had died by the last follow-up date.

Based on the response to first-line chemotherapy, all patients were divided into two groups: 239 with disease control (CR+PR+SD) and 34 with PD. As shown in Figure 1, the area under the ROC curve (AUC) was 0.627 (95% confidence interval [CI]: 0.526-0.729) and the

optimal cut-off value of PLR was defined as 201.6, based on the most prominent point with a sensitivity of 47.1% and specificity of 78.7%. In view of the best cut-off value of PLR for predicting the response by the ROC curve, patients were divided into two groups: low PLR group (<201.6) and high PLR group (≥201.6).

3.2 | PLR and clinicopathological characteristics

All the patient characteristics according to PLR group are presented in Table 1. The low PLR group had a lower neutrophil count (*P*=.002) and platelet count (*P*<.001) than the high PLR group had. Lymphocyte count (*P*<.001) and hemoglobin (*P*<.001) were both higher in the low PLR group. Other clinicopathological characteristics were not significantly different between the two groups.

3.3 | PLR and first-line chemotherapeutic response

The distribution of the treatment response after two cycles of chemotherapy with reference to PLR subgroup is systematically evaluated in Table 2. Overall, 0 and 55 patients (20.1%) had CR and PR, while 184 (67.4%) and 34 (12.5%) had SD and PD, respectively. The low PLR group had a significantly higher disease control rate (91.3%) compared with the high PLR group (76.1%, *P*=.002).

The potential markers for predicting tumor response and survival were investigated to determine the best therapeutic response factors, including: gender; age; ECOG PS; tumor differentiation; lung, liver, and peritoneal metastasis; and PLR. To this end, a logistic regression model was used to analyze the independent risk factors for response after two cycles of chemotherapy (Table 3). Pre-treatment PLR was an independent risk factor for response to chemotherapy in patients with metastatic gastric cancer (odds ratio [OR]: 3.256, 95% CI: 1.521-6.969; *P*=.002).

3.4 | PLR and OS

The median OS of all patients was 12.0 months (95% CI: 10.4-13.6). The median OS was longer in the low PLR group (PLR <201.6) than in the high PLR group (PLR ≥201.6) [13.4 months (95% CI: 11.4-15.5) vs 9.2 months (95% CI: 10.4-13.6), *P*=.020] (Figure 2).

In subgroup analysis, OS curves of patients who received an oxaliplatin-based regimen, stratified by PLR, are shown in Figure 3A. Patients in the high PLR group (n=36) had a significantly poorer OS (9.1 months) when compared with patients in the low PLR group (n=94; 15.4 months, *P*=.004). Kaplan-Meier survival curves, stratified by PLR, in patients who received a taxane-based regimen are shown in Figure 3B. OS for the low PLR group (n=63) and high PLR group (n=17) was 12.6 and 10.3 months (*P*=.054), respectively.

In some previous studies, cut-off values of PLR were chosen as a dichotomous cutoff (150) or triple subsets cutoff (<150/150-300/>300).[11,21] We validated our data using these varying thresholds of PLR. The observed OS curves showed significant differences regardless of the different cut-off values. The *P* values were .006 and

TABLE 2 Chemotherapeutic response to first-line chemotherapy with reference to PLR subgroup

Response	Total patients (n=273)	Low PLR group (n=206)	High PLR group (n=67)
Non-progression of disease*			
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	55 (20.1%)	44 (21.4%)	11 (16.4%)
Stable disease	184 (67.4%)	144 (69.9%)	40 (59.7%)
Progressive disease	34 (12.5%)	18 (8.7%)	16 (23.9%)

PLR, platelet-to-lymphocyte ratio.
**P*=.002 for disease control rate between the low PLR group and the high PLR group.

TABLE 3 Logistic regression analysis of independent risk factors for response to chemotherapy in patients with metastatic advanced gastric cancer

	P value	OR	95% CI
Gender	.174	1.737	0.784-3.850
Age	.807	0.996	0.961-1.032
ECOG	.326	0.683	0.319-1.463
Differentiation	.438	1.140	0.819-1.586
Lung metastasis	.436	1.712	0.443-6.621
Liver metastasis	.923	0.860	0.378-2.255
Peritoneum metastasis	.658	0.814	0.327-2.027
PLR	.002	3.256	1.521-6.969
Constant	.066	0.091	

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PLR, platelet-to-lymphocyte ratio.

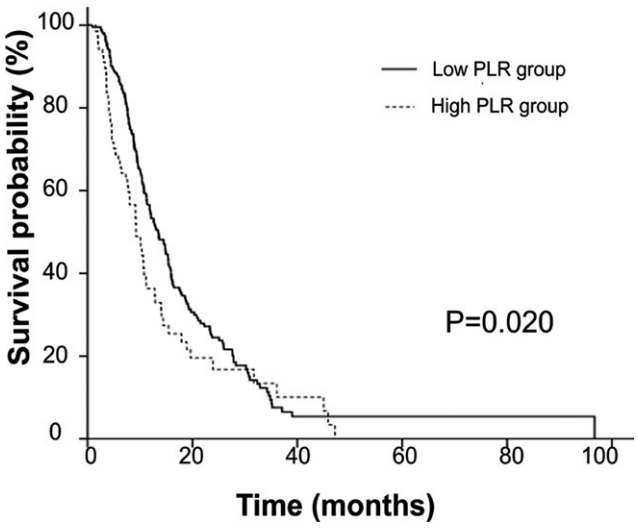

FIGURE 2 Kaplan-Meier survival curves of all patients (high and low platelet-to-lymphocyte ratio group patients)

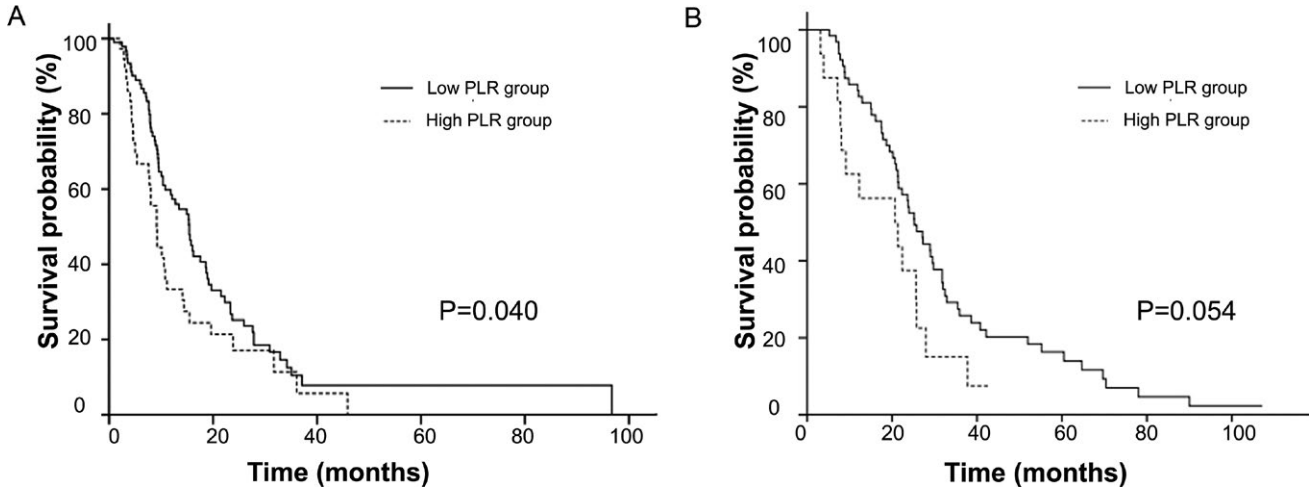

FIGURE 3 Kaplan-Meier curves for the overall survival in patients who received two larger regimen subgroups. (A) Patients who received oxaliplatin-based regimen. (B) Kaplan-Meier survival curves in patients who received taxane-based regimen

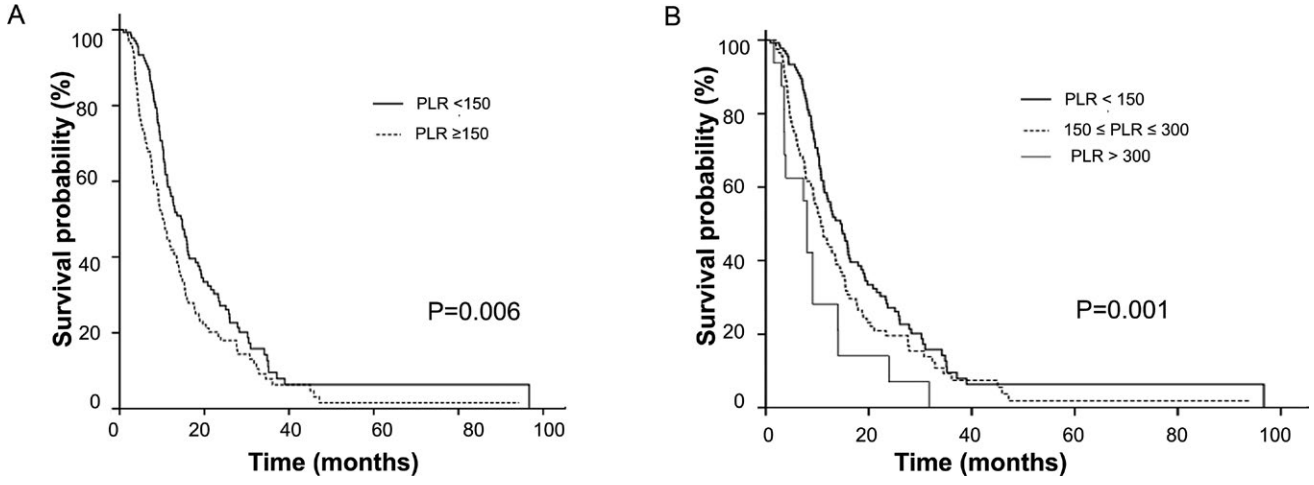

FIGURE 4 Kaplan-Meier survival curves in all the patients using different cutoff values of platelet-to-lymphocyte ratio (PLR). (A) the overall survival of patients using dichotomized cutoff value for PLR. (B) the overall survival of patients using triple subsets cutoffs for PLR

.001 for the PLR cutoff of dichotomous and triple subsets, respectively (Figure 4).

Univariate and multivariate analyses were performed for clinicopathological variables shown in Table 4. Univariate predictors of OS were gender (P=.037), liver metastasis (P<.001), white blood cell count (P=.010), platelet count (P=.032), and PLR (P=.001). In multivariate analysis, PLR (HR 1.002, 95% CI: 1.000-1.003; P=.020), white blood cell count (HR 1.062, 95% CI: 1.003-1.126; P=.041), liver metastasis (HR 1.599, 95% CI; 1.166-2.194; P=.004) and gender (HR 1.377, 95% CI: 1.036-1.829; P=.027) were independent predictors of OS.

4 | DISCUSSION

This study is believed to be the first attempt to evaluate PLR, which reflects systemic inflammatory response, for the prediction of response to first-line chemotherapy, and prediction of survival in patients with metastatic gastric cancer.

Pre-therapeutic indices of systemic inflammatory response provide much important information in the evolution and progression of cancer,[22] as well as in the response to therapy.[23] On this basis, inflammatory markers of response prediction have been suggested, such as C-reactive protein, neutrophil-to-lymphocyte ratio and PLR.[24] Nevertheless, studies about the relationship between PLR and chemotherapeutic response in metastatic cancer are limited. Only one retrospective study with 210 patients with advanced non-small lung cancer has shown that PLR is associated with the clinical benefit and OS.[25] There have been no studies about PLR predicting chemotherapeutic response in metastatic gastric cancer. In our study we demonstrated that patients with low PLR had a significantly higher disease control rate. A logistic regression model showed that PLR was an independent risk factor for the response to first-line chemotherapy in metastatic gastric cancer.

TABLE 4 Results of univariate and multivariate analyses of OS

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age				
≤57	1 (reference)			
>57	0.948 (0.724-1.240)	.695		
Gender				
Male	1 (reference)		1.421 (1.063-1.901)	.018
Female	1.351 (1.018-1.792)	.037		
ECOG				
0	1 (reference)			
1	1.064 (0.782-1.449)	.693		
2	1.013 (0.500-2.051)	.972		
Chemotherpeutic regimen				
Oxaliplatin-based	1 (reference)			
Taxane-based	1.175 (0.866-1.593)	.300		
Other regimens	1.009 (0.707-1.439)	.961		
Lung metastasis				
No	1 (reference)			
Yes	1.071 (0.642-1.789)	.792		
Peritoneum metastasis				
No	1 (reference)			
Yes	1.201 (0.877-1.645)	.254		
Liver metastasis				
No	1 (reference)		1.599 (1.166-2.194)	.004
Yes	1.715 (1.270-2.317)	<.001		
WBC count	1.079 (1.018-1.144)	.010	1.062 (1.003-1.126)	.041
Hemoglobin	0.999 (0.992-1.006)	.787		
Platelet count	1.001 (1.000-1.003)	.032		
PLR	1.002 (1.001-1.004)	.001	1.002 (1.000-1.003)	.020

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; PLR, platelet-to-lymphocyte ratio.

In recent studies, PLR has also been shown to be a prognostic factor in many malignant solid tumors.[11-16] In a study carried out on 374 prostate cancer patients treated with radiotherapy, increased PLR was an independent prognostic factor of poor distant metastasis-free survival (HR=2.24, *P*=.036), cancer-specific survival (HR=3.99, *P*=.025) and OS (HR=1.87, *P*=.044).[15] Apart from these, elevated PLR is associated with poor clinical outcome in patients with non-small cell lung cancer, colorectal cancer, pancreatic cancer, ovarian clear cell carcinoma, gastrointestinal stromal tumors and hepatocellular cancer.[10-14] The prognostic role of PLR in gastric cancer has been studied mainly in patients with operable gastric cancer and rarely in those with metastatic disease.[16-19] Wang et al.[18] reviewed the medical records of 439 patients with metastatic gastric cancer and found that elevated PLR was associated with shorter OS in the univariate but not in the multivariate analysis. In another similar study in patients with advanced gastric cancer who received FOLFOX combination chemotherapy, PLR did not have significant prognostic value for predicting progression-free survival or OS.[26] In a retrospective study including 71 (31.1%) patients with distant metastatic gastric cancer, PLR values were significantly higher than in non-metastatic gastric cancer (*P*<.001) and PLR was an independent prognostic factor for tumor burden (*P*=.003). However, there was no survival analysis involved.[19] Our study demonstrated longer OS in the low PLR group compared with the high PLR group. This was in accordance with the findings of other studies. In addition, PLR showed a significant relationship with OS in multivariate analysis, which differed from some other studies. The possible reasons for this were population diversity and differences in treatment.

There is much evidence to show the correlation of PLR with chemotherapeutic response and prognostic survival outcomes. The specific mechanisms involved are complex and remain to be elucidated. One potential explanation involves inflammatory cytokines and chemokines. Several studies have shown that interleukin-1and -6 can stimulate megakaryocyte proliferation and thrombopoietin production, which can lead to thrombocytosis in patients with cancer.[27]

Thrombocytosis and the consequent release of platelet-derived chemokines in the tumor microenvironment also promote tumor cell growth.[28] Lymphocytes have an important role in cancer immune surveillance and prevent development of malignancy.[29] The decrease in $CD4^+$ T-helper lymphocytes may result in a suboptimal lymphocyte-mediated immune response to tumor cells.[30] Therefore, thrombocytosis and lymphocytopenia are considered as negative prognostic markers in various cancers and are related to poor response in solid tumors.[31-34] However, an increase in platelet count and decreased lymphocyte count alone may not reflect the host systemic inflammatory response, including mediated immune response and tumorigenesis process. Thus, the PLR, which combines platelet and lymphocyte counts, may reflect the bonding prognostic information of these two processes, and be a stronger predictor of outcome than platelet or lymphocyte count alone. An elevated PLR (high platelet and low lymphocyte count) might protect tumor cells from lysis by natural killer cells, thereby facilitating metastasis.[35]

Although none of the patients in this study received identical chemotherapeutic regimens, the values of PLR were not influenced by different regimens. Our subgroup analyses confirmed the role of PLR in the two larger subgroups of patients treated with oxaliplatin and taxane-based regimens. The results showed that PLR was a significant prognostic factor for patients treated with oxaliplatin-based regimens (P=.04), in accordance with the overall population. Although PLR was not a significant prognostic factor in the taxane-based regimen subgroup (P=.054), there was a strong trend towards worse OS in the high PLR group. Apparently, PLR is a prognostic factor regardless of the regimen received by the patients.

In our study, the cut-off value of PLR was calculated as 201.6 with an ROC curve according to the response after two cycles of first-line chemotherapy. Kaplan-Meier survival analysis showed that the curves for OS in patients with pre-treatment PLR <201.6 and PLR ≥201.6 had significant differences. We obtained significantly different survival curves in our evaluation, using dichotomous and trifurcate cut-off values of PLR. Therefore, the results might strengthen the viewpoint that PLR is a reliable parameter for predicting prognosis.

Our study had some limitations. First, this was a retrospective study with a small study population. Second, lymphocyte and platelet counts may have been influenced by some anti-inflammatory drugs that could not be accounted for in our analysis. Third, AUC for PLR with 0.627 is low as a predictive value. Similarly, some studies determined the optimal cut-off values of PLR with low AUC as 0.57-0.613.[17,25,36,37] Finally, since other inflammatory markers such as C-reactive protein were not routinely measured, we could not clarify the relationship between PLR and other inflammatory markers. Therefore, further, large prospective studies are required to confirm our results.

5 | CONCLUSIONS

Pre-treatment PLR has a significant association with first-line chemotherapeutic response and prognosis in metastatic advanced gastric cancer. PLR is an independent risk indicator for response to first-line chemotherapy. An elevated PLR as a prognostic marker predicts poor survival.

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