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 longer than 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 prognostic 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 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 death. 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

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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 \( \chi^2 \) 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 form 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>=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 >=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 medianOS was obviously higher in the lowPLR group than the elevated one (11.1m vs9.9m, 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% CI0.399-0.920, P=0.019; HR=0.556,95% CI0.353-0.877, 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[11,18,19]. 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 <816.43and PLR ≥ 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 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 form 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.

**References**

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.
2. N. Boku1 MHR, D.-Y. Oh3 SCO, H.C. Chung5 K-WL, et al. Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/ gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. 2020 ESMO.
3. Moehler M, Shitara K, Garrido M, et al. Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study. 2020 ESMO, LBA6.
4. Xie X, Luo KJ, Hu Y, Wang JY, Chen J. Prognostic value of preoperative platelet-lymphocyte and neutrophil-lymphocyte ratio in patients undergoing surgery for esophageal squamous cell cancer. Dis Esophagus. 2016. 29(1): 79–85.
5. Miyatani K, Saito H, Kono Y, et al. Combined analysis of the pre- and postoperative neutrophil-lymphocyte ratio predicts the outcomes of patients with gastric cancer. Surg Today. 2018. 48(3): 300–307.
6. Hirahara T, Arigami T, Yanagita S, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer. 2019. 19(1): 672.
7. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg. 2009. 137(2): 425–8.
8. Kim HS, Ku JH. Systemic Inflammatory Response Based on Neutrophil-to-Lymphocyte Ratio as a Prognostic Marker in Bladder Cancer. Dis Markers. 2016. 2016: 8345286.
9. Kim EY, Lee JW, Yoo HM, Park CH, Song KY. The Platelet-to-Lymphocyte Ratio Versus Neutrophil-to-Lymphocyte Ratio: Which is Better as a Prognostic Factor in Gastric Cancer. Ann Surg Oncol. 2015. 22(13): 4363–70.

10. Mungan İ, Dicle ÇB, Bektas Ş, et al. Correction to: Does the preoperative platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio predict morbidity after gastrectomy for gastric cancer. Mil Med Res. 2020. 7(1): 12.

11. Ohe Y, Fushida S, Yamaguchi T, et al. Peripheral Blood Platelet-Lymphocyte Ratio Is Good Predictor of Chemosensitivity and Prognosis in Gastric Cancer Patients. Cancer Manag Res. 2020. 12: 1303–1311.

12. Ota Y, Takahari D, Suzuki T, et al. Changes in the neutrophil-to-lymphocyte ratio during nivolumab monotherapy are associated with gastric cancer survival. Cancer Chemother Pharmacol. 2020. 85(2): 265–272.

13. Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018. 392(10142): 123–133.

14. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020. 21(10): 1353–1365.

15. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017. 357(6349): 409–413.

16. Zhang D, He W, Wu C, et al. Scoring System for Tumor-Infiltrating Lymphocytes and Its Prognostic Value for Gastric Cancer. Ann Surg. 2019. 269(3): 471–478.

17. Chen L, Zhang F, Sheng XG, Zhang SQ, Chen YT, Liu BW. Peripheral platelet/lymphocyte ratio predicts lymph node metastasis and acts as a superior prognostic factor for cervical cancer when combined with neutrophil: Lymphocyte. Medicine (Baltimore). 2016. 95(32): e4381.

18. Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev. 2017. 58: 1–13.

19. 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(1): 164–70.

20. Wang Z, Peng S, Wang A, et al. Platelet-to-lymphocyte ratio acts as an independent predictor of prognosis in patients with renal cell carcinoma. Clin Chim Acta. 2018. 480: 166–172.

21. Song S, Li C, Li S, Gao H, Lan X, Xue Y. Derived neutrophil to lymphocyte ratio and monocyte to lymphocyte ratio may be better biomarkers for predicting overall survival of patients with advanced gastric cancer. Onco Targets Ther. 2017. 10: 3145–3154.

22. Li J, Qu J, Li Z, et al. Pretreatment platelet-to-lymphocyte ratio is associated with the response to first-line chemotherapy and survival in patients with metastatic gastric cancer. J Clin Lab Anal. 2018. 32(1).

23. Cao W, Yao X, Cen D, Zhi Y, Zhu N, Xu L. The prognostic role of platelet-to-lymphocyte ratio on overall survival in gastric cancer: a systematic review and meta-analysis. BMC Gastroenterol. 2020. 20(1): 16.

24. Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. J Hematol Oncol. 2018. 11(1): 125.

25. Haemmerle M, Stone RL, Menter DG, Afshar-Kharghan V, Sood AK. The Platelet Lifeline to Cancer: Challenges and Opportunities. Cancer Cell. 2018. 33(6): 965–983.

26. Spranger S. Mechanisms of tumor escape in the context of the T-cell-inflamed and the non-T-cell-inflamed tumor microenvironment. Int Immunol. 2016. 28(8): 383–91.

27. Quigley DA, Kristensen V. Predicting prognosis and therapeutic response from interactions between lymphocytes and tumor cells. Mol Oncol. 2015. 9(10): 2054–62.

Tables
| Characteristics | PLR <816.43 | PLR >=816.43 | p value |
|-----------------|-------------|--------------|---------|
| No. patients    | 91          | 46           |         |
| Gender n (%)    |             |              | 0.561   |
| Male            | 60          | 28           | 76.9%   | 60.9%   |
| Female          | 31          | 18           | 23.1%   | 39.1%   |
| Age median =59 n (%) |     |              |         |
| <59             | 36          | 20           | 39.6%   | 43.5%   | 0.661   |
| >=59            | 55          | 26           | 60.4%   | 56.5%   |
| PD-L1 n (%)     |             |              | 0.528   |
| Positive (CPS>1%)| 16         | 9            | 17.6%   | 19.6%   |
| Negative (CPS<1%)| 18         | 11           | 19.8%   | 23.9%   |
| Unknown         | 57          | 26           | 62.6%   | 56.5%   |
| ECOG PS n (%)   |             |              | 0.896   |
| 0               | 26          | 10           | 28.6%   | 21.7%   |
| 1               | 53          | 33           | 59.3%   | 71.7%   |
| >=2             | 12          | 3            | 13.2%   | 6.5%    |
| Tumor_location n (%) |         |              | 0.573   |
| Cardia          | 24          | 15           | 26.4%   | 32.6%   |
| Body/Fundus     | 60          | 27           | 65.9%   | 58.7%   |
| Pylorus         | 7           | 4            | 7.7%    | 8.7%    |
| Histological_differentiation n (%) |     |              | 0.080   |
| Poorly          | 43          | 28           | 47.3%   | 60.9%   |
| Moderately      | 42          | 18           | 46.2%   | 39.1%   |
| Well            | 6           | 0            | 6.6%    | 0.0%    |
| No. of metastasis organs n (%) |     |              | 0.947   |
| <2              | 50          | 25           | 72.5%   | 54.3%   |
| >=2             | 41          | 21           | 27.5%   | 45.7%   |
| Liver metastasis n (%) |         |              | 0.753   |
| Yes             | 54          | 26           | 59.3%   | 56.5%   |
| No              | 37          | 20           | 40.7%   | 43.5%   |
| CEA   n (%)     |             |              | 0.307   |
| <5 ng/ml        | 48          | 20           | 52.7%   | 43.5%   |
| >=5 ng/ml       | 43          | 26           | 47.3%   | 56.5%   |
| CA199 n (%)     |             |              | 0.863   |
| <37 U/mL        | 52          | 27           | 57.1%   | 58.7%   |
| >=37 U/mL       | 39          | 19           | 42.9%   | 41.3%   |
| ICIs therapy line n (%) |     |              | 0.321   |
| First line      | 47          | 19           | 51.6%   | 41.3%   |
| Second line     | 39          | 25           | 42.9%   | 54.3%   |
| Third line      | 5           | 2            | 5.5%    | 4.3%    |
| Treatment type n (%) |         |              | 0.327   |
| Anti-pd-1 monotherapy | 9    | 6            | 9.9%    | 13.0%   |
Variable Category | Category | Univariate analysis | Multivariate analysis
|------------------|----------|-------------------|-------------------|
| 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 (0.744-1.381) | 0.911 |
| Histological differentiation | Poorly versus Moderately and Well | 0.050 | 0.664 (0.435-1.012) | 0.057 |
| No. of metastasis organs | >=2 versus <2 | 0.772 | 0.957 (0.652-1.403) | 0.820 |
| Liver metastasis | Yes versus No | 0.974 | 1.106 (0.719-1.702) | 0.647 |
| ICIs therapy line | First line versus Second line and Third line | 0.007 | 1.223 (0.746-2.006) | 0.424 |
| Treatment type   | ICIs plus chemotherapy versus ICIs monotherapy or antiagens | 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 versus <2                                 | 0.149               | 1.111 (0.750-1.646)   | 0.601                 |
| Liver metastasis       | Yes versus No                                 | 0.393               | 1.015 (0.634-1.625)   | 0.952                 |
| ICl therapy line       | First line versus Second line and Third line  | 0.002               | 1.229 (0.737-2.051)   | 0.429                 |
| Treatment type         | ICl plus chemotherapy versus ICI monotherapy or antiagens | 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