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Differences and Predictive Value for Clinical Staging of Preoperative NLR and PLR in Gastric Cancer Patients

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1. Abstract

1.1. Context: Gastric Cancer (GC) is one of the most prevalent types of malignancies, and its mortality rate ranks third among malignant tumors. The treatment of gastric cancer is mainly divided into surgical treatment, chemotherapy and radiotherapy, etc. Clinically, stage I, II and III tumors are radical resectable tumors and surgical treatment is the first choice, while stage IV tumors are non-radical resectable tumors and non-surgical treatment should be considered first.

1.2. Aims: To explore the differences between the preoperative neutrophil to lymphocyte ratio (NLR) and platelet lymphocyte ratio(PLR)in the clinical stages of gastric cancer(GC). To find a simple and effective preoperative forecast of the clinical staging of gastric cancer and make a preliminary guidance on the treatment.

1.3. Methods and Material: We retrospectively reviewed the clinical data of 370 patients with gastric cancer. By comparing the two groups of patients with preoperative NLR and PLR is statistically significant, these patients were divided into two groups according to the clinical stages. The prediction efficiency of the NLR, PLR and combine the two for the clinical stages of gastric cancer patients was evaluated by calculating the area under curve.

1.4. Statistical Analysis Used: Continuous variables were expressed as mean±standard deviation, and independent sample t test was performed between the two groups. Chi-square test (Fisher's accurate test) was used for the clinical pathological data of the two groups. Use binary logistic regression to further analyze and determine independent risk factors. Preoperative NLR and PLR and other independent clinicopathological characteristics were compared and evaluated by the area under the ROC curve AUC, using Delong test. By calculating Youden index to determine the optimal cut-off value of NLR and PLR before surgery. P<0.05 (two-tailed) was considered to be statistically different, and all statistical analyses were performed by SPSS software (version 23.0).

1.5. Results: Among the 370 patients with GC, the mean values of the NLR and PLR were 3.18 (range 0.56-32.00) and 157.6（range 25.6-795.0）. The mean values of the NLR （2.35±0.96 vs 5.14±4.08, P<0.001）and PLR（134.60±64.11 vs 216.42±152.96, P<0.001）were significantly different in the two groups. The two groups were significantly different in the invasion depth, differentiation, CEA (P < 0.05). The optimal NLR and PLR cutoff values of 2.83 and 139.0 were calculated respectively by using the Youden index. The area under the curve （AUC） of the NLR was 0.852 (95% CI: 0.812 ~0.891), the sensitivity was 79%, and the specificity was 75%, P <0.01. The AUC of the PLR was 0.719(95% CI: 0.509-0.732), the sensitivity was 70%, and the specificity was 66%, P < 0.01.

1.6. Conclusions: Preoperative NLR, PLR and combine the two can predict clinical stages of the GC patients effectively.

2. Key Messages

This is an investigation of the relationship between inflammation-related factors (NLR and PLR) and preoperative clinical staging of gastric cancer. We found that both NLR and PLR are bio-

markers closely related to clinical staging, and NLR is particularly important. This study proves that preoperative NLR and PLR are economical, convenient and reliable tools for predicting clinical stage and it is possible to choose a more reasonable personalized plan for the clinical treatment of gastric cancer patients, especially stage IV patients.

3. Introduction

Gastric Cancer (GC) is one of the most prevalent types of malignancies, and its mortality rate ranks third among malignant tumors [1]. The treatment of gastric cancer is mainly divided into surgical treatment, chemotherapy and radiotherapy, etc. Clinically, stage I, II and III tumors are radical resectable tumors and surgical treatment is the first choice, while stage IV tumors are non-radical resectable tumors and non-surgical treatment should be considered first [2]. At present, Computer Tomography (CT), Magnetic Resonance Imaging (MRI), PET-CT and other inspection methods are commonly used for preoperative clinical staging. There is still a lack of simple and (Table 1) effective preoperative biomarkers that can assist in predicting the clinical stage of gastric cancer patients. In recent years, many studies have shown that systemic inflammatory response is closely related to tumor progression [3], and it has been confirmed that the two inflammation-related markers, NLR and PLR, are closely related to the prognosis of a variety of tumors [4-6]. This study aims to explore the relationship between preoperative NLR and PLR and preoperative clinical staging of gastric cancer to predict the preoperative clinical staging of gastric cancer (Figure 1).

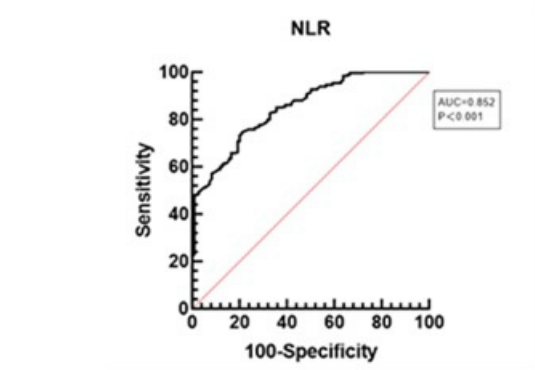

Figure 1: ROC curve for NLR

Table 1: Comparison of the Inflammatory biomarkers between two groups (mean ± standard deviation)

Inflammation indicators	Control group	Observation group
Neutrophil count（×109/L）	3.52±1.28	5.44±2.74*
Lymphocyte count（×109/L）	1.61±0.52	1.26±0.51*
Platelet count（×109/L）	198.48±68.78	228.07±95.69*
NLR	2.35±0.96	5.14±4.08*
PLR	134.60±64.11	216.42±1152.96*

4. Subjects and Methods

4.1. General Information

We retrospectively collected case data of gastric cancer patients from January 2014 to October 2018 in the Department of Gastrointestinal Surgery, Affiliated Hospital of Jiangsu University (Table 2). Inclusion criteria: 1. Patients who were pathologically diagnosed as gastric cancer by gastroscopy before surgery or underwent radical tumor resection and were pathologically diagnosed as gastric cancer after surgery; 2. Patients who were diagnosed with gastric cancer for the first time; 3. Patients who did not receive chemotherapy, blood transfusion, anti-inflammatory and immune treatment before surgery. Exclusion criteria: 1. Gastric cancer complicated with intestinal obstruction, perforation (Figure 2), bleeding and other complications and undergoing emergency surgery; 2. Patients with previous abdominal surgery; 3. Patients with infections, autoimmune diseases, blood system diseases; 4. With other malignant tumors Patients; 5. Patients who take drugs for a long time that affect blood cell values. Finally, 370 patients were included in the study, and the tumor staging was based on the eighth edition of the International Anti-Cancer Alliance. The patients were divided into two groups: the control group (stage I, II, and III) with 260 cases (70.3%) and the observation group (stage IV) with 110 cases (29.7%). Among the 370 gastric cancer patients, 268 were males (72.4%), 102 were females (27.6%), and their age was 64.7±10.1 years (27-67 years) (Table 3).

4.2. Clinical Parameters

Collect general clinical information of patients, including age, gender, pathological type, degree of differentiation, depth of infiltration, etc.

4.3. Obtaining Blood Data

Collect the patient's peripheral blood test results 3-4 days before surgery, including white blood cell, neutrophil, lymphocyte and platelet counts, and Carcinoembryonic Antigen (CEA) levels.

5. Statistical Methods

Continuous variables were expressed as mean±standard deviation, and independent sample t test was performed between the two groups. Chi-square test (Fisher's accurate test) was used for the clinical pathological data of the two groups. Use binary logistic regression to further analyze and determine independent risk factors. Preoperative NLR and PLR and other independent clinicopathological characteristics were compared and evaluated by the area under the ROC curve AUC, using Delong test. By calculating Youden index to determine the optimal cut-off value of NLR and PLR before surgery. $P<0.05$ (two-tailed) was considered to be statistically different, and all statistical analyses were performed by SPSS software (version 23.0) (Figure 3).

Table 2: Univariate analysis for clinicopathologic features between two groups

Clinical factors	quantity	Control group	Observation group	χ2 value	P value
Gender				2.951	0.127
Male	268	182	86		
Female	102	78	24		
Age				5.407	0.023
＜65y	179	136	43		
≥65y	191	124	67		
Degree of infiltration				54.925	0.000*
No invasion of the serosal membrane	101	100	1		
Invasion of extraserous membrane	269	160	109		
Differentiation				14.384	0.000*
Moderate to well differentiated	130	108	22		
Poorly differentiated	240	152	88		
NLR value				94.891	0.000*
Low group	216	194	22		
High group	154	66	88		
PLR value				41.993	0.000*
Low group	203	171	32		
High group	167	89	78		
CEA value				10.955	0.001*
＜5ng/ml	266	200	66		
≥5ng/m	104	60	44		

Table 3: Multivariate analysis to evaluate potential predictive factors for clinical staging and scoring for every item

Clinical factors	multi-factor analysis			Risk score
	P	95%CI	OR	
Degree of infiltration				
No invasion of the serosal membrane				
Invasion of extraserous membrane	0	5.059~289.236	38.254	15.8
Differentiation				
Moderate to well differentiated				
Poorly differentiated	0.046	1.012~3.697	1.934	2.7
NLR value				
Low group				
High group	0	3.868~13.305	7.174	8.6
PLR value				
Low group				
High group	0.027	1.079~3.560	1.96	2.9
CEA value				
＜5ng/ml				
≥5ng/m	0.892	0.529~1.741	0.959	-0.2

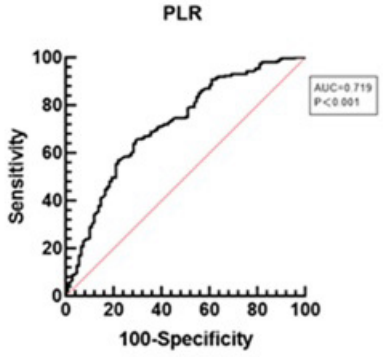

Figure 2: ROC curve for NLR

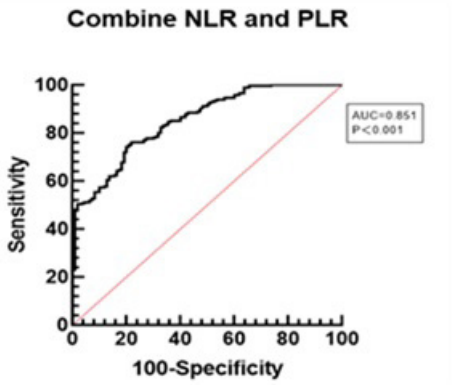

Figure 3: ROC curve for combine NLR and PLR

6. Results

6.1. The Difference Between the Two Groups of Inflammation Indicators

The mean ± standard deviation of the preoperative peripheral blood neutrophil, lymphocyte and platelet counts of 370 patients enrolled in this study were (4.09 ± 2.03) × 109 / L, (1.51 ± 0.54) × 109 / L, (207.28±78.80) ×109/L. In the comparison between the two groups, there were significant differences in the counts of neutrophils, lymphocytes and platelets (P<0.01). The NLR of the observation group was significantly higher than that of the control group (5.14±4.08 vs 2.35±0.96, P=0.000, and the preoperative PLR of the observation group was significantly higher than that of the control group (216.42±152.96 vs 134.60±95.69, P=0.000), and the difference was statistically significant.

Independent sample t test, * P＜0.01 is considered statistically significant (Figure 4).

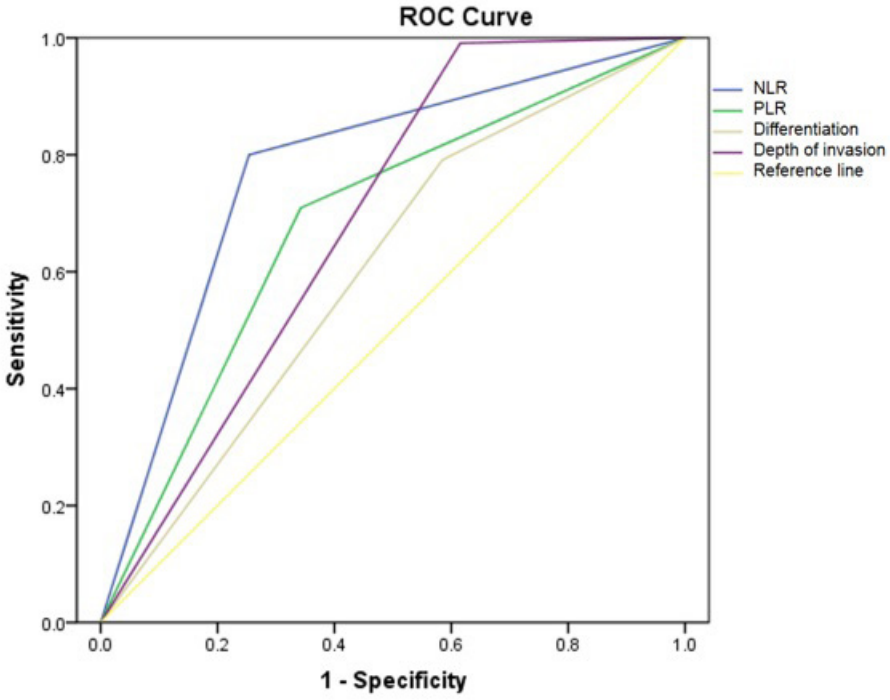

Figure 4: Comparison of ROC curves for NLR, PLR, depth of invasion and differentiation

6.2. Optimal Thresholds for NLR and PLR

The 95% Confidence Interval (CI) was used to express. In this study, by analyzing the ROC curve, the area under the curve (AUC) of the NLR before surgery was 0.852 (95% CI: 0.812 ~ 0.891), the sensitivity was 79%, the specificity was 75%, and P <0.001. The AUC of preoperative PLR was 0.719 (95% CI: 0.662~0.777), the sensitivity was 70%, the specificity was 66%, and P <0.001. The Youden Index shows that the optimal cut-off values for NLR and PLR are 2.83 and 139.0, respectively. Cases were divided into high NLR group (≥2.83) and low NLR group (<2.83), as well as high PLR group (≥139.0) and low PLR group (<139.0) by cut-off value. The numbers of patients in the high NLR group and high PLR group were 154 (41.6%) and 167 (45.1%), respectively.

From the above-mentioned area under the ROC curve of NLR and PLR, it can be concluded that NLR and PLR have certain diagnostic value in the diagnosis of gastric cancer staging. Further

regression analysis of the two can be obtained NLR (OR=3.04, P<0.001), PLR (OR=1.99, P<0.05), both of which are independent predictors of clinical staging, so the ROC curve is analyzed again for the regression results. The AUC of NLR combined with PLR to predict clinical staging is 0.851. It can be concluded that NLR and NLR combined with PLR have relatively high diagnostic value for the staging of gastric cancer.

6.3. Univariate and Multivariate Analysis Related To The Observation Group (Phase IV)

Univariate analysis showed that preoperative high PLR group, high NLR group, depth of invasion, degree of differentiation, and CEA were significantly related to clinical staging. However, gender and age are not significantly related to clinical grouping.

Note: * P＜0.01 is considered statistically significant.

Further logistic regression analysis showed that extraserous invasion (OR=38.254, P <0.001), poorly differentiated (OR=1.934, P=0.046), NLR≥2.83 (OR=7.174, P＜0.001), PLR≥139.0 (OR= 1.960, P=0.027), CEA≥5ng/ml (OR=0.959, P=0.892), in which infiltration will extra-membrane, poorly differentiated, high-group NLR and high-group PLR are independent predictors of clinical staging. According to the logistic regression analysis results, the risk coefficient is marked for each independent risk factor and the risk ratio is logarithmic transformed and then multiplied by 10 (n=10×log(X), X=OR) to calculate the predictive scoring system. Analysis of the ROC curve results for these predictors showed that the preoperative NLR AUC after the cut-off value grouping was 0.773 (95% CI: 0.720 to 0.826) than the PLR AUC after the preoperative grouping was 0.624 (95% CI: 0.624 to 0.743) , The depth of invasion AUC=0.688 (95% CI: 0.635~0.741), the degree of differentiation AUC=0.603 (95% CI: 0.542~0.664), which has better accuracy in predicting clinical staging.

Note: OR= odds ratio; * P＜0.05 is considered statistically significant

Note: (the low and high groups) NLR AUC=0.77(95% CI:0.720~0.826), (the low and high groups) PLR AUC=0.683(95% CI:0.624~0.743), depth of invasion

AUC=0.688(95% CI:0.645~0.798), differentiation

AUC=0.603(95% CI:0.542~0.664)

7. Discussion

The clinical staging of gastric cancer patients is closely related to its prognosis [7]. It is of great significance to improve the accuracy of clinical staging before surgery. It helps predict clinical gastric cancer stage IV cases, improves accuracy, and can provide correct and individualized treatment plans [8].

Systemic inflammation plays an important role in tumor formation, progression and metastasis [9,10]. Inflammation plays a key role in repairing tissue damage caused by tumors, and this inflammatory response is very important in the tumor microenvironment [11]. Cancer cells can produce a variety of tumor-related inflammatory factors, such as interleukin-1, interleukin-3 and interleukin-6, tumor necrosis factor-α causes neutrophils and thrombocytosis [12-14]. The upregulation of neutrophils leads to DNA damage and peripheral genome instability, promotes carcinogenesis and helps establish the tumor microenvironment [15]. Tumor progression up-regulates peripheral platelets through growth factors secreted by activated platelets, which in turn protects tumor cells from immune attack, promotes tumor cell growth, and enhances tumor proliferation and metastasis [16]. Compared with neutrophils and platelets, lymphocyte reaction is the main anti-cancer factor, providing immune surveillance and inhibiting tumor development [17]. The active immune response reflects the degree of tumor lymphocyte infiltration, which greatly increases the survival of various tumors [18]. Therefore, the down-regulation of peripheral lymphocytes may lead to insufficient immune response to tumor cells. Summarizing these factors, tumor-related inflammation leads to neutrophils, thrombocytopenia, and lymphocyte reduction, which promote tumor growth and metastasis, leading to a poor prognosis. The preoperative Neutrophil to Lymphocyte Ratio (NLR) and Platelet Count to Lymphocyte Ratio (PLR) are easy to calculate from the neutrophil, platelet, and lymphocyte counts in the routine preoperative blood test, which is simple and economical. These two biomarkers have confirmed that they are prognostic indicators for many types of tumors [19-21]. However, few articles mention the correlation between NLR and PLR and the clinical staging of gastric cancer.

In this study, we discovered the predictive effect of NLR and PLR on the clinical staging of gastric cancer. We found that the distribution of PLR and NLR in gastric cancer clinical stage IV and I/II/III stages are significantly different, and there is a statistical difference between them. We can use ROC curve analysis to conclude that both NLR and PLR have diagnostic value for gastric cancer staging, and NLR and NLR combined with PLR have higher diagnostic accuracy for staging. The cut-off value was determined by ROC curve. In univariate analysis, both high NLR and high PLR were related to clinical stage. In multivariate analysis, both high NLR and high PLR proved to be independent risk factors. Therefore, we conclude that NLR and PLR can be used as predictors of gastric cancer clinical staging.

This is an investigation of the relationship between inflammation-related factors (NLR and PLR) and preoperative clinical staging of gastric cancer. We found that both NLR and PLR are biomarkers closely related to clinical staging, and NLR is particularly important. This study proves that preoperative NLR and PLR are economical, convenient and reliable tools for predicting clinical stage and it is possible to choose a more reasonable personalized plan for the clinical treatment of gastric cancer patients, especially stage IV patients.

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