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Original Article

The impact of systemic inflammatory markers on survival in metastatic gastric cancer patients receiving first-line chemotherapy

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Abstract

Aim: The prognostic impact of elevated systemic inflammatory tools, including the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), remains moot in cancer patients. This research was performed to explore the predictive worth of these markers for prognoses in metastatic gastric cancer (mGC) patients receiving chemotherapy.

Material and Methods: We retrospectively appraised 158 patients diagnosed with mGC between February 2009 and November 2017. According to threshold values that were identified by receiver operating characteristic (ROC) curve analysis, the NLR and PLR were each divided into two groups: ≤ 2.11 and >2.11, ≤ 158.8, and >158.8, respectively. The Cox proportional hazards model was applied to uncover the probable predictors of progression-free survival (PFS) and overall survival (OS).

Results: According to univariate analysis, poor performance status, high NLR, high PLR, and anemia were significantly correlated with inferior OS receiving first-line palliative chemotherapy. High NLR, high PLR, and anemia were significantly correlated with poor PFS. In the multiple analysis, an elevated NLR was identified to be an independent predictor of inferior OS (OR: 2.70, 95% CI: 1.75-4.16, $p<0.001$) and PFS (OR: 1.47, 95% CI: 1.00-2.17, $p=0.047$). Additionally, anemia was independent prognostic factors for the OS (OR: 0.69, 95% CI: 0.47-0.99, $p=0.046$).

Conclusion: Findings of this research revealed that NLR was an independent prognostic tool of PFS and OS in mGC patients undergoing first-line chemotherapy.

Keywords: Metastatic gastric cancer; neutrophil to lymphocyte ratio; platelet-to-lymphocyte ratio; prognosis.

INTRODUCTION

Gastric cancer is the fifth most frequent malignant tumor and one of the common causes of cancer-related death worldwide (1). Most patients with gastric cancer have locally advanced or metastatic gastric cancer (mGC) at the initial diagnosis, (2,3) and have an inferior prognosis, particularly in patients with mGC (1,4).

Systemic chemotherapy is the main treatment choice for locally advanced and mGC. The primary aims of chemotherapy for recurrent and metastatic gastric cancers are palliation and improvement of survival. Despite treatment with standard platinum-based chemotherapy, the median survival time is approximately 12 months and there is a pronounced heterogeneity in clinical result among mGC patients (5). In addition, in clinical practice, the adverse results of chemotherapy are likely to diminish the quality of life in these patients. Hence, the identification of patients who would probably not benefit from palliative chemotherapy reduces both the constant side effects associated with ineffective treatment, as well as improving survival outcomes.

Recently, there has been an enhancement document supporting the role of inflammation in cancer initiation, progression, and metastasis (6). Emerging research has demonstrated that inflammatory tools, including NLR and PLR, were found to be related to cancer mortality and employed as useful in the prediction of survival in many malignant neoplasms (7–10). However, the prognostic impact of elevated systemic inflammatory markers

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remains controversial in mGC patients. Therefore, we intended to explore whether the NLR and PLR can be used as a prognostic tool for predicting the survival outcome in mGC patients undergoing first-line chemotherapy.

MATERIAL and METHODS

Study population

We analyzed the data of 158 patients who had received first-line palliative chemotherapy with a target agent or not according to Her2 receptor status from February 2009 and November 2017. Erciyes University Medical School ethics committee endorsed the retrospective research.

The inclusion criterion included: (a) patients with gastric cancer substantiated by pathology, (b) patients who had taken first-line chemotherapy, and (c) patients with existing and complete clinical archives including demographic data, pathologic properties of the tumor, therapeutic interventions, and laboratory data. The following exclusion criteria were exerted: (a) patients with clinical verification of acute infection, systemic inflammation or other autoimmune disturbances, (b) patients suffering from hematologic disorders, and (c) patients diagnosed with second malignant neoplasm arising from different regions.

Chemotherapy protocol, tumor response, and laboratory data

Palliative chemotherapy was implemented for all patients after the diagnosis of mGC. Platinum-based chemotherapy (n= 139, 88%) was implemented most often, and DCF (docetaxel, cisplatin, and 5-fluorouracil) was the most pervasive protocol. The chemotherapy regimen was chosen at the request of the treating physician. Pre-chemotherapy blood assays, involving complete blood count (CBC) was conducted up to 24 hours before applying chemotherapy.

All patients underwent staging screening with computed tomography of the abdomen and thorax to verify the extent of the tumor. Additional assistive imaging methods, such as magnetic resonance imaging, bone scan, and positron emission tomography were contemplated considering the patients' symptoms or necessity required by the attending physician. Baseline scanning was implemented 1-3 week before the beginning of chemotherapy, and follow-up images were implemented every 8 ± 4 weeks after the start of chemotherapy. The Response Evaluation Criteria for Solid Tumors (RECIST) criteria were used to appraise the radiological response. Disease control rates (DCR) was characterized as complete response, partial response and stable disease. The NLR and PLR values were determined by dividing the counts of neutrophils and platelets by lymphocyte counts, respectively. ROC curves were used to detect the discriminative influence of NLR and PLR in predicting the survival status in gastric cancer patients.

Statistical analysis

For the statistical analyses of the study data, SPSS Statistics 22 software was used (IBM, United States). Histogram and q-q plots were perused to detect the datum normality. A two-sided independent sample *t*-test was implemented to compare differences between continual factors, while Fisher exact test or Pearson chi-square test was implemented to compare differences between categorical factors. The area under the ROC curves was calculated with 95% confidence intervals. Specificity, sensitivity, positive and negative predictive values were computed with 95% confidence intervals. Survival probabilities were predicted with the Kaplan-Meier method and group comparisons were applied with the Log-rank test. Furthermore, the univariate and multivariate Cox regression analysis was used to determine the most significant risk factors. All *p*-values represent two-sided tests of statistical significance, with $p< 0.05$ considered statistically significant.

RESULTS

The median patient age was 59 years (range: 30–79 years), and the 158 patients included 104 men (65.8%) and 54 women (34.2%). The most frequent location of metastasis was the liver (45.6%) in 72 patients, followed by the peritoneum (28.5%) in 45 patients, and the lymph node (8.2%) in 13 patients. Human epidermal growth factor receptor (Her-2) results were reached in 76(48%) of 158 patients and Her2 positivity rate was found to be 19.7% in our study.

Regarding the chemotherapy regimen, 139 patients (88%) received platinum-based chemotherapy, 19 (12%) patients received non-platinum-based chemotherapy.

According to the chemotherapy response, patients were grouped as partial response (24.1%), stable disease (29.7%), progressive disease (44.3%), and complete response (1.9%). According to the threshold levels that were detected by ROC curve analysis, the NLR and PLR were each divided into two groups: ≤ 2.11 and >2.11 (the sensitivity was 75% and the specificity was 50%, p=0.001), ≤ 158.8 and >158.8 (the sensitivity was 73.6% and the specificity was 50%, p=0.02), respectively (Figure 1).

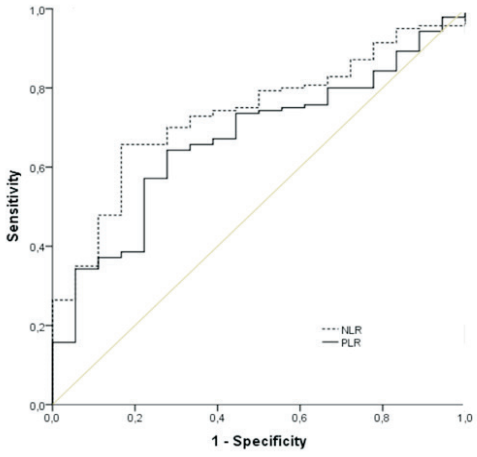

Figure 1. Receiver operating characteristic curve for the NLR platelet-to-lymphocyte ratio and PLR according to overall survival

The clinicopathological features except for performance status and gender were not significantly different between the NLR groups. The clinicopathological characteristics except hemoglobin were not significantly different between the PLR groups. The baseline features of mGC patients according to the NLR and PLR groups are seen in Table-1.

Potential prognostic elements that were analyzed included gender, age, ECOG PS (The eastern cooperative oncology group; PS, performance status), HER-2 status, histologic subtype, resection status of primary gastric, hemoglobin, albumin, NLR and PLR.

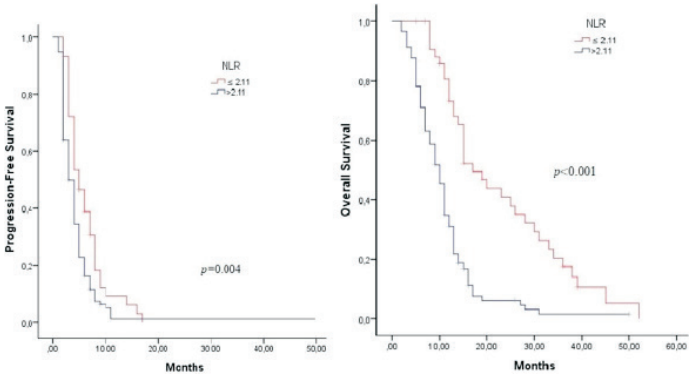

Figure 2. Kaplan–Meier curves for PFS and OS according to the pre-chemotherapy of NLR

According to univariate analysis, poor performance status(OR:0.67, 95% CI: 0.48-0.95, *p*=0.025) high NLR (OR:2.90, 95% CI:1.92-4.38, p<0.001), high PLR(OR:1.60, 95% CI:1.09-2.33, *p*=0.015) and anemia (OR:0.67, 95% CI: 0.47-0.95, *p*=0.025) were significantly correlated with inferior OS during the first-line palliative chemotherapy (Table-2). High NLR (OR:1.61, 95% CI: 1.11-2.33, *p*=0.011), high PLR (OR:1.76, 95% CI:1.21-2.56, *p*=0.003), and anemia (OR:0.66, 95% CI: 0.47-0.94, *p*= 0.019) were significantly correlated with poor PFS (Table-3). In the multiple analysis, an elevated NLR was identified to be an independent determinator of reduced OS (OR: 2.70, 95% CI: 1.75-4.16, *p*<0.001) and PFS (OR: 1.47, 95% CI: 1.00-2.17, *p*=0.047). Additionally, anemia was an independent prognostic element for the OS (OR: 0.69, 95% CI: 0.47-0.99, *p*=0.046) (Table 2,3).

The median PFS was three (95% CI 2.37-3.62) months in the group with an elevated NLR, and five (95% CI 3.66-6.34) months in the group with a low NLR (*p=0.004*) (Fig. 2). The median OS was 10 (95% CI 8.85-11.1) months in the group with an elevated NLR and 17 (95% CI 12.6-21.3) months in the group with a low NLR(*p<0.001*) (Fig. 2). There was a significant correlation between the NLR status and the DCR (low NLR group, high NLR group: 79.5%, 46.5%, respectively; *p* <0.001).

Table 1. Characteristics of participants according to NLR and PLR

Variable, n (%)	NLR		p	PLR		p
	≤2.14	>2.14		≤158.8	>158.8	
Gender						
Male	21(47.7)	33(28.9)	0.039	29(63.00)	75(67.00)	0.384
Female	23(52.3)	81(71.1)		17(37.00)	37(33.00)	
Age (years)						
<65	34(77.30)	71(62.30)	0.091	28(60.90)	77(68.80)	0.359
≥65	10(22.70)	43(37.70)		18(39.10)	35(31.03)	
ECOG performance status						
0	30(68.20)	56(49.10)	0.034	28(60.90)	58(51.80)	0.380
1-2	14(31.80)	58(50.90)		18(39.10)	54(48.20)	
Peritoneal carcinomatosis						
Yes	12(27.3)	33(28.9)	1.000	12(26.1)	33(29.5)	0.703
No	32(72.7)	81(71.1)		34(73.9)	79(70.5)	
Hemoglobina[a]						
Normal	21(47.70)	39(34.20)	0.144	25(54.30)	35(31.30)	0.011
Anemi	23(52.30)	75(65.80)		21(45.70)	77(68.80)	
Weight loss						
Yes	29(65.09)	75(65.80)	1.000	27(58.70)	77(68.80)	0.269
No	15(34.01)	39(34.20)		19(41.30)	35(31.30)	
Albumin						
≥4 g/d	14(31.80)	28(24.60)	0.442	15(32.60)	27(24.10)	0.322
<4 g/d	30(68.20)	86(75.40)		31(67.40)	85(75.90)	
First line chemotherapy						
Platinum based regimen	35(79.50)	104(91.20)	0.056	38(82.60)	101(90.20)	0.189
Non-platinum based regimen	9(20.50)	10(8.80)		8(17.40)	11(9.80)	

n(%): Number and percent
[a]**Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL.**
EGOG:Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

Table 2. Univariate and Multiple Cox Regression Analysis of Variables for OS

Variables	OS			
	Univariate HR(95% CI)	P-value	Multiple HR(95% CI)	P value
Age, years (65 ≥, 65 <)	1.41(0.99-2.00)	0.054	-	
Gender (Male/ Female)	1.35(0.94-1.93)	0.092	-	
Albumin (≥4 g/d. <4 g/d)	0.99(0.68-1.44)	0.965	-	
Hemoglobina (Normal/Anemia)	0.67(0.47-0.95)	0.025*	0.69(0.47-0.99)	0.046*
Gastrectomy(Present/Absent)	0.84(0.56-1.27)	0.415	-	
HER2 status(+/-)	0.80(0.42-1.55)	0.521	-	
Pathologic type (Adenocarcinoma/Other)	1.04(0.67-1.61)	0.844	-	
Peritoneal carcinomatosis (Yes /No)	1.42(0.97-2.07)	0.066	-	
EGOG PS (0/ 1-2)	0.67(0.48-0.95)	0.025*	0.75(0.53-1.06)	0.111
NLR (High/Low)	2.90(1.92-4.38)	<0.001*	2.70(1.75-4.16)	<0.001*
PLR (High/ Low)	1.60(1.09-2.33)	0.015*	1.10(0.73-1.65)	0.647

* Statistically significant
Abbreviation: CI:Confidence interval, HR: Hazard ratio, OS: Overall survival, EGOG:Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, Other: Ring cell carcinoma and undifferentiated carcinoma

Table 3. Univariate and Multiple Cox Regression Analysis of Variables for PFS

Variables	PFS			
	Univariate HR(95% CI)	P-value	Multiple HR(95% CI)	P-value
Age, years (65 ≥, 65 <)	1.35(0.95-1.90)	0.085	-	
Gender (Male/ Female)	1.16(0.82-1.63)	0.398	-	
Albumin (≥4 g/d, <4 g/d)	0.97(0.67-1.40)	0.883	-	
Hemoglobina (Normal/Anemia)	0.66(0.47-0.94)	0.019*	0.71(0.50-1.02)	0.069
Gastrectomy(Present/Absent)	0.74(0,49-1,10)	0.141	-	
HER2 status(+/-)	1.03(0.58-1.84)	0.901	-	
Pathologic type (Adenocarcinoma/Other)	1.14(0,75-1.74	0.524	-	
Peritoneal carcinomatosis (Yes /No)	1.26(0.88-1.80)	0.197	-	
EGOG PS (0/ 1-2)	0.87(0.63-1.21)	0.420	-	
NLR (High/Low)	1.61(1.11-2.33)	0.011*	1.47(1.00-2.17)	0.047*
PLR (High/ Low)	1.76(1.21-2.56)	0.003*	1.46(0.98-2.18)	0.060

* Statistically significant
Abbreviation: CI:Confidence interval, HR: Hazard ratio, PFS: Progression-free survival, EGOG:Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, Other: Ring cell carcinoma and undifferentiated carcinoma

The median PFS was three (95% CI 2.39-3.60) months in the group with an elevated PLR and five (95% CI 4.23-5.77) months in the group with a low PLR (p=0.001) (Figure 3). The median OS was 10 (95% CI 8.66-11.3) months in the group with an elevated PLR group and 13 (95% CI 10.5-15.4) months in the group with a low PLR (p= 0.01) (Figure 3). There was a statistically significant correlation between the PLR status and the DCR (low PLR group, high PLR group: 71.7%, 49.1%, respectively; p=0.013).

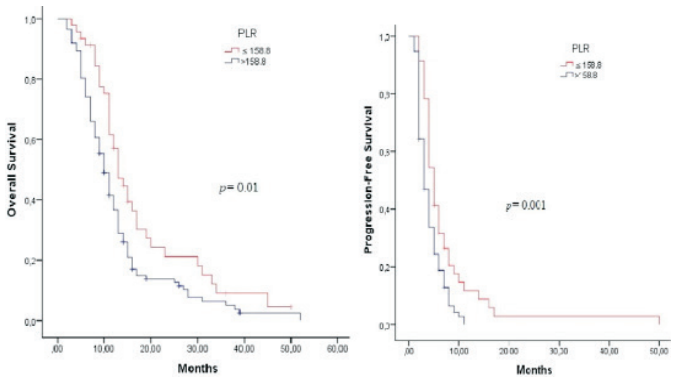

Figure 3. Kaplan ®Meier curves for PFS and OS according to the pre-chemotherapy of PLR.

DISCUSSION

Gastric cancer is among the oncological malignancies with an aggressive course. Although standard treatments are applied to these patients, survival rates are variant even among patients with equal disease stage and neoplasm subtype. In gastric cancer patients, there is no molecular biomarker with clinical use except for HER-2 (11). Therefore, predictive and prognostic tools are promptly required to aid the definite prediction of patient outcomes and to ease the identification of novel therapeutic targets.

A series of research studies has declared that the immune system plays a pivotal role in controlling cancer growth, and neutrophils, platelets, and lymphocytes are considerable in the tumor-induced systemic inflammatory response (12,13).

In the tumor micro environment, increased neutrophil level can extricate more cytokines and chemokines, which may stimulate the proliferation, angiogenesis, metastasis of cancer cell and suppress lymphocyte activity (14,15). At the same time, an elevated neutrophil level in the microenvironment might depress the task of natural killer cells and T lymphocytes (16). Hence, a high level of circulating neutrophils may reduce the anti-tumor cellular immune response on the tumor-bearing host, giving rise to a negative correlation between the neutrophil amount and patient outcome.

Lymphocytes are an important element of the anti-tumor cellular immune response of the host against malignant cells and can assault tumor cells and exterminate emerging malignant cells (17). Patients with lymphocyte infiltration around the neoplasm may have a superior outcome to those without infiltration (18,19), and research has indicated that a low total lymphocyte level can be used as an indicator of a poor outcome in the malignant pancreatic tumor (20). NLR, one of the indexes of systemic inflammation, may indicate the proangiogenic/pro-inflammatory situation in cancer tissues as well as the ratio between neutrophils and lymphocytes, thereby reflecting patients' immune activities. A high NLR in patients might immediately demonstrate worse lymphocyte-related immune response against cancers, leading to poor prognosis (21).

Much previous research focused on NLR as a prognostic tool in early-stage patients with GC (22,23), whereas, research about the correlation between NLR and survival in metastatic cancer patients receiving chemotherapy is limited (24-26).

Cho et al. uncovered that pre-chemotherapy low NLR group patients had remarkably superior disease control and longer PFS and OS than the elevated NLR group patients. Another study discovered that an increased prechemotherapy NLR was correlated with shorter PFS and OS in mGC patients treated with first-line chemotherapy (24). Li et al. retrospectively explored the terms of the effect of inflammatory indexes on prognosis in 384 patients with advanced or mGC treated with first-line chemotherapy and demonstrated elevated pretreatment neutrophil level to be independent predictors of shorter OS (25). Musri et al. declared that elevated NLR is an independent prognostic element related to worse survival in patients with mGC (26). Lee et al. retrospectively investigated the prognostic significance of NLR and PLR in 174 advanced gastric cancer patients who received chemotherapy. They reported that NLR was an independent prognostic tool for OS (7).

Ogata et al. detected that the median PFS and OS were poorer in the high NLR group in gastric cancer treated with nivolumab (27). Biomarkers such as PD-L1 or PD-L2 expression, mutation load and mismatch repair deficiency(dMMR) were explored in patients receiving immunotherapy (28-30). However, the rate of positivity for PD-L1 and mutation burdens were not very high in patients with gastric cancer (28,31). In addition, the dMMR is declared as a predictive tool for immunotherapy response and has been uncovered in 27% of patients with gastric cancer (32). The determination of these markers involved the use of archival specimen, and so did not externalize the present condition. On the other hand, the use of NLR in patients treated with immunotherapy can be a simple and effective biomarker.

In the current research, the findings of univariate analysis discovered that higher pretreatment NLR was related to worse OS and PFS. The findings of multivariate analysis showed that higher pretreatment NLR was an independent prognostic tool of PFS and OS in mGC patients undergoing first-line chemotherapy.

Thrombocyte counts may be increased owing to the release of inflammatory molecules such as interleukin-1 and-6 by inflammatory or tumors cells leading to the excitation of megakaryocytes to generate platelets (33). Thrombocytes can support tumor growth by enhancement angiogenesis via the cytokine vascular endothelial growth factor (34). They also boost the adherence, sequestration, and penetration of cancer cells through the endothelium, and hinder the immune system from cleaning neoplastic cells from the circulatory system (35). There is a growing

finding that PLR, another serum based inflammatory index, is a useful prognostic tool in diverse types of malignancies (36–38). A high PLR represents both a reduced lymphocyte count and an enhanced thrombocyte count. So high PLR level may be conducive to a reduced anti-tumor function of the body.

Wang et al. analyzed the data of 439 patients with mGC treated with chemotherapy and discovered that increased PLR was linked with inferior OS in the univariate but not in the multivariate analysis (39). In another study, Dogan et al.discovered that elevated PLR had significantly shorter PFS and OS in patients with mGC (40). In retrospective research in patients with advanced gastric cancer who received chemotherapy, PLR did not have considerable prognostic worth for predicting PFS or OS (7). In a meta-analysis of 4513 patients with gastric cancer, a high PLR was not an exact predictor for OS (41). Our research found longer OS and PFS in the reduced PLR group compared with the elevated PLR group. Nevertheless, findings of multivariate analysis demonstrated that higher pretreatment PLR was not an independent prognostic tool of PFS and OS in mGC patients undergoing first-line chemotherapy.

This research has several limitations. First, the research has a comparatively small sample size, non-randomized, retrospective plan, and came from our single center in Turkey. Second, thrombocyte and lymphocyte counts might have been affected by some anti-inflammatory medicines that could not be taken into account in this analysis. The chemotherapy regimens applied to the patients at the metastatic stage were not homogeneous. Finally, there is no consensus on the definite cut-off level for NLR, although previous analyses have reported the level of NLR for the prognosis of gastric cancer (8, 22, 24,36). In the present exploration, the NLR cut-off level of 2.11 was chosen using ROC analysis with the method reported in other investigations (8,36). Some previous research used a median value of NLR to detect the cut-off level (22, 24). This lack of concurrence on the cut-off level makes NLR hard to use in daily clinical practice. Like NLR, there is no consensus for the threshold value of PLR. Therefore, we recommend prospective validation of these consequences in clinical research to evaluate the clinical benefit of NLR in mGC patients prior to the routine use of this marker in clinical practice.

In conclusion, a retrospective study declared that although both the PLR and NLR can forecast the outcome, the NLR is a clearer forecast of OS than the PLR (36). In the current research, we also discovered that high NLR and high PLR were related to worse OS and PFS. According to multivariate analysis, NLR was detected as an independent prognostic tool for PFS and OS. We believe that pretreatment inflammatory markers, particularly NLR, have more predictive value than PLR. However, further large prospective research should be performed to verify whether pretreatment inflammatory markers have prognostic and predictive markers in patients with mGC.

Competing interests: The authors declare that they have no competing interest.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancerstatistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Digklia A, Wagner AD. Advanced gastric cancer: current treatment landscape and future perspectives. World J Gastroenterol 2016;22:2403-14.
3. Ku GY, Ilson DH. Management of gastric cancer. Curr Opin Gastroenterol 2014;30:596-602.
4. Yang D, Hendifar A, Lenz C, et al. Survival of metastatic gastric cancer: significance of age, sex and race/ethnicity. J Gastrointest Oncol 2011;2:77-84.
5. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010;17:CD004064.
6. Rajput S, Wilber A. Roles of inflammation in cancer initiation, progression, and metastasis.Front Biosci (Schol Ed). 2010;2:176-83
7. Lee S, Oh SY, Kim SH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013;13:350.
8. Jiang N, Deng JY, Liu Y, et al. The role of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after radical resection for gastric cancer. Biomarkers 2014;19:444-51.
9. Chrom P, Stec R, Bodnar L, et al. Incorporating neutrophil-tolymphocyte ratio and platelet-to-lymphocyte ratio in place of neutrophil count and platelet count improves prognostic accuracy of the international metastatic renal cell carcinoma database consortium model. Cancer Res Treat 2017;50:103-10.
10. Sun X, Liu X, Liu J, et al. Preoperative neutrophil-tolymphocyte ratio plus platelet-to-lymphocyte ratio in predicting survival for patients with stage I-II gastric cancer. Chin J Cancer 2016;35:57.
11. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open- label, randomised controlled trial. Lancet 2010;376:687-97.
12. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12:223-6.
13. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011;331:1565-70.
14. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
15. Coffelt SB, Wellenstein MD, de Visser KE.Neutrophils in cancer: neutral no more. Nat Rev Cancer 2016;16:431-46.

16. Jin H, Zhang G, Liu X, et al. Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy. World J Surg Oncol 2013;11:112.
17. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006; 90:1–50.
18. Santoiemma PP, Powell DJ Jr. Tumor infiltrating lymphocytes in ovarian cancer. Cancer Biol Ther 2015;16:807-20.
19. Martinet L, Garrido I, Filleron T, et al. Human solid tumors contain high endothelial venules: association with T- and B-lymphocyte infiltration and favorable prognosis in breast cancer. Cancer Res 2011;71:5678–87.
20. Fogar P, Sperti C, Basso D, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas 2006;32:22–8.
21. Zhu Y, Zhou S, Liu Y, et al.Prognostic value of systemic inflammatory markers in ovarian Cancer: a PRISMA compliant meta-analysis and systematic review. BMC Cancer 2018;18:443.
22. Jung MR, Park YK, Jeong O, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 2011;104:504–10.
23. Shimada H, Takiguchi N, Kainuma O, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 2010;13:170–6.
24. Cho IR, Park JC, Park CH, et al. Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer 2014;17:703-10.
25. Li QQ, Lu ZH, Yang L, et al. Neutrophil count and the inflammation based glasgow prognostic score predict survival in patients with advanced gastric cancer receiving first-line chemotherapy. Asian Pac J Cancer Prev 2014;15:945-50.
26. Musri FY, Mutlu H, Eryilmaz MK, et al. The neutrophil to lymphocyte ratio is an independent prognostic factor in patients with metastatic gastric cancer. Asian Pac J Cancer Prev 2016;17:1309-12.
27. Ogata T, Satake H, Ogata M, et al. Neutrophil-to-lymphocyte ratio as a predictive or prognostic factor for gastric cancer treated with nivolumab: a multicenter retrospective study. Oncotarget. 2018;9:34520-7.
28. Wang L, Zhang Q, Ni S, et al. Programmed death-ligand 1 expression in gastric cancer: correlation with mismatch repair deficiency and HER2-negative status. Cancer Med 2018;7:2612–20.
29. Takahashi M. [Genetic mutation accumulation and clinical outcome of immune checkpoint blockade therapy] [Article in Japanese]. Gan To Kagaku Ryoho 2016;43:678–82.
30. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, et al. PD-1 blockade in tumors with mismatchrepair deficiency. N Engl J Med 2015;372:2509-20.
31. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415–21.
32. Pereira MA, Ramos MFK, Faraj SF, et al. Clinicopathological and prognostic features of Epstein-Barr virus infection, microsatellite instability, and PD-L1 expression in gastric cancer. J Surg Oncol 2018;117:829–39.
33. Alexandrakis MG, Passam FH, Moschandrea IA, et al. Levels of serum cytokines and acute phase proteins in patients with essential and cancer-related thrombocytosis. Am J Clin Oncol 2003;26:135–40.
34. Bambace NM, Holmes CE. The platelet contribution to cancer progression. J Thromb Haemost 2011;9:237–249.
35. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123–34
36. Kim EY, Lee JW, Yoo HM, et al.The platelet-to-lymphocyte ratio versus neutrophil-to-lymphocyte ratio: which is better as a prognostic factor in gastric cancer? Ann Surg Oncol 2015;22:4363-70.
37. 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;139:164–70.
38. Yodying H, Matsuda A, Miyashita M, et al. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-tolymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2016;23:646-54.
39. Wang Q, Yang Y, Zhang YP, et al. Prognostic value of carbohydrate tumor markers and inflammation-based markers in metastatic or recurrent gastric cancer. Med Oncol 2014;31:289.
40. Dogan M, Eren T, Ozdemir N, et al. The relationship between platelet lymphocyte ratio, neutrophil-lymphocyte ratio, and survival in metastatic gastric cancer on first line modified docetaxel and cisplatinum plus 5- Fluorourasil Regimen: A single institute experience. Saudi J Gastroenterol 2015;21:320-4.
41. Xu Z, Xu W, Cheng H, et al. The Prognostic Role of the Platelet-Lymphocytes Ratio in Gastric Cancer: A Meta-Analysis. PLoS One 2016;11:e0163719.