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Original Article

Clinical value of neutrophil/lymphocyte ratio in predicting postoperative complications, lymph node positivity and prognosis in gastric cancer patients who underwent curative surgical resection

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Abstract

Aim: In this study, we aimed to determine the clinical value of neutrophil / lymphocyte ratio (NLR) in predicting postoperative complications, lymph node positivity and prognosis in patients who underwent curative surgical resection.

Material and Methods: Patients who underwent total gastrectomy for gastric adenocarcinoma between 2015 and 2018 were included in the study. Two groups, Group 1 (LowNLR) and Group 2 (HighNLR), were formed. Demographic and clinical characteristics, intraoperative and postoperative outcomes, and mean survival were compared. The value of NLR in predicting lymph node positivity and postoperative complications was evaluated at the cutoff value determined for NLR.

Results: Patients were divided into two groups according to the cutoff value of 2.14. Group 1 consisted of 36 patients and Group 2 consisted of 68 patients. Female sex was higher in Group 2 (72% vs 52%) (p:0.41). Postoperative complication rates according to Clavien Dindo classification were similar (p:0.9). The number of dissected positive lymph nodes was higher in Group 2 than in Group 1 (9 vs 6) (p:0.041). Pathological stage (p:0.188), and overall survival (24.61vs21.12,p:0.206) were similar between the groups. We found NLR as a risk factor for survival in multivariate analysis (HR=0.255, 95%CI: 0.024–0.427, p:0.029). If the NLR value was less than 2.14, the patient had According to Clavien Dindo classification Grade 2 and above complications, with a sensitivity of 46.3% and specificity of 76.0%. A positive lymph node was detected with 44.26% sensitivity and 65.12% specificity.

Conclusion: Preoperative high NLR is a risk factor for survival in patients with gastric cancer. High NLR is also closely associated with the risk of postoperative complications.

Keywords: Gastric cancer; neutrophil lymphocyte ratio; postoperative complication.

INTRODUCTION

Despite its reduced incidence in recent years, gastric cancer (GC) remains a major health problem worldwide (1). According to the World Health Organization's GLOBOCAN database, it is the fifth most common cancer worldwide, with approximately one million (952,000) new cases diagnosed each year and were the third leading cause of cancer deaths in 2012 (723,000 deaths) (2). Looking at the 2015 statistics of Turkey, while gastric cancer incidence was 14.2/100,000 in men and 6.3/100,000 in women; in the order of frequency of cancer-related deaths, it was 2nd in men and 4th in women (3). Despite the rapid developments in surgery, chemotherapy and molecular therapy in recent years, the clinical outcome of GC is still not promising.

It is increasingly recognized that changes in clinical outcomes in cancer patients are influenced not only by the oncological characteristics of the tumor, but also by host response factors (4).

The possibility of combining a large number of clinically available host and tumor-related factors is of great interest as it can provide an excellent basis for clinical decision making, treatment planning, and follow-up plans (5).

Inflammation response plays a key role in tumor formation and progression. Cancer-related inflammation can cause DNA damage, promote angiogenesis and cell proliferation,

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affect tumor cell invasion and metastasis, so estimating inflammation through circulating inflammatory cells may indirectly reflect the severity and prognosis of the neoplasm (6,7).

The first study on NLR and gastric cancer was published in 1998 (8). After that, many studies have shown that a high NLR is associated with poor prognosis in gastric cancer patients (6,9).

In this study, we aimed to determine the clinical value of neutrophil / lymphocyte ratio in predicting postoperative complications, lymph node positivity and prognosis in patients who underwent curative surgical resection.

MATERIAL and METHODS

After obtaining permission from the Ethics Committee of Çukurova Univesity Faculty of Medicine dated 04.09.2019 and numbered 91/25, 104 patients who underwent total gastrectomy for gastric adenocarcinoma between January 2015 and October 2018 were included in the study. A common database was created by examining patient files and hospital information system records. Patients were analyzed retrospectively using this database. Patients who underwent palliative surgery, with Stage 4 disease, who were pregnant, and they had chronic inflammatory (Tuberculosis, Sarcoidosis), autoimmune diseases, hematologic diseases, steroid use, those whose records couldn't be reached and with a pathological diagnosis other than adenocarcinoma were excluded from the study. Cut off value was determined by ROC curves and the cases were divided into two groups according to the cutoff value, Group 1 (Low NLR) and Group 2 (High NLR). Demographic characteristics, body mass index (BMI), American Society of Anesthesiologists (ASA) score, neoadjuvant treatment status, type and nature of the operation, tumor localization, and pathological stage of the tumors were recorded. The groups were compared in terms of total and metastatic lymph nodes removed, pathological stage, operation time, mean blood loss, mean time to onset of oral intake, postoperative complication status according to Clavien Dindo classification (10), anastomosis leakage rate, postoperative hospital stay, 30-day mortality, 30-day re-hospitalization and overall survival. The value of NLR in predicting lymph node positivity and postoperative complications was evaluated at the cutoff value determined for NLR.

Tumor-nod-metastasis (TNM) 2010 and 2016 systems were used for tumor staging.

Unplanned hospitalization within the first 30 days after discharge was accepted as unplanned re-admission to hospital.

Anastomosis leakage was defined as deterioration in the integrity of the anastomosis documented by the combination of clinical, radiological and operative tools.

Wound infection was defined as superficial or deep incisional surgical site infection according to the definition of the Centers for Disease Control (CDC) (11).

When the depth of invasion of the tumor was suspicious, the cases were evaluated with endoscopic ultrasound. Contrast-enhanced thorax, upper and lower abdominal computed tomography were performed for staging and PET-CT was added to screening tests in suspicious cases.

The total blood count was measured by an automated hematology analyzer (Roche Hitachi Cobas® 8000 Roche Diagnostics, Indianapolis, IN, USA), NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Discharge criteria were similar in both groups and included meal tolerance without nausea or vomiting, defecation, adequate pain control with oral analgesia, and independent mobilization.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) as well as Student's t test were used for the comparison of quantitative data, and Mann Whitney U test was used for the evaluation of neutrophil/lymphocyte ratio, which did not show normal distribution. Pearson's Chi-square test and Fisher's Exact test were used to compare qualitative data, and logistic regression was used for multivariate evaluations. The patients were divided into two groups according to survival and ROC analysis was performed according to these groups. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis. Appropriate cut-off values were identified, and sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated for parameters with an area under the curve (AUC) of above 0.600. To assess the association of NLO with gastric cancer overall survival, multivariate Cox's proportional hazard model was conducted to estimate Hazard ratios (HRs) and their 95% confidence intervals (CIs). Kaplan-Meier and Log Rank tests were used for survival analysis. A p value of <0.05 was considered statistically significant.

RESULTS

In our study, ROC analysis and ROC curve were created to establish a cutoff value for NLR. As a result of the ROC analysis, the area under the ROC curve was calculated as 61.7%. In other words, the cutoff value obtained gives the correct answer at a rate of 61.7%. According to our cut off value, if the NLR value is below 2.14, it is assumed that the patient develops According to Clavien Dindo Grade 2 and above complications, with a sensitivity of 46.3% and specificity of 76.0%. It is shown in Table 1 and Figure 1.

ROC analysis and ROC curve were created to establish a cutoff value for NLR. As a result of the ROC analysis, the area under the ROC curve was calculated as 51.6%. In other words, the cutoff value obtained gives the correct answer at a rate of 51.6%. According to our cut off value, in terms of lymph node positivity, if the NLR value is above 2.9, it is assumed that the patient has lymph node positivity, with a sensitivity of 44.26% and specificity of 65.12%. It is shown in Table 2 and Figure 2.

Table 1. Proposed cut-off values for significant parameters in postoperative complications, according to Clavien Dindo Grade 2 and above

	NLR
AUC	0.617
Cutoff	≤2.14
Specificity	76.0
95%-CI (%)	61.8 - 86.9
Sensitivity (%)	46.3
95%-CI (%)	32.6 - 60.4
PPV	67.6
NPV	56.7
pLLR	1.93
nLLR	0.71
p	**0.035**

Neutrophil-to-lymphocyte ratio (NLR), AUC: Area under the curve, PPV: Positive predictive value; NPV: Negative predictive value; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio.

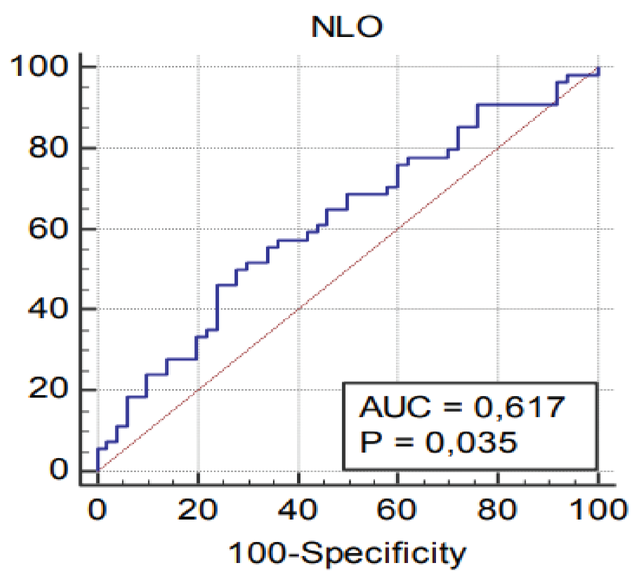

Figure 1. Receiver operating characteristic (ROC) curve analyses for postoperative complications.

Patients were divided into two groups according to the cutoff value of 2.14. Group 1 consisted of 36 patients and Group 2 consisted of 68 patients. There was no statistically significant difference between the groups in terms of mean age, ASA scores and neoadjuvant treatment (p>0.05). Female sex was higher in Group 2 (72% vs 52%) (p:0.41). Body mass index was higher in Group 1 (25.56% vs 23.83%) (p:0.037). Demographic characteristics and preoperative findings of the patients are shown in Table 3.

Conventional surgical operations were more common in both groups (91.1% vs 80.9%, p:0.120). Operation durations were similar in the groups (222 vs 232min, p:0.90). Mean onset of oral food intake was similar (p:0.292). Postoperative complication rates according to Clavien Dindo classification were similar (p:0.9).

Table 2. Proposed cut-off values for significant parameters in lymph node positivity

	NLR
AUC	0.516
Cutoff	>2.90
Specificity	65.12
95%-CI (%)	49.1 - 79.0
Sensitivity (%)	44.26
95%-CI (%)	31.5 - 57.6
PPV	64.3
NPV	45.2
pLLR	1.27
nLLR	0.86
p	0.7850

Neutrophil-to-lymphocyte ratio (NLR), AUC: Area under the curve, PPV: Positive predictive value; NPV: Negative predictive value; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio.

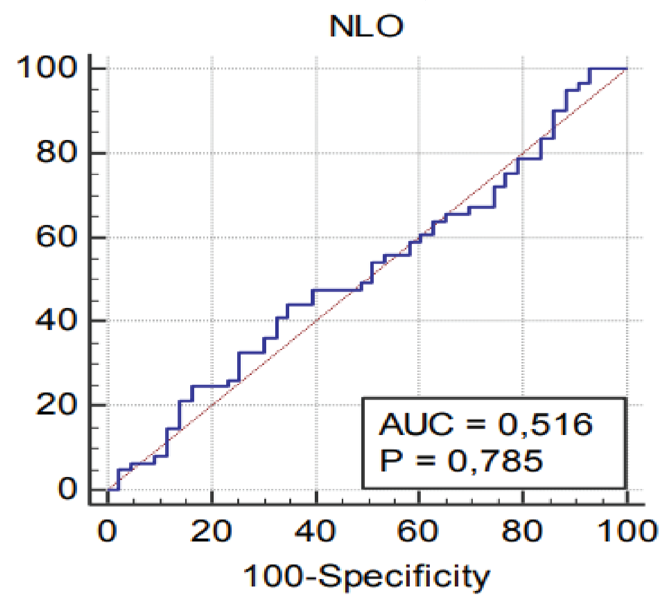

Figure 2. Receiver operating characteristic (ROC) curve analyses for lymph node positivity

Table 3. Characteristics of patients

		Group 1 Low NLR	Group2 High NLR	p*
Age (min-max)		57.02+12.47 (32-79)	60.04+16.18 (14-89)	0.332
Sex	Male	17 (47.2)	19 (27.9)	**0.041**
	Female	19 (52.8)	49 (72.1)	
ASA score	1	20 (55.6)	38 (55.9)	0.989
	2	11 (30.6)	20 (29.4)	
	3	5 (13.9)	10 (14.7)	
BMI (min-max)		25.56+4.32 (16-36)	23.83+3.73 (17-40.3)	0.037
Neoadjuvant Chemoterapy	No	26 (72.2)	49 (72.1)	0.588
	Yes	10 (27.8)	19 (27.9)	

*** p<0.05**

Table 4. Intraoperative and Postoperative outcomes				
		Group 1 Low NLR	**Group 2 High NLR**	**p**
Operation type	Open	33 (91.7)	55 (80.9)	0.120
	Laparoscopic	3 (8.3)	13 (19.1)	
Operation duration (min)		222.77+58.62 (160-480)	232.20+59.38 (170-500)	0.441
Average oral intake duration (day)		4.50+1.18 (3-8)	5.12+3.40(0-28)	0.294
Complication (accrording to Clavien Dindo classification)	1	7 (19.4)	11 (16.2)	0.900
	2	21 (58.3)	40 (58.8)	
	3A	6 (16.7)	10 (14.7)	
	3B	1 (2.8)	2 (2.9)	
	5	1 (2.8)	5 (7.4)	
Anastomosis leakage	No leak	32 (88.9)	61 (89.7)	0.966
	Stump leak	2 (5.6)	3 (4.4)	
	Oesophagojejunostomy	2 (5.6)	4 (5.9)	
Postoperative mortality	Yes	2 (5.6)	7 (10.3)	0.337
	No	34 (94.4)	61 (89.7)	
Postoperative hospitalization duration (day)		10.61+6.52 (4-40)	11.60+8.99 (2-46)	0.560
30-day hospital readmission	None	31 (86.1)	58 (85.3)	0.277
	İleus	2 (5.6)	0 (0.0)	
	Oral intake disorder	0 (0.0)	1 (1.5)	
	Pneumonia	0 (0.0)	1 (1.5)	
	Wound site infection	3 (8.3)	8 (11.8)	

Table 5. Characteristics of tumor				
		Group 1 Low NLR	**Group 2 High NLR**	**p***
Tumor localization	Antrum	13 (36.1)	25 (36.8)	0.173
	Cardia	3 (8.3)	8 (11.8)	
	Corpus	10 (27.8)	23 (33.8)	
	Small curvature	7 (19.4)	6 (8.8)	
	Linitis Plastica	1 (2.8)	6 (8.8)	
	GOJ	2 (5.6)	0 (0.0)	
Total number of removed lymph nodes (mean) (min-max)		27.63+11.84 (10-60)	32.89+14.72 (3-63)	0.067
Positive lymph node number (mean) (min-max)		4.86+5.85 (0-20)	9.23+11.92 (0-47)	**0.041**
Lymph node positivity	Negative	15 (41.7)	28 (41.2)	0.562
	Positive	21 (58.3)	40 (58.8)	
pSTAGE	1A	7 (19.4)	7 (10.3)	0.188
	1B	2 (5.6)	5 (7.4)	
	2A	3 (8.3)	2 (2.9)	
	2B	9 (25.0)	16 (23.5)	
	3A	5 (13.9)	6 (8.8)	
	3B	4 (11.1)	4 (5.9)	
	3C	6 (16.7)	28 (41.2)	
Pathological grade	Poor differentiated	14 (38.9)	28 (41.2)	0.979
	Undifferentiated	7 (19.4)	11 (16.2)	
	Well differentiated	8 (22.2)	15 (22.1)	
	Moderately differentiated	7 (19.4)	14 (20.6)	

* $p<0.05$

Anastomosis leakage rates were similar (p:0.966). Postoperative mortality rates were similar (5.6% vs 10.3%, p:0.337). Postoperative hospital stay was similar between the groups (p:0.560). The most common reason for re-admission to the hospital within 30 days after discharge was wound infection (8.3% vs 11.8%, p:0.277). Intraoperative and postoperative outcomes are given in Table 4.

The most common tumor localization was the antrum in both groups and were similar (p:0.173). The total number of dissected lymph nodes was close to each other in the groups (27 vs 32, p:0.067). The number of dissected positive lymph nodes was statistically higher in Group 2 than in Group 1 (9 vs 6, p:0.041). Lymph node positivity rates were similar between the groups (p:0.562). Pathological stage and pathological grade were similar between the groups (p:0.188, p:0.979; respectively). The pathological characteristics of the tumors are shown in Table 5.

Total survival duration was similar in the groups (24.61 vs 21.12, p:0.206). It is shown in Table 3 and Figure 3.

Univariate and multivariate analyzes of age, sex, pathological grade, pathological stage, NLR level, lymph node positivity and tumor localization variables were evaluated in Table 7. There were statistically significant differences in univariate and multivariate analyzes regarding sex and NLR groups (p<0.01). There was no statistically significant difference between the patients' age, pathological grade, pathological stage, lymph node positivity and tumor localization (p>0.05).

Table 6. Total survival duration according to NLR groups

		Mean (Mean+sd(Min-Max))	Median (Mean+sd(MinMax))	p
NLR Group	Low NLR	24.61+2.57 (19.57-29.64)	22.75+2.09 (18.65-26.85)	0.206
	High NLR	21.12+1.80 (17.58-24.66)	**(14.70-21.80)**	

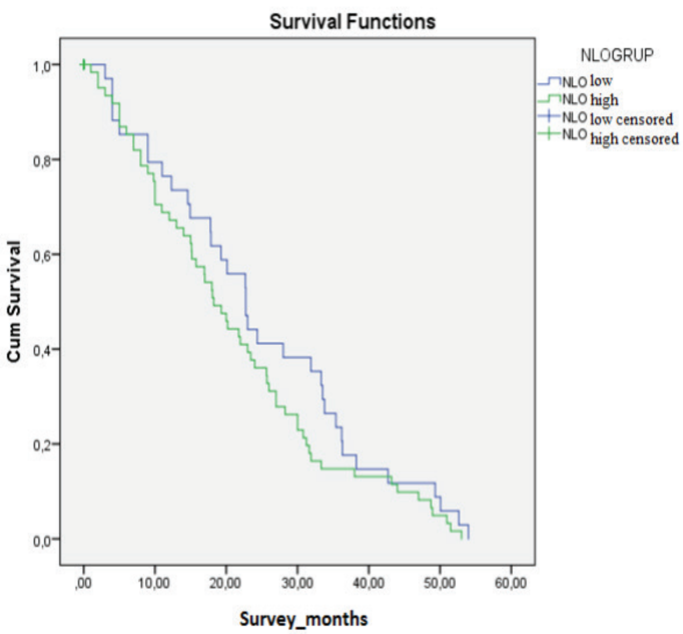

Figure 3. Total survival duration according to NLR groups

Table 7. Univariate and multivariate analysis of factors associated with overall survival in gastric cancer

Measurements		Univariate P	Multivariate HR (95% - CI)	p
Age group	≤59	0.165	1.00	0.179
	> 59		0.144(0.60-0.348)	
Sex	Male	**0.050**	1.00	**<0.050**
	Female		0.193(0.000-0.386)	
Pathological grade	Poor differentiated	0.980	1.00	0.921
	Undifferentiated			
	Well differentiated		0.014(0.276 -0.305)	
	Moderately differentiated			
Pathological stage	1A	0.191	1.00	0.064
	1B			
	2A			
	2B			
	3A			
	3B		0.424(0.025 -0.872)	
	3C			
NLR	≤2.14	**0.029**	1.00	**0.029**
	> 2.14		0.255(0.024 -0.427)	
Lymph node positivity	Negative	0.962	1.00	0.962
	Positive		0.102(0.198 -0.208)	
Tumor localization	Antrum	0.098	1.00	0.057
	Cardia			
	Corpus			
	Small curvature		0.658(0.021-1.337)	
	Linitis Plastica			
	GOJ			

DISCUSSION

Several articles on the prognostic effect of NLR in solid tumor patients have been published in the literature (12). The neoplastic process is mediated by different inflammatory cells.

The combined effect of neutrophilia and lymphopenia results in tumor development and progression. Neutrophils exhibit pro-tumoral behavior because they promote angiogenesis, damage DNA, inhibit T cell activity against tumor cells, and facilitate metastatic processes. In contrast, lymphocytes show an anti-tumoral function when they recognize tumor cell antigens and they promote cytolytic activity against these cells (13-15).

Postoperative complications after radical gastrectomy are still important and the estimated incidence is 12.8-14% (16-20). Postoperative complications may be associated with long-term prognosis, as well as undermining short-term survival. Nowadays, an increasing number of observational studies have shown that postoperative general complications, infectious complications and gastrointestinal leakages correlate with poor overall survival (OS) and/or relapse-free survival (RFS) (21-23). Therefore, it is important to predict postoperative complications and to take preventive measures. There are different views in the literature regarding the relationship between NLR and postoperative complications in gastric cancer. A study by N. Jiang et al. found that postoperative complication rates were similar between NLR Groups with a cut-off value of 1.44 (10.3% vs 13.3%, p:0.505). In the same study, high NLR rate was not a risk factor for postoperative complications in multivariate analyses (p>0.5) (24). Miyamoto R et al. concluded that preoperative NLR is a useful indicator of short-term results in gastric cancer patients. Postoperative complications were significantly different between the low NLR group (n = 110) and the high NLR group (n = 44) (2.7% vs 11.3%; p =

0.015). In multivariate analysis, they found High NLR as an independent factor for postoperative complications (HR, 2.698; p <0.001) (25).

In our study, when we calculated 2.14 as the NLR cutoff value, we found the following; sensitivity: 46, specificity: 76, Area Under Curve (AUC): 0.617, p:0.035. We found NLR to be valuable in detecting postoperative complications with Clavien Dindo classification Grade 2 and more. However, we found the complication rates classified according to Clavien Dindo classification similar in the groups (p:0.9).

As we all know, preoperative treatments are the methods that affect the possibility of complete resection by reducing the N stage in gastric cancer (26,27). Determining the N stage is valuable to help in selecting appropriate surgical methods and creating a personalized treatment plan, so it is worth discussing to find a precise and appropriate preoperative index to estimate the N stage of gastric cancer. Zhang et al. found that NLR was higher in the lymph node positive group (2.27 vs 2.03, p:0.005). In the same study, when they calculated 2 as the NLR cutoff value, they found the following; sensitivity: 52.6, specificity:54.4, Area Under Curve (AUC):0.594, P<0.001. In multivariate analyzes, NLR above 2 was also a risk factor for lymph node positivity (1.257 HR (95%CI) (1.031, 1.532) 0.024) (28).

Although the rate of lymph node positivity was found to be similar in the NLR groups (58.3% vs 58.8%), the number of dissected positive lymph nodes was significantly higher in the high NLR group (9.23 vs 4.86, p:0.041). When we calculated 2.9 as the NLR cutoff value, we found the following; sensitivity:44, specificity:65, Area Under Curve (AUC):0.512; P>0.05. We found the value of NLR in detecting lymph node positivity as lower than the studies in the literature.

In their NLR in gastric cancer study, Zhang et al. found a median survival of 28.5 months for all patients and found that the mean survival was worse in the High-NLR group (OS: 36.0 vs 20.5 months, p <.001) (29). In the meta-analysis of Chen et al., with heterogeneity (I 2 65%, P= 0.004), the pooled HR of 2.16 (95% CI: 1.86 to 2.51, P< 0.001) showed that patients with elevated NLR were expected to have shorter OS after treatment (30). In our study, mean survival was similar in low and high NLR groups (24 vs 21 months, p:206). In univariate and multivariate analyzes, we found a NLR higher than 2.14 to be an independent risk factor for survival.

The most important limitation of our study was its retrospective nature and being a single center study. However, our patient population was as large as those reported in the literature. We believe that our study provides comprehensive data on the relationship and prognosis of NLR in gastric cancer and contributes to valuable reference data.

CONCLUSION

We found preoperative high NLR as a risk factor for survival in patients with gastric cancer. High NLR is also closely associated with the risk of postoperative complications. NLR is an easy access and inexpensive biomarker. In addition, this method offers the opportunity to minimize treatments by identifying patients with poor prognosis and allowing them to be monitored more closely or to receive modified adjuvant therapy. Further research is needed to use NLR levels as independent prognostic factors in gastric cancer and to determine optimal cut-off values. Future studies focusing on the creation of surveillance programs for personalized cancer treatment with prognostic tools are needed.

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