Pretreatment Platelet-to-Lymphocyte Ratio (PLR) is associated with prognosis in gastric cancer patients with immunotherapy

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Research Article

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Abstract

Background: previous studies had demonstrated that system inflammation indexes were associated with prognosis ability in various cancers. We aim to explore the prognostic value of platelet to lymphocyte ratio (PLR) in patients with advanced or metastatic gastric cancer (AGC or MGC) receiving immunotherapy.

Method: patients with AGC and MGC who received anti-PD-1 treatment at the Chinese PLA General Hospital between January 2016 and August 2020 were reviewed. The study analyzed the association of PLR and overall survival (OS) or progression-free survival (PFS) and anti-tumor response rate with immunotherapy.

Results: 137 patients were included in the final analysis. The area under the curve values of PLR for 6 months PFS was 0.68 ($P < 0.05$). The best cut-off value for PLR was 816.43. Patients in PLR < 816.43 group had PFS of 7.9m compared to 4.3m in PLR ≥ 816.43 group ($HR = 0.61$, 95% CI, 0.42 - 0.89, $p < 0.001$). OS in PLR < 816.43 group was $11.1m$ vs $9.2m$ in PLR ≥ 816.43 group ($HR = 0.62$, 95% CI, 0.42-0.93, $p < 0.001$). The objective response rate (ORR) and disease control rate (DCR) were 34.1% and 84.6% respectively in PLR < 816.43 group while 30.4% and 80.4% in the ≥ 816.43 group. No significant difference was observed among two group in terms of ORR and DCR ($p = 0.669$, $p = 0.536$). Univariate analysis and multivariate analysis found that PLR was an independent prognosis biomarker for PFS and OS ($p < 0.05$).

Conclusions: Pre-treatment PLR was significantly associated with PFS and OS in patients with AGC and MGC who received immunotherapy. Clinicians might consider patients with elevated PLR as one factor for decisions on immunotherapy strategy.

Background

Gastric cancer is the fifth most common cancer worldwide and has the fourth highest mortality rate, accounting for 7.7% of cancer-related deaths^[1]. With the recognition of cancer, the interventions for advanced or metastatic gastric cancer (AGC or MGC) had entered into the era of immunotherapy. Although the prolonged PFS and OS of chemotherapy in combination with immunotherapy for advanced gastric cancer has been confirmed in the ATTRICATION4 and Checkmate649 studies^[2,3], partial patients remain not benefit from treatment from pd-1 involved regime. Several common system inflammation index, such as the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), have been reported to have prognostic value in various cancers^[4-8], and the elevated NLR or PLR were considered as poor prognostic maker in gastric cancer whenever patients suffered chemotherapy or neoadjuvant therapy^[6, 9-11]. The study had showed that NLR during nivolumab monotherapy as third line are associated with advanced gastric cancer survival^[12]. However, as a convenient index, to our knowledge, few studies have investigated the prognostic value of PLR for patients with AGC or MGC receiving the anti-programmed death protein 1 (pd-1) therapy. Our study was first time to explore the prognostic value of PLR in patients with anti-pd-1 monotherapy or combined with other agents

Patients And Methods

Patients with AGC or MGC administered with immunotherapy between October 1st, 2016 and August 31st, 2020 at Chinese PLA General Hospital were enrolled in the present study retrospectively. Eligible patients must meet the criteria as follows: (1) pathology diagnosed with gastric cancer (2) receiving at least two cycles of anti-PD-1 treatment (3) presence of measurable lesions (4) complete clinical features such as age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), serum tumor makers and response evaluation (5) complete blood count prior to any treatment. Patients received programmed death protein ligand 1 (PD-L1) antibodies or Cytotoxic Lymphocyte Antigen 4 (CTLA4) inhibitor was excluded. Finally, 137 patients were included in the present study. This retrospective observational study was approved by the Ethics Committee of Chinese PLA general hospital. All the patients signed the consent.

Treatment and assessment of tumor response

With regard to treatment type, three types of combination compromise of options for patients with AGC and MGC; anti-pd-1 monotherapy or combined with chemotherapy or anti-angiogenic therapy. PD-1 –targeting antibodies include Nivolumab, Pembrolizumab, Sintilimab, Toripalimab (both domestic PD-1 inhibitor in China). Chemotherapy regimens included XELOX (capecitabine 1000 mg/m² twice daily on days 1 to 14 of each cycle plus intravenous oxaliplatin 130 mg/m² on day 1 of each cycle), SOX (S-1 40–60 mg twice daily on days 1–14 plus oxaliplatin 130mg/m² on day 1) or DCF (docetaxel 75 mg/m² cisplatin 75 mg/m² on day 1 plus fluorouracil 750 mg/m²/d), and other alternatives. Angiogenesis inhibitors are striated into small-molecule tyrosine kinase inhibitors (TKI) such as Apatinib and monoclonal antibody such as Bevacizumab. The regimen was based on the patients' condition and preference. All patients signed informed consent for treatment.

The evaluation of tumor shrinkage was in accordance with response Evaluation Criteria in Solid Tumors 1.1. The response degree was categorized as follows: complete response (CR) and a partial response (PR), stable disease (SD), progression disease (PD). Disease control rate was defined as CR; PR or SD. Objective responses include CR and PR. Overall survival (OS) was calculated from the initiation of each line treatment to death or the date of the last follow-up. Progression-free survival (PFS) was defined as from the date of any active treatment initiation until the date of either the first progression or death.

Blood sample analysis

Peripheral blood platelet, lymphocyte count before the initiations of pd-1 treatment within one week were obtained from medical laboratory records. The PLR was determined as the platelet count divided by the lymphocyte count. The receiver operating characteristic analyses for predicting 6 months and 12 months PFS was used to identify an appropriate and optimal cutoff level by the PLR. And then, patients were divided into two group based on the cutoff value of PLR.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables were present as medians and range. Comparisons of the categorical data were using Pearson's chi-square or Fisher's exact test. The relationships between tumor response and the PLR were assessed using the χ^2 test. Survival data were analyzed using the Kaplan-Meier method. Comparison of survival curves was performed using log-rank analysis. Cox multivariate was used to verify the independent prognostic parameters. The optimal cut-off value was determined by the Youden Index in ROC analysis.

Result

Finally, a total of 137 patients from October 1st, 2016 and August 31st, 2020 at Chinese PLA General Hospital were eligible to enroll in the final analysis. The patients include 88 males and 49 females with median age 59 years (range from 34 to 86). The median PFS and OS were 5.2m and 10.9m respectively. 48.2% patients were received immunotherapy in the first line. The rest patients had previous first or second line treatment with chemotherapy alone. 92 patients had received immunotherapy combined with chemotherapy, whereas 45 patients had undertaken immunotherapy monotherapy or with anti-angiogenesis. All the patients were microsatellite stable (MSS) type. The median PLR was 895.24(range, 144.51–2025.00).

Area for PLR under ROC curve (AUC) at 6 months and 12 months was 0.68 and 0.6 respectively (Figure1). With regard to AUC value, the optimal parameter was PLR at 6 months as cut off level of 816.43($P<0.001$). Furthermore, the significant difference of PFS and OS was observed when patients stratified into four cohort according with PLR quartiles ($P<0.05$) (Figure 2).

With regard to the ROC analysis, patients were separated into two groups: PLR <816.43 group (low PLR) and PLR $\geq$ 816.43 group (elevated PLR).

Patients' characteristics in two groups are shown in Table 1. no significant difference were seen when comparing the clinical features in the two groups in terms of age, gender, Eastern Cooperative Oncology Group performance status(SCOG PS), and number of metastatic sites,PD-L1 expression status, primary tumor site, histological differentiation, presence of liver metastasis, CEA (carcino-embryonic antigen)and CA199 (carbohydrate antigen 199)and anti-PD-1 treatment line and type (Table 1).

Among 137 patients, 34.1% patients had objective response with 1 CR and 30 PR in the PLR <816.43 group and 14 out of 46 patients (30.4%) in the PLR $\geq$ 816.43 group. The confirmed disease control rate (DCR) was 84.6% in the low PLR group and 80.4% in the elevated group. No statistical difference of ORR and DCR was observed in the two groups ($p=0.669$, $p=0.536$) (Table2).

Univariate analyses were performed to explore the association between clinic features and PFS or OS. The median PFS was 7.9m in the low PLR group as compared with 4.3m in the elevated group (HR = 0.61, 95% CI, 0.42 - 0.89, $p < 0.001$) (Figure3). The median OS was obviously higher in the low PLR group than the elevated group (11.1m vs 9.2m, HR = 0.42, 95% CI, 0.42-0.93, $p < 0.001$) (Figure 3). Univariate analysis showed those patients receiving immunotherapy in the first-line or ICI plus chemotherapy had better PFS and OS than patients with immunotherapy in the second line or further line or ICI monotherapy or antigenic ($P<0.05$). Patients with EGOC PS ≥ 2 are associated with poorer PFS (HR=1.382, 95% CI, 0.990-1.929, $p=0.023$). However, multivariate analysis found only PLR were independent prognosis biomarkers for PFS (HR=0.613, 95% CI, 0.408-0.922, $P=0.019$). PLR and histology difference were two independent prognosis factors for OS in the multivariate analysis (HR=0.606, 95% CI, 0.399-0.920, $P=0.019$; HR=0.556, 95% CI, 0.353-0.877, $P=0.012$, respectively). Therefore, elevated PLR were associated with inferior PFS and OS. (Table3, 4).

Discussion

Notwithstanding the model of immunotherapy for AGC or MGC patients had become a trend recently; few studies have investigated the value of routine blood parameters in predicting the prognosis in immunotherapy setting. Although PD-L1 expression and tumor mutation burden(TMB) and microsatellites unstable, tumor infiltrating lymphocyte(TIL), which were associated with prognosis in patients with cancer when given immunotherapy have been identified^[13–17], these biomarkers largely depend on expensive equipment, difficult technology, time-consuming, and some of them obtained after resection of the primary tumor. Therefore, reliable and convenient prognostic factors were of importance when making decisions for patients in system therapy.

Systemic inflammation indexes such as NLR, PLR, and MLR were proved as predictors of survival condition in many cancers at great lengths^[9, 18–22]. PLR had been demonstrated that play an important role on prognosis of gastric cancer whenever at local advanced or metastatic stage^[11, 23]. As far as we concerned whether the PLR can also predict the immunotherapy outcomes for AGC or MGC remains unclear. Our study was at first time providing the evidence that elevated PLR was linked to poor survival and caution must paid on the choices of immunotherapy for patients with GC when PLR level prior to treatment was elevated. Kaplan-Meier survival analysis showed that the curves for PFS and OS in patients with pre-treatment PLR < 816.43 and PLR $\geq$ 816.43 had significant differences. Multivariate analysis further demonstrated the predictive value of PLR both in PFS and OS. The finding was consistent with other studies with patients treated with chemotherapy^[24]. The underlying mechanisms were lack of substantial evidence. Some potential reasons might explain why high PLR is associated with poor survival time. Experimental evidence has showed platelets acts active in all steps of tumor genesis including tumor growth, tumor cell extravasation, and metastasis^[25]. Additionally, thrombocytosis in cancer patients is associated with adverse patient survival^[26]. The presence of T cells is now a well-supported marker of better prognosis in many tumor types, which attribute to immune regulatory cell populations that promote tumor escape from immune surveillance and metastasis^[27]. Lymphocytic infiltration of tumors (TIL) is also linked to the success of immune checkpoint therapeutic strategies^[28]. Combined with these findings, increased platelet-to-lymphocyte was related to negative anti-tumor environment, especially to poor response condition for immunotherapy. Therefore, patients with elevated PLR had inferior survival due to high proportion of tumor-promoting platelet and reduction of tumor-killer lymphocyte.

However, our study analyzed that PLR did not have significant prognostic value for predicting the response rate of anti-pd-1 treatment in AGC or MGC. Instead, in some studies, the PLR was correlated with chemotherapeutic response^[6, 23]. The specific reasons for different results remain to be elucidated. It is assumed that toxicity of chemotherapy direct effects on local tumor cells while the function of immunotherapy induced the long-term effect instead of short-term outcomes.

In our study, the cut-off value of PLR was calculated as 816.43 with an ROC curve according to the 6 months PFS. The cut-off level was much higher compared with previous studies. The study from Jin Wang analyzed the relationship between PLR and response and survival in first-line chemotherapy at a cut-off of 201.6^[23]. The highest PLR level from the meta-analysis^[24] was at level of 350 based on 28 studies. Differences cut-off between studies might due to different laboratory reference standards.

The study had some limitations. First, this was a retrospective study with limited population. Second, other inflammatory markers such as NLR, MLR were not calculated. Third, the outcome needs validation series.

Conclusion

Pre-treatment PLR has association with prognosis in patients with immunotherapy of metastatic and advanced gastric cancer in this retrospective study. Attention might be paid when immunotherapy was opting to patients with elevated PLR.

Declarations

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Ethics and Consent to participate: This study was approved by the Ethics Committee of Chinese PLA general hospital.

Consent to publish:

Consent to publish this study and all details and images

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: There were no conflicts of interest.

Authors Contributions: Miaomiao Gou is in charge of writing, Yong Zhang take charge of data analysis.

We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

All experimental protocols were approved by the Ethics Committee of Chinese PLA general hospital.

We obtained informed consent from all patients.

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Tables

Table1 The characteristics of the analyzed patients in different groups

Characteristics	PLR <816.43		PLR ≥816.43		p value
	N	%	N	%	
No. patients	91		46		
Gender n (%)					0.561
Male	60	76.9%	28	60.9%	
Female	31	23.1%	18	39.1%	
Age median =59 n (%)					
<59	36	39.6%	20	43.5%	0.661
≥59	55	60.4%	26	56.5%	
PD-L1 n (%)					0.528
Positive (CPS>1%)	16	17.6%	9	19.6%	
Negative (CPS<1%)	18	19.8%	11	23.9%	
Unknown	57	62.6%	26	56.5%	
ECOG PS n (%)					0.896
0	26	28.6%	10	21.7%	
1	53	59.3%	33	71.7%	
≥2	12	13.2%	3	6.5%	
Tumor_location n (%)					0.573
Cardia	24	26.4%	15	32.6%	
Body/Fundus	60	65.9%	27	58.7%	
Pylorus	7	7.7%	4	8.7%	
Histological_differentiation n (%)					0.080
Poorly	43	47.3%	28	60.9%	
Moderately	42	46.2%	18	39.1%	
Well	6	6.6%	0	0.0%	
No. of metastasis organs n (%)					0.947
<2	50	72.5%	25	54.3%	
≥2	41	27.5%	21	45.7%	
Liver metastasis n (%)					0.753
Yes	54	59.3%	26	56.5%	
No	37	40.7%	20	43.5%	
CEA n (%)					0.307
<5 ng/ml	48	52.7%	20	43.5%	
≥5 ng/ml	43	47.3%	26	56.5%	
CA199 n (%)					0.863
<37 U/mL	52	57.1%	27	58.7%	
≥37 U/mL	39	42.9%	19	41.3%	
ICIs therapy line n (%)					0.321
First line	47	51.6%	19	41.3%	
Second line	39	42.9%	25	54.3%	
Third line	5	5.5%	2	4.3%	
Treatment type n (%)					0.327
Anti-pd-1 monotherapy	9	9.9%	6	13.0%	

Combination therapy				
anti-pd-1 plus chemotherapy	60	65.9%	32	69.6%
anti-pd-1 plus anti-angiogenic therapy	22	24.2%	8	17.4%

CPS, Combined Positive Score ECOG PS, Eastern Cooperative Oncology Group Performance Status

ICI, immune checkpoint inhibitor

Table 2 Treatment response in the PLR<816.43 group and in the PLR>=816.43 group

Response	PLR<816.43		PLR>=816.43		P value
	N	%	N	%	
No. patients	91		46		
Response					
CR	1	1.1%	2	4.3%	
PR	30	33.0%	12	26.1%	
SD	46	50.5%	23	50.0%	
PD	14	15.4%	9	19.6%	
ORR					0.669
CR+PR		34.1%		30.4%	
DCR					0.536
CR+PR+SD		84.6%		80.4%	

Table 3 Univariate analysis and multivariate analysis of progression free time (PFS)

Variable Category	Category	Univariate analysis	Multivariate analysis		Table4
		p-value	HR (95% CI)	p-value	
Gender	Female versus Male	0.241	0.808(0.515-1.27)	0.356	
Age	>=59 versus <59	0.177	1.162(0.744-1.817)	0.509	
ECOG	>=2 versus 0-1	0.023	1.375(0.958-1.975)	0.084	
Tumor location	Cardia versus Body/Fundus versus Pylorus	0.404	1.020(0.725-1.434)	0.911	
Histological differentiation	Poorly versus Moderately and Well	0.050	0.664(0.435-1.012)	0.057	
No. of metastasis organs	>=2 verse <2	0.772	0.957(0.652-1.403)	0.820	
Liver metastasis	Yes verse No	0.974	1.106(0.719-1.702)	0.647	
ICIs therapy line	First line verse Second line and Third line	0.007	1.223(0.746-2.006)	0.424	
Treatment type	ICIs plus chemotherapy verse ICI monotherapy or antiagenis	0.030	1.157(0.692-1.937)	0.578	
PLR	<816.43 versus >=816.43	0.004	0.613(0.408-0.922)	0.019	
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PLR, platelet to lymphocyte ratio HR, hazard ratio.					

Univariate analysis and multivariate analysis of overall survival time (OS)

Variable Category	Category	Univariate analysis	Multivariate analysis	
		p-value	HR (95% CI)	p-value
Gender	Female versus Male	0.236	0.79(0.50-1.27)	0.341
Age	>=59 versus <59	0.200	1.282(0.81-2.03)	0.289
ECOG	>=2 versus 0-1	0.379	1.319(0.940-1.852)	0.109
Tumor location	Cardia versus Body/Fundus versus Pylorus	0.468	1.046(0.727-1.505)	0.807
histological differentiation	Poorly versus Moderately and Well	0.001	0.556(0.353-0.877)	0.012
No.of metastasis organs	>=2 verse <2	0.149	1.111(0.750-1.646)	0.601
Liver metastasis	Yes verse No	0.393	1.015(0.634-1.625)	0.952
ICIs therapy line	First line verse Second line and Third line	0.002	1.229(0.737-2.051)	0.429
Treatment type	ICIs plus chemotherapy verse ICI monotherapy or antiagenis	0.000	1.531(0.894-2.620)	0.121
PLR	<816.43 versus >=816.43	0.004	0.606(0.399-0.920)	0.019

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PLR, platelet to lymphocyte ratio HR, hazard ratio.

Figures

Figure 1

A: Receiver operating characteristic curves for predicting 6 months and 12 months PFS by the Platelet-to-Lymphocyte Ratio (AUC area under the curve are 0.68 and 0.6). B: AUC by PFS time

Figure 2

Progression-free survival (PFS)(A) and Overall survival (OS) (B)in PLR based on quartile

Figure 3

Progression-free survival (PFS)(A) and Overall survival (OS) (B)in PLR based on the PLR cut-off value