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Preoperative Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio Cannot Predict Lymph Node Metastasis and Prognosis in Patients with Early Gastric Cancer: a Single Institution Investigation in China

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Summary: In the present study, we aimed at exploring the applied value of preoperative neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in the prediction of lymph node metastasis (LNM) and prognosis in patients with early gastric cancer (EGC). We retrospectively analyzed a total of 248 consecutive patients who underwent curative gastrectomy to be identified T1 stage gastric adenocarcinoma between January 1, 2010 and May 1, 2016 in a single institution. According to median preoperative NLR and PLR value, we divided the patients into four groups: high NLR ≥1.73 and low NLR <1.73, high PLR ≥117.78 and low PLR <117.78. Furthermore, to evaluate the relationship between preoperative NLR and PLR values, we categorized patients according to cutoff preoperative NLR-PLR score of 2 [high NLR (≥1.73) and high PLR (≥117.78)], 1 [either high NLR or high PLR], and 0 [neither high NLR nor high PLR]. Statistical analyses were conducted using SPSS 20.0 software. The results showed that the preoperative NLR or PLR values, lower or higher, could not predict the LNM in patients with EGC (both P=0.544>0.05). The invasive depth of tumor was significantly correlated with LNM of EGC (P<0.001). Kaplan-Meier plots illustrated that preoperative NLR and PLR values were not associated with overall survival (OS) in patients with EGC. It was concluded that the preoperative NLR and PLR may be the predictors for LNM and prognosis in patients with advanced gastric cancer; nevertheless, they cannot predict LNM and prognosis in patients with EGC.

Keywords: early gastric cancer; neutrophil lymphocyte ratio; platelet lymphocyte ratio; lymph node metastasis; prognosis

Gastric cancer (GC) ranks as the fourth among all malignancies and the second leading cause of cancer mortality worldwide[1]. Countries in East Asia (including China, Japan and Korea) have a high incidence of GC (>40 cases/100 000 men), and 47% new cases of GC diagnosed were in China every year[2, 3]. It has been clinically recognized that lymph node metastasis (LNM) is the most important way for GC diffusion and the most significant factors influencing the curative effect and prognosis of GC. The overall 5-year survival rates among GC patients undergoing curative gastrectomy have been reported to be only about 30%[4–6]. Nevertheless, the prognosis of these patients with early GC (EGC), in which the tumors located in mucosal or submucosal of stomach (pT1 stage)[7], has been improved[8].

Inflammation is associated with the development and malignant progression of most cancers[9]. The systemic inflammatory response is clearly associated with the progressive nutritional and functional decline in cancer patients and their subsequent poor outcome[10]. Previous studies suggested that neutrophils, lymphocytes and platelets are important in tumor-induced systemic inflammatory response[11]. Furthermore, increased preoperative NLR and PLR levels have been shown to be correlated with the increase in tumor-induced systemic

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inflammatory response, and independent predictors of outcome amongst several types of cancers[12]. Based on these theories, the relationships between preoperative NLR or PLR and LNM or prognosis in patients with malignancies, including GC, have been researched for many years[13–15]. Moreover, GC is a typical infection and inflammation-driven cancer in which H pylori play a critical role[16]. Up to now, accumulating studies have demonstrated the role of preoperative NLR and PLR in predicting LNM and prognosis patients with resectable GC[15, 17, 18].

The occurrence and progression of GC are complex processes involving multi-factors, and multi-steps. Despite improvements in therapeutic strategies, such as surgical technique and adjuvant chemotherapy, the prognosis of GC patients remains unsatisfactory. The main reason for such low survival is that GC is generally diagnosed at advanced stage. Therefore, better biomarkers are needed to predict GC at its early stage. So far, few studies have assessed the preoperative NLR and PLR and their potential role in LNM and prognosis of EGC. Therefore, the aim of our investigation was to explore the applied value of preoperative NLR and PLR in the prediction of LNM and prognosis in patients with EGC.

1 MATERIALS AND METHODS

1.1 Patients

The present study included patients who fulfilled the following criteria: (1) curative gastrectomy; (2) histopathologically confirmed pT1 gastric adenocarcinoma; (3) available results from preoperative routine blood tests for review. And the exclusion criteria included: (1) preoperative chemoradiotherapy; (2) complicated serious systemic disease; (3) infectious diseases before surgery; (4) a previous history of gastric surgery. We retrospectively enrolled 248 consecutive patients who underwent curative gastrectomy to be identified pT1 stage gastric adenocarcinoma, according to the 7th edition of the American Joint Committee on Cancer and International Union Against Cancer classification for gastric cancer, between January 1, 2010 and May 1, 2016 in the Department of General Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The clinicopathological characteristics of the patients enrolled in the present study are detailed in table 1. The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology.

Table 1 The clinicopathological features of all the patients

Variables	*n* (%)	Variables	*n* (%)
All patients	248	LNM	
Age (years)		N0	192 (78%)
Median (range)	53 (27–86)	N1	28 (11%)
Sex		N2	23 (9%)
Male	153 (62%)	N3	5 (2%)
Female	95 (38%)	AJCC stage	
Tumor location		ⅠA	192 (78%)
Upper	25 (10%)	ⅠB	28 (11%)
Middle	42 (17%)	ⅡA	23 (9%)
Lower	181 (73%)	ⅡB	5 (2%)
Degree of differentiation		Operation method	
Signet ring cell carcinoma	51 (21%)	Proximal gastrectomy	19 (8%)
Poorly	91 (37%)	Distal gastrectomy	180 (72%)
Moderately	65 (26%)	Total gastrectomy	49 (20%)
Highly	41 (16%)	Blood types	
Depth of invasion		O	78 (31%)
pT1a	114 (46%)	A	88 (36%)
pT1b	134 (54%)	B	58 (23%)
		AB	24 (10%)

1.2 Blood Samples and Routine Blood Tests

The peripheral venous blood samples were obtained between 7:00 and 7:30 a.m. before surgery within a week. The samples were collected into a sterile ethylenediaminetetraacetic acid (EDTA) tube. Routine blood tests were performed by electrical impedance with a Beckman coulter LH750 instrument (Beckman Coulter, Inc., USA) within 30 min after collection. The neutrophils, platelets and lymphocytes were counted from the routine blood tests. The NLR or PLR was calculated by dividing the neutrophil or platelet count by the lymphocyte count, respectively. We used the median NLR and PLR values as the cutoff by which the patients were divided into four groups: high

NLR ≥1.73 and low NLR <1.73, high PLR ≥117.78 and low PLR <117.78. Furthermore, to evaluate the relationship between preoperative NLR and PLR values, we categorized patients according to the cutoff preoperative NLR-PLR score of 2 [high NLR (≥1.73) and high PLR (≥117.78)], 1 [either high NLR or high PLR], and 0 [neither high NLR nor high PLR].

1.3 Survival Data

Main survival data were acquired by follow-up. The follow-up protocol included clinical review and telephone follow-up 4 weeks after discharge, then performed every 3 months for the 1st year, every 6 months for the 2nd year, and then annually until the last follow-up. The last follow-up date was September 1, 2016. Survival time was defined as the time from the date of surgery until the patient succumbed or last follow-up. The cancer-specific survival analyses were performed to determine the overall survival (OS).

1.4 Statistical Analysis

Statistical analyses were conducted using SPSS 20.0 software (SPSS, Inc., USA). The associations between preoperative NLR or PLR levels and LNM were explored and assessed by the chi-square tests. Univariate logistic regression analysis was used to examine the effect of variables on LNM. For the analysis of survival data, Kaplan-Meier curves were illustrated, and statistical analysis was carried out using the log-rank test. OS was defined as the time from the date of surgery to death from any cause. Univatiate Cox regression was performed for each outcome parameter, using a backwards elimination technique to derive a potentially suitable set of predictors. All values of $P<0.05$ were considered statistically significant.

2 RESULTS

2.1 Patients' Characteristics

A total of 248 patients who had undergone D2 curative gastrectomy (72% distal gastrectomy, 20% total gastrectomy and 8% proximal gastrectomy) and been histopathologically confirmed EGC were eligible for inclusion in study. The clinicopathological features of all the patients are listed in table 1. Our research comprised 153 males and 95 females, with a mean age of 53 (27–86) years. The most common pathological features included tumors of poorly differentiated type (58%), lower location (73%), N0 (78%), AJCC stage IA (78%).

2.2 Relationship between Preoperative NLR and PLR Levels with Clinicopathological Features

The cutoff values, according to median preoperative NLR or PLR values, were defined as 1.73 and 117.78, respectively. According to these cutoff values, we divided the patients into the four groups: high NLR (NLR ≥1.73) and low NLR (NLR <1.73), high PLR (PLR ≥117.78) and low PLR (PLR <117.78), respectively. As presented in table 2, no significant difference was observed in age, gender, degree of differentiation and tumor location between these four groups. In addition, the different preoperative NLR and PLR levels had no statistically significant differences in depth of invasion (P=0.074>0.05, P=0.610>0.05 respectively), LNM (P=0.544>0.05, P=0.544>0.05 respectively) and AJCC stage (P=1.000>0.05, P=0.229>0.05 respectively).

Table 2 Relationships between preoperative NLR and PLR levels with clinicopathological features

Clinicopathological features	*n*	NLR (*n*)				PLR (*n*)			
		Low	High	χ^2	*P* value	Low	High	χ^2	*P* value
Gender				4.931	0.026			0.017	0.896
Male	153	68	56			77	76		
Female	95	85	39			47	48		
Age(years)				2.573	0.109			0.286	0.593
<65	211	110	101			107	104		
>65	37	14	23			17	20		
Degree of differentiation				0.000	1.000			0.264	0.608
Poorly and Signet ring cell	142	71	71			73	69		
Highly and moderately	106	53	53			51	55		
Tumor location				1.002	0.317			0.020	0.886
Upper and Middle	67	30	37			33	34		
Lower	181	94	87			91	90		
LNM				0.369	0.544			0.369	0.544
Positive	56	26	30			26	30		
Negative	192	98	94			98	94		
Depth of invasion				3.182	0.074			0.260	0.610
pT1a	114	64	50			59	55		
pT1b	134	60	74			65	69		
AJCC stage				0.000	1.000			1.449	0.229
IA, IB	220	110	110			107	113		
IIA, IIB	28	14	14			17	11		

2.3 Risk Factors for Lymph Node Metastasis

According to tables 3 and 4, there was a significant association between depth of invasion and LNM (P<0.001), with a higher positive rate of LNM in pT1b. Nevertheless, high preoperative NLR and PLR levels had no significant relationship with LNM (P=0.977>0.05, and P=0.608>0.05, respectively). Moreover, no significant correlations were found between preoperative NLR-PLR score and LNM (P=0.572>0.05).

Table 3 Risk factors for lymph node metastasis

Variables	LNM		
	OR	95% CI	*P* value
Male	0.541	(0.276–1.060)	0.073
Age >65 years	1.730	(0.720–4.156)	0.220
Poorly differentiated	1.743	(0.859–3.539)	0.124
Lower tumor location	0.729	(0.357–1.488)	0.385
T1b	5.111	(2.439–10.711)	<0.001
High NLR	1.010	(0.509–2.004)	0.977
High PLR	1.191	(0.611–2.323)	0.608

Table 4 Relationship between LNM and preoperative NLR-PLR score

LNM	NLR-PLR score			*P* value
	0 (n=79)	1 (n=90)	2 (n=79)	
Positive	17	18	21	0.572
Negative	62	72	58	

2.4 Correlation between Preoperative NLR and PLR Levels with OS

Of the 248 patients studied, 13 (5.2%) died during the mean follow-up period of 38 months. The Kaplan-Meier plots indicated that preoperative NLR (A) and PLR (B) have no significant correlations with OS of patients with EGC (P=0.124>0.05, P=0.955>0.05 respectively) (fig. 1), moreover, preoperative NLR-PLR score cannot be the predictor of OS (P=0.204>0.05) (fig. 2). As shown in table 5, univariate analysis reveals that 0/10 risk factor affected OS.

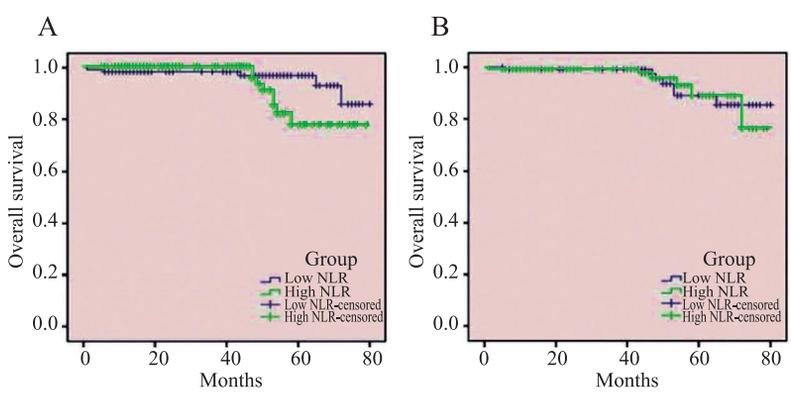

Fig. 1 Kaplan-Meier survival curves for patients with EGC based on preoperative NLR (A) and PLR (B)

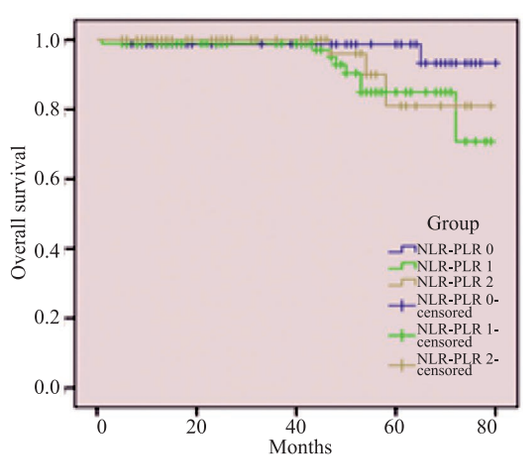

Fig. 2 Kaplan-Meier survival curves for patients with EGC based on preoperative NLR-PLR score

Table 5 Univariate analysis of risk factors for OS

Variables	OS		
	HR	95% CI	*P*
Gender			
(Male or female)	0.464	(0.098–2.207)	0.335
Age			
(<65 or >65 years)	0.452	(0.056–3.667)	0.457
Degree of differentiation			
(Poorly or highly and moderately)	0.837	(0.233–3.004)	0.784
Tumor location			
(Lower or upper and middle)	2.044	(0.612–6.825)	0.245
LNM			
(Positive or negative)	1.235	(0.203–7.505)	0.819
Depth of invasion			
(pT1a or pT1b)	2.259	(0.628–8.120)	0.212
AJCC stage			
(IA, IB or IIA, IIB)	0.817	(0.062–10.804)	0.878
NLR			
(Low or high)	4.645	(0.875–24.661)	0.071
PLR			
(Low or high)	4.008	(0.618–25.985)	0.145
NLR-PLR Score			
(0, 1, 2)	0.130	(0.012–1.374)	0.090

3 DISCUSSION

This study showed that preoperative NLR and PLR have no significant association with LNM in patients with EGC. The invasive depth of tumor was significantly correlated with the LNM of EGC, with a higher positive rate of LNM in pT1b (P<0.001). In addition, neither preoperative NLR nor PLR can predict the OS in patients with EGC.

It is well known that inflammation is the root cause of many cancers[9]. Meanwhile, inflammation also participates in the process of tumor formation and development[19, 20]. It has been accepted that neutrophils, platelets, and lymphocytes play prominent roles in the tumor related inflammation and immunology[11]. More and more articles have been demonstrated that preoperative NLR and PLR, the biomarkers of systemic inflammation, have significant associations with the prognosis of malignancy, particularly with colon, gastric, pancreatic, esophageal, ovarian, lung and breast cancers[21–27]. Indeed, Zhang *et al*[15] have found that a high preoperative NLR might be associated with poor prognosis of patients with GC from a meta-analysis of 10 studies (involving a total of 2952 patients). Zhou *et al*[18] confirmed that high preoperative PLR could serve as an independent unfavorable prognostic factor in patients with resectable GC.

Several mechanisms between inflammation and malignancy have been proposed. At first, tumor microenvironment inhabited by inflammatory cells can enhance tumor progression by increasing cells proliferation and migration[28, 29]. Furthermore, tumor cells and tumor-associated leukocytes could produce various inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and vascular endothelial growth factor. These inflammatory cytokines and chemokines can effectively potentiate cancer growth, invasion, and metastasis[30]. At last, cancer-related inflammation can recruit regulatory T cells and activate chemokines, which suppress antitumor immunity[31, 32]. However, the underlying mechanisms between inflammation and malignancies, especially early tumor, are still poorly understood yet.

Surprisingly, we found that the preoperative NLR and PLR have no significant associations with LNM and prognosis in patients with EGC. Our findings disagreed with those of previous studies, in which preoperative NLR and PLR were significantly related with LNM and prognosis in patients with resectable GC[17, 18].

Karin[33] advocated that inflammation has an influence on the whole progression of tumorigenesis, from initiation through tumor promotion, even to the metastasis progression. What we are interested in is the relationship between preoperative NLR or PLR and LNM and prognosis of EGC, in other words, the interaction between inflammation and tumor initiation along with early period of tumorigenesis. Tumor initiation and early period of tumorigenesis is a process in which normal cells acquire the mutational hit that sends them on the tumorigenic track and mutated cells prepare to proliferate and grow. Grivennikov *et al*[34] asserted that in established tumors, the balance of tumor-promoting inflammation and antitumor immunity is profoundly tilted toward tumor-promoting inflammation, since advanced tumors rarely regress without therapeutic intervention. Nevertheless, it is hardly to unequivocally assess the overall impact of immunity and inflammation on early tumorigenic events, because further suitable models for evaluating the effects of these phenomenon initial tumor growths are nonexistent. According to the consequence of our study, the relationship between inflammation and early growth and LNM of tumor, such as EGC, is still unclear.

In our study, the cutoff values, according to median preoperative NLR or PLR values, were defined as 1.73 and 117.78, respectively. We found that these were significantly lower than the median values in advanced GC (4.02, 208, respectively)[17]. Meanwhile, what we can acquire from Lian *et al*[17] was that our median preoperative NLR and PLR levels of EGC patients are even lower than the healthy subjects (1.73 and 2.18, 117.78 and 140, respectively), which may indicate both a non-heightened neutrophil-dependent or platelet-dependent inflammatory response and a stable lymphocyte-mediated antibacterial immune reaction

promote tumorigenesis in the early period. Thus, it may accept that the sensitivity of prediction, indicated by preoperative NLR and PLR value, was limited in a low level in EGC. Nevertheless, Qian and Pollard demonstrated that at the early stage of the neoplastic progression, inflammation definitely promoted benign neoplasms to cancers[9]. Therefore, more work should be done to explore the interaction between inflammation and early tumorigenic events in the future.

In addition, we found that the invasive depth of tumor is significantly correlated with the LNM of EGC, the deeper the invasion is, the higher the LNM positive rate is (P<0.001). Our findings agreed with these of previous studies[35–37], which advocated that the reason of higher rate of LNM in submucosal carcinoma may be associated with rich submucosal lymphatic capillaries and blood vessels, which are vulnerably invaded by cancer cells.

There are some limitations in our study. First, this was a retrospective study despite comprising a relatively large and consecutive data set. Second, this was a single institution study, which may lead to some potential biases. Third, our study included some censored cases who did not reach 5 years after surgery, and therefore, the results may indicate the possibility of bias in the survival analysis. All in all, a larger sample size prospective multicenter study to confirm our results is warranted; meanwhile, more work is required to elucidate the interplay between inflammation and early tumorigenic processes.

Conflict of Interest Statement

The authors declare no potential conflicts of interest.

REFERENCES

1 Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015,136(5):E359-E386

2 Shen L, Shan YS, Hu HM, *et al*. Management of gastric cancer in Asia: Resource-stratified guidelines. Lancet Oncol, 2013,14(12):e535-547

3 Leung WK, Wu MS, Kakugawa Y, *et al*. Screening for gastric cancer in Asia: Current evidence and practice. Lancet Oncol, 2008,9(3):279-287

4 Bittoni A, Faloppi L, Giampieri R, *et al*. Selecting the best treatment for an individual patient. Recent Results Cancer Res, 2012,196:307-318

5 Wang W, Li YF, Sun XW, *et al*. Prognosis of 980 patients with gastric cancer after surgical resection. Chin J Cancer, 2010,29(11): 923-930

6 Sasako M, Sakuramoto S, Katai H, *et al*. Five year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol, 2011,29(33): 4387-4393

7 Japanese Gastric Cancer Association (2011) Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer, 2011,14(2):101-112

8 Goto A, Nishikawa J, Okamoto T, *et al*. Outcomes of endoscopic submucosal dissection for early gastric cancer and factors associated with incomplete resection. Hepatogastroenterology, 2013,60:46-53

9 Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell, 2010,141(1):39-51

10 McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care, 2009,12(3):223-226

11 Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science, 2011,331(6024):1565-1570

12 Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, *et al*. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol, 2012,23(4):265-273

13 Templeton AJ, McNamara MG, Seruga B, *et al*. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst, 2014,106(6):dju124

14 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(3):170-176

15 Zhang X, Zhang W, Feng LJ, *et al*. Prognostic significance of neutrophil lymphocyte ratio in patients with gastric cancer: a meta-analysis. PLoS One, 2014,9(11):e111906

16 Ilhan N, Ilhan Y, Akbulut H, *et al*. C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. World J Gastroenterol, 2004,10(8):1115-1120

17 Lian L, Xia YY, Zhou C, *et al*. Application of platelet/lymphocyte and neutrophil/ lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. Cancer Biomark, 2015,15(6):899-907

18 Zhou X, Xu L, Huang Z, *et al*. The hematologic markers as prognostic factors in patients with resectable gastric cancer. Cancer Biomark, 2016,17(3):359-367.

19 Kim DK, Oh SY, Kwon HC, *et al*. Clinical significances of preoperative seruminterleukin-6 and C-reactive protein level in operable gastric cancer. BMC Cancer, 2009,9:155

20 Kilincalp S, Ekiz F, Basar O, *et al*. Mean platelet volume could be possible biomarker in early diagnosis and monitoring of gastric cancer. Platelets, 2014,25(8):592-594

21 Walsh SR, Cook EJ, Goulder F, *et al*. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol, 2005,91(3):181-184

22 Gwak MS, Choi SJ, Kim JA, *et al*. Effects of gender on white blood cell populations and neutrophil-lym-

phocyte ratio following gastrectomy in patients with stomach cancer. J Korean Med Sci, 2007,22 Suppl: S104-108
23 Smith RA, Bosonnet L, Raraty M, *et al*. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg, 2009,197(4):466-472
24 Sharaiha RZ, Halazun KJ, Mirza F, *et al*. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol, 2011,18(12):3362-3369
25 Thavaramara T, Phaloprakarn C, Tangjitgamol S, *et al*. Role of neutrophil to lymphocyte ratio as a prognostic indicator for epithelial ovarian cancer. J Med Assoc Thai, 2011,94(7):871-877
26 Kemal Y, Yucel I, Ekiz K, *et al*. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev, 2014,15(6):2651-2654
27 Azab B, Bhatt VR, Phookan J, *et al*. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol, 2012,19(1):217-224
28 Elinav E, Nowarski R, Thaiss CA, *et al*. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer, 2013,13(11):759-771
29 Browder T, Folkman J, Pirie-Shepherd S. The hemostatic system as a regulator of angiogenesis. J Biol-Chem, 2000,275(3):1521-1524
30 Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001,357(9255):539-545
31 Sica A. Role of tumour-associated macrophages in cancer-related inflammation. Exp Oncol, 2010,32(3):153-158
32 Wang DS, Luo HY, Qiu MZ, *et al*. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Med Oncol, 2012,29(5):3092-3100
33 Karin M. Nuclear factor-kappaB in cancer development and progression. Nature, 2006,441(7092):431-436
34 Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell, 2010,140(6):883-899
35 Okabayashi T, Kobayashi M, Nishimori I, *et al*. Clinicopathological features and medical management of early gastric cancer. Am J Surg, 2008,195(2):229-232
36 Skoropad V, Berdov B, Zagrebin V. Clinicopathological features and outcome of surgical treatment of 149 patients with early (pTl) gastric cancer. Onkologie, 2005,28(5):247-252
37 Ye BD, Kim SG, Lee JY, *et al*. Predictive factors for lymph node metastasis and endoscopic treatment strategies for undifferentiated early gastric cancer. J Gastroenterol Hepatol, 2008,23(1):46-50

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