Original Article
Neutrophil/lymphocyte ratio predicts lymph node metastasis in patients with gastric cancer

Houhong Wang[1*], Huihui Gong[2*], Amao Tang[3], Yayun Cui[4]

[1]Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, Bozhou 236800, Anhui, China; [2]Faculty of Health and Life Sciences, Oxford Brookes University, Oxford OX3 0BP, United Kingdom; [3]Department of Gastroenterology, The Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; [4]Department of Cancer Radiotherapy, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China (Anhui Provincial Cancer Hospital), Hefei 230031, Anhui, China. *Equal contributors.

Abstract: Objective: To identify the independent risk factors of gastric cancer (GC) lymph node metastasis and to determine whether the preoperative neutrophil and lymphocyte ratio (NLR) and the platelet and lymphocyte ratio (PLR) can be used as the indicators of gastric cancer lymph node metastasis. Methods: The pathological data of 221 patients with gastric cancer were retrospectively analyzed, and the risk factors of lymph node metastasis were evaluated. The relationship between preoperative NLR and PLR and the clinical pathology of patients were analyzed, and the effect of these two indexes on lymph node metastasis was predicted through receiver operating characteristic (ROC) curve. Results: Lymph node metastasis correlated with tumor diameter, depth of invasion, Tumor-Node-Metastasis (TNM) stage, preoperative NLR and preoperative PLR (all P<0.05), but not with gender, age and tumor location (all P>0.05). According to the result of multivariate analysis, the degree of differentiation, depth of invasion, TNM staging and NLR were independent risk factors for GC lymph node metastasis. Conclusion: The sensitivity and specificity of PLR, tumor staging and tumor size are lower than NLR. Preoperative NLR can be used as an independent risk factor for the prediction of lymph node metastasis, and one of the effective indicators for predicting the prognosis of patients. Preoperative NLR may be an effective auxiliary tool to assess lymph nodes in GC patients.

Keywords: Lymph node metastasis, NLR, PLR, prognosis

Introduction

Gastric cancer (GC) is a highly malignant tumor of the digestive tract, and the third risk factor of tumor death in the world [1, 2]. Limited by the current gastric cancer screening methods, the detection rate of early gastric cancer in China only accounts for about 20% of new onset gastric cancers, about 80% of gastric cancers are already in the advanced stage when they are diagnosed, and the overall survival rate is less than 50% [3]. The lymph node metastasis is the main and impressive factor for the prognosis of GC [4]. Accurate assessment of lymph node metastasis before surgery is of great value for the selection of surgical methods and the evaluation of the prognosis of gastric cancer [5].

Inflammation is one of the hallmark features of tumors, and the body's inflammatory response reflects the nonspecific response of tumor tissue to hypoxia, tissue damage, and necrosis [6]. In the early stage of tumors, cytokines promote the massive accumulation of inflammatory cells around the tumor, providing a very favorable tumor microenvironment for tumor initiation and progression, thereby promoting tumor angiogenesis, cell proliferation, and metastasis [7]. At present, a large number of studies have shown that inflammation plays a key role in the occurrence and development of tumors, especially in tumor invasion and metastasis to other organs and lymph nodes, which is directly related to the prognosis of patients [8]. Therefore, identification of the inflammation

markers, which are closely related to tumor occurrence and development, has become the focus of research.

White blood cells such as neutrophils are markers of inflammation [9]. Neutrophils can produce cytokines to stimulate tumor blood vessel growth, promote tumor progression, and enhance tumor metastasis and invasiveness [10]. On the other hand, neutrophils, as an inflammatory cell, can inhibit lymphocytes [11]. Activated T cells and natural killer cells can suppress the immune system and reduce the body's immune defense capabilities. Compared with the traditional single inflammatory indicators such as white blood cells, neutrophils, lymphocytes, and monocytes, more attention has been paid to the composite indicators of inflammation such as NLR and PLR in tumor applications [12, 13]. Studies have found that the increase in NLR and PLR are prognostic factors for many malignant tumors [14, 15]. Therefore, the present study aimed to investigate the association between NLR or PLR and the prediction of the lymph node metastasis.

Materials and methods

General data

This is a retrospective study. Data of 221 GC patients admitted to our hospital from January 2018 to January 2021 were collected. All study subjects had provided informed consent form, and the research was also reviewed and approved by the Medical Ethics Committee of Affiliated Bozhou Hospital of Anhui Medical University (Bozhou Hospital Ethical Approval-2022-17). The influencing factors that were observed and recorded were the patient's gender, age, tumor size, degree, depth of invasion, Tumor-Node-Metastasis (TNM) staging, preoperative NLR and preoperative PLR. Specifically: gender (male/female), age (<60/≥60), tumor diameter (<4/≥4), tumor location (cardia/gastric body), depth of invasion, TNM staging (I-II/III-IV), preoperative NLR (<2.26/≥2.26) and preoperative PLR (<142.37/≥142.37).

Inclusion and exclusion criteria

The inclusion criteria are as the following: diagnosed as gastric cancer by pathology or imaging; no active bleeding or coagulation dysfunction within four weeks before surgery, and no blood transfusion treatment; no other tumor-related medical history; no serious perioperative complications; Not accompanied by other serious organic diseases.

Exclusion criteria: Active infection; Chronic inflammatory; Long-term use of steroids or immunosuppressants; Hematological diseases, preoperative data is not adequate; Collect patients including gender, age, tumor location, and clinical data mainly include tumor size, depth of tumor invasion, lymph node metastasis and TNM staging. We collected the routine blood indicators before surgery, such as neutrophil and lymphocyte count, platelet count, and calculate NLR and PLR.

Research content

Univariate analysis of the relationship between lymph node metastasis in this kind of patients and gender, age, tumor diameter, tumor location, depth of invasion, TNM stage, NLR and PLR. Multivariate variable assignment of lymph node metastasis (LNM) in GC patients. Receiver operating characteristic (ROC) curve analysis NLR and PLR were used to predict the area under the curve (AUC) of lymph node metastasis (LNM), the sensitivity and specificity of it.

Statistical methods

Experiment data were analyzed using SPSS-20.0 software. Chi-square test was used to analyze the relationship between GC lymph node metastasis and clinical and pathological characteristics, significant difference was judged based on P<0.05. The clinical variables with result of P<0.05 were included into the multivariate logistic regression analysis. GraphPad was used to draw ROC to judge the predictive function of NLR.

Results

Univariate analysis of lymph node metastasis in patients with gastric cancer

Lymph node metastasis in patients with GC was related to tumor size, tumor location, depth of invasion, TNM stage, and preoperative NLR and PLR (all P<0.05), but has no relation with gender and age, such as (**Table 1**) shows.

Multivariate analysis of lymph node metastasis

The variable assignments of multivariate analysis are shown in **Table 2**, according to the result,

Table 1. Univariate analysis of factors affecting lymph node metastasis

Factor		Lymph node metastasis		χ^2	P
		LN (-, n = 56)	LN (+, n = 165)		
Gender	Male	37	91	0.716	0.529
	Female	28	65		
Age	<60	39	62	0.485	0.637
	≥60	45	75		
Tumor diameter (mm)	<4	23	46	23.257	<0.001
	≥4	60	92		
Tumor location	Cardia	17	30	4.864	0.027
	Gastric body	69	105		
NLR	<2.26	29	59	32.693	<0.001
	≥2.26	53	70		
PLR	<142.37	32	49	7.974	0.039
	≥142.37	51	89		
Infiltration depth	T1-T2	27	47	35.863	<0.001
	T3-T4	53	94		
TNM staging	I-II	38	43	36.286	<0.01
	III-IV	45	95		

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging.

Table 2. Variable assignment table for multivariate analysis

Factor	Variable	Assignment
Gender	X1	Male = 1, Female = 2
Age	X2	<60 y = 1, ≥60 y = 2
Tumor diameter	X3	<4 mm = 1, ≥4 mm = 2
Tumor location	X4	Cardia = 1, Gastric body = 2
NLR	X5	<2.26 = 1, ≥2.26 = 2
PLR	X6	<142.37 = 1, ≥142.37 = 2
TNM staging	X7	I-II = 1, III-IV = 2
Infiltration depth	X8	T1-T2 = 1, T3-T4 = 2

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging.

it can be inferred that tumor size, TNM stage, depth of invasion and preoperative NLR were risk factors for GC (**Table 3**).

ROC curve analysis result

The AUC for predicting lymph node metastasis by preoperative NLR was 0.729 (0.576-0.881), the best cut-off value was 2.26, the sensitivity was 90.0%, and the specificity was 21.5%. The sensitivity and specificity of PLR, tumor staging and tumor size are lower than NLR (**Table 4**; **Figure 1**).

Predictive of NLR in subsets of patients

We performed the analysis in the different subgroups of patients to explore the association between NLR and lymph node metastasis. The results are presented in the **Figure 2**. We found that high level of NLR was significantly associated with the status of the lymph node. Patients with a high level of NLR were at high risk of lymph node metastasis.

A nomogram to predict the lymph node metastasis

After having obtained the independent risk factors for the lymph node metastasis in multivariate analysis, we used the tumor diameters, NLR and tumor stage to perform the nomogram analysis. The nomogram for the prediction of the lymph node metastasis are presented in the **Figure 3**.

Lymph node metastasis and survival of patients

All included patients were followed for their survival status. Then we performed the survival

Table 3. Multivariate analysis of factors affecting lymph node metastasis in GC patients

Factor	B	SE	Wald χ^2	P	OR	95% CI
Tumor diameter	1.512	0.725	5.846	0.019	2.896	1.354-7.231
Tumor location	0.472	0.479	0.832	0.673	1.298	0.325-2.896
NLR	1.326	0.489	5.635	0.019	2.853	1.563-7.025
PLR	0.284	0.376	0.618	0.594	1.627	0.386-2.637
TNM staging	1.864	0.896	7.986	0.015	3.428	1.386-6.297
Infiltration depth	1.196	0.378	5.365	0.023	2.426	1.065-5.276

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging; OR, Odds Ratio; CI, Confidence Interval.

Table 4. NLR and PLR predictive value of gastric cancer prognosis

Index	Optimal threshold	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Positive value (%)	Negative value (%)
NLR	2.38	0.736 (0.529-0.916)	81.7	32.6	81.4	92.5
PLR	136.25	0.533 (0.386-0.662)	72.8	29.3	52.6	89.6
TNM staging	37.5	0.426 (0.312-0.587)	75.3	28.4	54.1	75.6
Tumor diameter	49.3	0.398 (0.256-0.572)	65.1	31.8	42.9	78.2

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging; AUC, Area Under the Curve; CI, Confidence Interval.
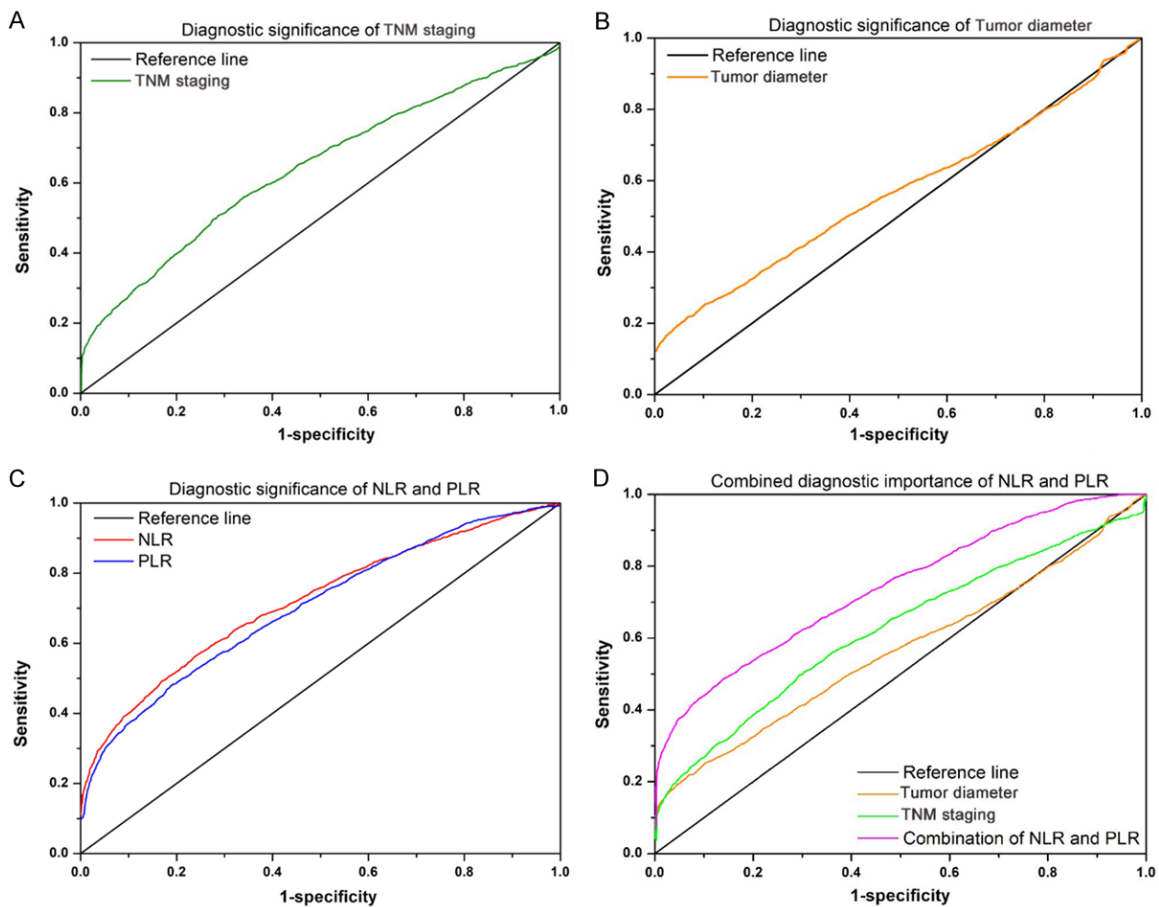
Figure 1. The receiver operating characteristic curve of the (A) TNM staging, (B) tumor diameter, (C) NLR/PLR, and (D) the combining NLR and PLR. Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging.
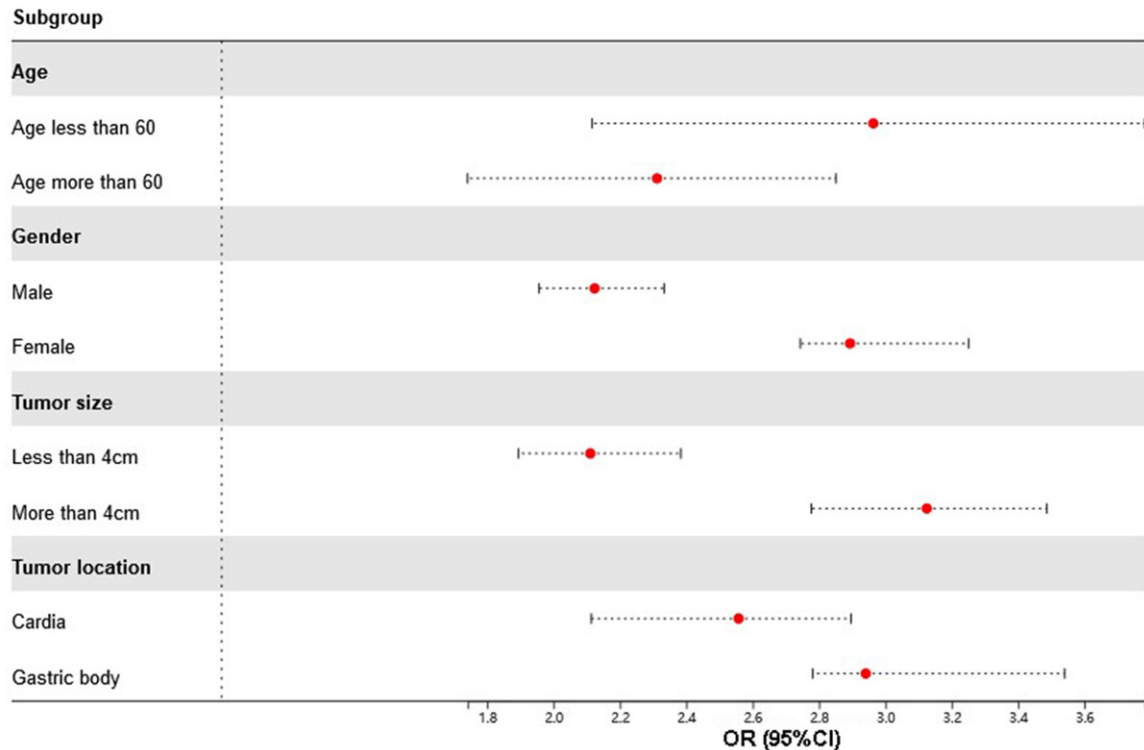
Figure 2. Subgroup analysis of the predictive value of NLR. Abbreviation: NLR, Neutrophil/Lymphocyte Ratio.

analysis to explore if the lymph status was associated with the survival of the patients. The results are presented in the **Figure 4**. As the Kaplan-Meier (KM) curve showed, significantly worse survival was observed in patients with the lymph nodes metastasis.

NLR/PLR and survival of patients

We subsequently explored the clinical factors that were associated with the survival of the patients. Survival analysis with Cox regression analysis was performed. The univariate analysis showed that both NLR and PLR were associated with the overall survival (**Table 5**). The multivariate analysis showed that the tumor diameters, tumor location, NLR, tumor stage, and infiltration depth were independently associated with the survival of patients (**Table 6**).

Discussion

It was previously found that the proportion of neutrophils in peripheral blood increased in patients with advanced cancer, and regression analysis confirmed the correlation between NLR and the prognosis of GC patients. In recent

years, the effect and mechanism of inflammatory factors on occurrence and development of cancer has attracted more and more attention [16-18]. Although the mechanism by which neutrophils affect gastric cancer is not fully understood, it is clinically believed that neutrophils can release cell growth factors, oxygen free radicals, proteases, chemokines and other components, and activate related nuclear factors to promote tumor cells growth [19, 20]. At the same time, neutrophils can also inhibit the body's immune response to tumor cells by secreting inflammatory factors, promote angiogenesis around the tumor and induce tumor cell metastasis [21-26]. Lymphocyte is a key link in human cellular immunity and humoral immunity, and it has a certain inhibitory effect on the proliferation of cancer cells, as well as hinders the metastasis of cancer cells. Therefore, the balance of inflammatory environment and anti-tumor immunity on tumor growth can be reflected by NLR [27-30].

As an indicator of inflammatory response, NLR can predict the gastric cancer risk effectively and a higher PLR also indicates a poor prognosis for GC [31-36]. It has been shown that
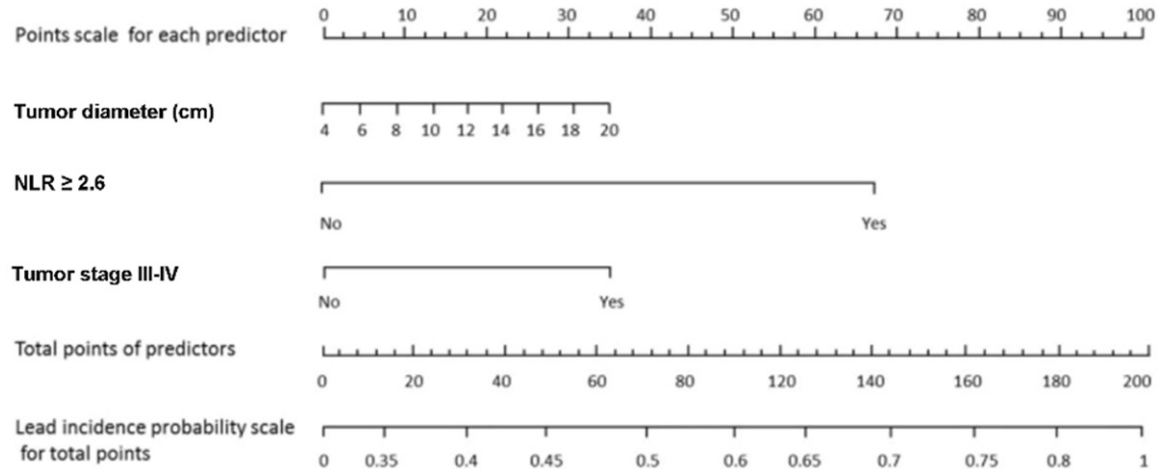
Figure 3. Nomogram for the prediction of lymph node metastasis. Abbreviation: NLR, Neutrophil/Lymphocyte Ratio.
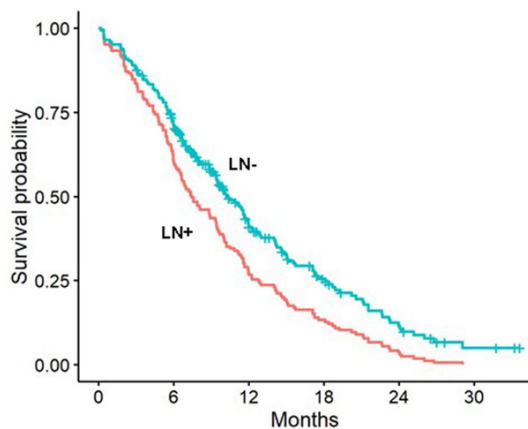
Figure 4. Kaplan-Meier curve of survival for the lymph node metastasis. Abbreviations: LN+, Lymph Node positive; LN-, Lymph Node negative.

Table 5. Univariate analysis of factors affecting survival in patients with gastric cancer

Factor	P	HR	95% CI
Age	0.084	1.231	0.887-1.557
Gender male	0.241	1.521	0.674-1.941
Tumor diameter	0.002	2.212	1.776-2.743
Tumor location	0.013	1.894	1.234-2.412
NLR	0.001	2.412	1.447-3.312
PLR	0.023	1.723	1.212-2.561
TNM staging	0.004	1.852	1.652-2.345
Infiltration depth	0.003	2.144	1.899-2.564

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging; HR, Hazard Ratio; CI, Confidence Interval.

inflammation caused by tumors may lead to changes in NLR. A low NLR indicates that the tumor is in non-active state, and thus a better prognosis of tumor patients. A higher NLR indicates the risk of tumor recurrence, and the preoperative and postoperative NLR values are equally important. Shimada et al. The preoperative average NLR of lymph nodes in GC was significantly higher than that in N0 patients, but they have not studied the predictive ability of NLR in lymph node metastasis in detail [37-39].

In this study, Tumor diameter, TNM stage and preoperative NLR were risk factors for gastric cancer lymph node metastasis. Although previous studies have shown the association between both NLR and PLR and the prediction of the lymph node metastasis [40]. However, in our study, the multivariate analysis result showed that there is no correlation between lymph node metastasis and PLR in gastric cancer. This is possibly due to the fact that small number of patients with gastric cancer were tested before surgery. The AUC for predicting lymph node metastasis by preoperative NLR was 0.729 (0.576-0.881), the sensitivity is 90.0%, while specificity is 21.5%. The limit values of NLR and PLR were determined based on ROC. The sensitivity of PLR, tumor staging and tumor size are lower than NLR. This is more objective for the assessment of lymph node metastasis in GC patient. Additionally, we found there was a significant higher predictive value when we combined NLR and PLR together for the prediction of lymph node metastasis than the TNM staging and also tumor diameter. To

Table 6. Multivariate analysis of factors affecting survival in patients with gastric cancer

Factor	P	HR	95% CI
Tumor diameter	0.003	2.344	1.987-2.784
Tumor location	0.002	2.564	1.452-3.122
NLR	0.003	2.512	1.347-3.411
PLR	0.052	1.621	0.798-2.322
TNM staging	0.004	1.859	1.655-2.447
Infiltration depth	0.002	2.213	1.778-2.664

Abbreviations: NLR, Neutrophil/Lymphocyte Ratio; PLR, Platelet/Lymphocyte Ratio; TNM staging, Tumor-Node-Metastasis staging; HR, Hazard Ratio; CI, Confidence Interval.

the best of our knowledge, this is the first study for the evaluation of the predictive value with the combination of the NLR and PLR in the clinical practice.

There exist some limitations for this study and the specific mechanism of the relationship between NLR, PLR and LNM has not been clarified. However, routine blood testing is simple, fast, low-cost, and does not increase the patient's physical pain and economic burden. The preoperative blood routine testing obtains NLR and PLR, which can be applied to assess LNM in patients with GC and guide surgery. There was one more limitation that we could not prove that NLR is just a proxy or a true prognostic indicator of more chance of lymph node metastasis in gastric cancer, which needs further exploration.

Conclusion

In summary, the lymph node metastasis of GC is related to many factors. Preoperative NLR can predict that precisely, and the increase of NLR is related to the aggressiveness of the tumor. Therefore, besides other factors, NLR and related inflammatory indicators should be tested to guide the treatment plan. This study affirmed the value of preoperative NLR in evaluating the prognosis of GC patients, but meanwhile, other immunonutritional indicators (such as prognostic nutritional index) may also be useful predictors of lymph nodes. The proper NLR threshold needs to be verified in further studies with a larger sample size.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Yayun Cui, Department of Cancer Radiotherapy, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China (Anhui Provincial Cancer Hospital), Hefei 230031, Anhui, China. E-mail: svqr93@163.com

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