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The clinical significance of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with gastric or colorectal cancer

Mide ve kolorektal kanserli hastalarda preoperatif nötrofil/lenfosit ve trombosit / lenfosit oranlarının klinik önemi

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Abstract

Aim: Gastrointestinal-related cancers, gastric cancer (GC) and colorectal cancer (CRC), have become major public health problems. Preoperative evaluation in such cases is very important to determine initial treatment strategies. This study was conducted to evaluate the possible clinical significance of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with GC or CRC.
Methods: This retrospective study included 50 consecutive patients with GC, 50 consecutive patients with CRC, and 60 consecutive age-matched healthy subjects (control group). Routine preoperative blood examination results detailing neutrophil, platelet, and lymphocyte counts were obtained from the patients' medical records.
Results: NLR and PLR values were significantly higher in both GC and CRC patients compared to the control group (both $p<0.001$). PLR values were also significantly higher in CRC patients compared to GC patients ($p<0.01$). NLR and PLR levels were significantly higher in both GC and CRC stage 4 patients compared to stage 3 patients (both $p<0.001$). The NLR was negatively related to lymphocyte count but positively related to neutrophil count, platelets, and PLR in both GC and CRC patients.
Conclusion: NLR and PLR may be significant predictive biomarkers in GC and CRC. As such, the NLR and PLR can be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. These promising results should be validated in further large-scale clinical studies.

Key words: Gastric cancer, colorectal cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Öz

Amaç: Gastrik kanser (GK) ve kolorektal kanser (KRK) gibi gastrointestinal ilişkili kanserler, önemli bir halk sağlığı problemi haline gelmiştir ve preoperatif değerlendirme, ilk tedavi stratejilerinin belirlenmesinde oldukça önemlidir. Bu çalışma, GK ve KRK hastalarında preoperatif nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (TLO)'nın olası prognostik değerini değerlendirmek için yapıldı.
Yöntemler: Bu retrospektif çalışmaya 50 GK, 50 ardışık KRK hastasını ve yaşları eşleştirilmiş 60 ardışık sağlıklı kişi (kontrol grubu) alındı. Preoperatif tam kan sayımı sonuçları (nötrofiller, trombositler ve lenfositler) hastanın tıbbi kayıtlarından alındı. Bulgular: NLO ve TLO değerleri hem GK hem de KRK hastalarında kontrol grubuna göre anlamlı olarak yüksek bulundu (her ikisi de $p <0.001$). KRK hastalarında TLO değerleri GK hastalarına göre anlamlı derecede yüksek bulundu ($p <0.01$). NLO ve TLO değerleri hem GK hem de KRK hastalarında kontrol grubuna göre anlamlı olarak yüksek bulundu (her ikisi de $p <0.001$). NLO ve TLO değerleri hem gastrik hem de kolorektal kanserin evre 4 hastalarında evre 3 hastalara göre anlamlı derecede yüksek bulundu (her ikisi de $p <0.001$). Hem GK hem de KRK hastalarında NLO, lenfosit sayısıyla negatif olarak ilişkiliyken, nötrofil sayısı, trombosit ve TLO ile pozitif olarak ilişkiliydi.
Sonuç: GC ve CRC'de, NLO ve TLO, önemli bir öngörücü biyobelirteç olabilir. NLO ve TLO değerlerinin, GK ve KRK hastalarında klinik önemi tahmin etmek için basit, uygulanabilir, ucuz ve kullanışlı parametreler olarak kullanılabileceği sonucuna varıldı. Sonuçlar klinik uygulamada daha geniş çaplı çalışmalarda doğrulanmalıdır.

Anahtar Kelimeler: Mide kanseri, kolorektal kanser, nötrofil-lenfosit oranı, trombosit-lenfosit oranı.

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Introduction

Cancer is a public health problem in our country as well as worldwide. Gastric cancer (GC) and colorectal cancer (CRC) are the most common cancers of the gastrointestinal system. Early diagnosis of GC and CRC is of great importance as it enables the provision of more effective treatments and reduced mortality and morbidity. Early diagnosis can be achieved with various screening and laboratory methods. A variety of biochemical biomarkers have been adopted for risk stratification of patients and prediction of survival outcomes [1].

Complete blood count (CBC) parameters are used as diagnostic biomarkers for many diseases associated with inflammatory processes. Abnormalities in peripheral blood cells such as neutrophilia, lymphopenia, and thrombocytosis, have been identified as responses to systemic inflammation [2,3]. Accumulating evidence indicates that inflammation is related to tumor development and progression [4]. Hematological parameters related to neutrophils, such as lymphocyte counts known to be important in the inflammatory process, are recommended as prognostic factors in several cancer types [5-9]. The relationships between cancer prognosis and hematologic parameters such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been studied in many cancers [10-13]. Various studies have demonstrated the prognostic significance of NLR, including evaluations in early-stage colon cancer, stage III colon cancer, and thrombocytosis in patients with GC. While PLR and NLR have been evaluated for early diagnosis and prognostic prediction in patients with resectable GC, limited information related to cross-comparisons of several easily accessible parameters is available for patients with GC and CRC [13-19].

Data regarding NLR, PLR, and their association with GC, CRC, and healthy people are lacking. Hence, the purpose of this study was to evaluate the possible clinical significance of preoperative NLR and PLR in patients with GC and CRC.

Material and methods

This study was approved by the ethics committee and conducted according to the principles described in the Declaration of Helsinki. Written informed consent was obtained from each subject after they were informed as to the purpose of the study.

Study design and patient selection

This was a retrospective case-control study conducted in the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of General Surgery and Department of Medical Oncology. A total of 50 consecutive patients with GC, 50 consecutive patients with CRC, and 60 consecutive age-matched healthy subjects (control group) were enrolled in this study.

The patients' age, sex, medical history, and routine preoperative blood examination, detailing neutrophil, platelet, and lymphocyte counts, were obtained from the medical records. Postoperative histopathological reports regarding tumor, lymph node involvement, and metastasis (tumor-node-metastasis (TNM) staging) were also recorded from the records. Inclusion criteria were as follows: biopsy-proven rectal cancer and measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Patients with incomplete follow-up data or active concurrent infections were excluded. Patients with a concomitant disease other than GC or CRC, a hematologic disease, or a history of blood transfusion were also excluded from the study. Healthy control subjects (n=60) had no demonstrated cancer, endocrine, cardiovascular, or inflammatory diseases.

Hematological analysis

Blood samples obtained before surgery were collected into standardized tubes containing ethylenediaminetetraacetic acid (EDTA) for CBC. Neutrophil (× 109/L), lymphocyte (× 109/L), and platelet (× 103/μL) counts obtained using an automatic hematology analyzer (Beckman Coulter, Brea, CA, USA) were transcribed from the patients' medical records.

Statistical analyses

The software program SPSS (Statistical Package for Social Sciences) 20.0 for Windows was used for statistical evaluations. Descriptive statistics were obtained and data were tested for normality using the Kolmogorov-Smirnov test for Gaussian distribution. For comparison of parameters with normal distribution, parametric tests were used and for comparison of parameters with abnormal distribution, non-parametric tests were used. One-way ANOVA, unpaired Student's-t test, Kruskal-Wallis, and Mann-Whitney U tests were used. Relationships between variables were assessed with Pearson's correlation coefficient. A p-value ≤ 0.05 was considered statistically significant.

Results

The demographic and hematologic parameters of the groups are shown in Table 1. There was no statistically significant difference between groups in terms of age and gender ($p > 0.05$). Neutrophil count and NLR were found to be significantly higher in patients with GC and CRC compared to the control group ($p<0.001$), while lymphocyte count was found to be significantly lower in patients with GC and CRC compared to the control group ($p<0.05$ and $p<0.001$, respectively). NLR and PLR were found to be significantly higher in patients with CRC compared to patients with GC (both $p<0.01$). There was no statistically significant difference between patients with GC and CRC with regard to neutrophil and lymphocyte counts. Platelet count and PLR were found to be significantly higher in patients with GC and CRC compared to the control group (both $p<0.001$). There was no statistically significant difference between patients with GC and CRC with regard to platelet count.

Table 1. Demographic and hematologic parameters.

	Control group (n=60)	Gastric cancer (n=50)	Colorectal cancer (n=50)
Age (years)	57.30± 5.18	58.62± 5.51	58.96± 5.36
Gender (F/M)	30/30	20/30	20/30
Neutrophil count ($\times 10^9$/L)	1.48±0.59	3.49±2.22[c]	5.01±3.26[c]
Lymphocyte count ($\times 10^9$/L)	3.02±0.73	2.42±1.32[a]	1.92±1.23[c]
NLR	1.48±0.59	3.49±2.22[c]	5.01±3.26[c,e]
Platelet count ($\times 10^3$/μL)	201.58±53.61	299.30±87.80[c]	311.08±99.61[c]
PLR	71.80±29.01	178.48±127.13[c]	257.92±172.00[c,e]

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio
Comparison with control group [a]p<0.05, [b]p<0.01, [c]p<0.001
Comparison with Gastric Cancer group [d]p<0.05, [e]p<0.01, [f]p<0.001

Neutrophil, platelet, and lymphocyte ratios according to the stage of GC and CRC are shown in Tables 2 and 3. Neutrophil count, NLR, platelet count, and PLR were found to be significantly higher in patients with stage IV cancer compared to stage III (all p<0.001), while lymphocyte counts were found to be significantly lower in patients with stage IV compared to stage III for both types of cancer (p<0.001).

Table 2. Neutrophil, platelet, and lymphocyte ratios according to gastric cancer stages.

	Stage III (n=20)	Stage IV (n=30)	p
Neutrophil count (× 10^9/L)	4.84±1.70	6.82±1.13	<0.001
Lymphocyte count (×10^9/L)	3.65±0.98	1.60±0.78	<0.001
NLR	1.45±0.63	4.85±1.82	<0.001
Platelet count (×10^3/μL)	237.75±86.91	340.33±61.00	<0.001
PLR	70.88±30.96	250.22±115.64	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 3. Neutrophil, platelet, and lymphocyte ratios according to colorectal cancer stages.

	Stage III (n=20)	Stage IV (n=30)	p
Neutrophil count (× 10^9/L)	5.32±1.24	6.77±1.13	<0.001
Lymphocyte count (× 10^9/L)	3.02±1.13	1.20±0.62	<0.001
NLR	2.52±2.57	6.61±2.59	<0.001
Platelet count (×10^3/μL)	229.75±77.30	363.55±74.14	<0.001
PLR	112.00±114.55	352.06±132.83	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

The relationships of hematological parameters in patients with GC and CRC are shown in Tables 4 and 5. There were significant positive correlations between NLR, neutrophil count, platelet count, and PLR, but a significant negative correlation with lymphocyte count in both types of cancer.

Table 4. Correlations of hematological parameters in gastric cancer.

		Lymphocyte count (× 10^9/L)	NLR	Platelet count (×10^3/μL)	PLR
Neutrophil count (× 10^9/L)	r	-0.369	0.541	0.533	0.353
	p	0.008	<0.001	<0.001	0.012
Lymphocyte count (× 10^9/L)	r	-	-0.837	-0.447	-0.803
	p	-	<0.001	<0.001	<0.001
NLR	r	-0.837	-	0.554	0.939
	p	<0.001	-	<0.001	<0.001
Platelet count (×10^3/μL)	r	-0.447	0.554	-	0.650
	p	0.001	<0.001	-	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 5. Correlation of hematological parameters in colorectal cancer.

		Lymphocyte count (× 10^9/L)	NLR	Platelet count (×10^3/μL)	PLR
Neutrophil count (× 10^9/L)	r	-0.622	0.719	0.521	0.542
	p	<0.001	<0.001	<0.001	<0.001
Lymphocyte count (× 10^9/L)	r	-	-0.861	-0.690	-0.880
	p	-	<0.001	<0.001	<0.001
NLR	r	-0.861	-	0.524	0.889
	p	<0.001	-	<0.001	<0.001
Platelet count (×10^3/μL)	r	-0.690	0.524	-	0.769
	p	<0.001	<0.001	-	<0.001

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Discussion

This study investigated the possible clinical significance of preoperative NLR and PLR values in patients with GC and CRC. NLR and PLR values increased in patients with GC and CRC. Our analysis suggests that NLR and PLR could be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. Systemic inflammation can be measured through inflammatory markers such as the NLR and PLR in patients with GC and CRC.

NLR has been reported as a simple marker of the systemic inflammatory response in GC and CRC patients [14-17]. Inflammation is a critical component of tumor progression. A systematic review and meta-analysis focused on high levels of inflammatory markers indicated that NLR appeared to be associated with worse overall survival (OS) for those with solid tumors. Evaluation of the NLR is a cost-effective method that is widely available in preoperative settings. Furthermore, it can effectively predict clinical significance, as high values of this biomarker are related to more aggressive tumor characteristics. This ratio can also be used for risk stratification in patients within the same disease stage and may be used to assist in planning individualized follow-up and treatment [18].

Lian et al. [19] investigated the application value of systemic inflammatory response markers PLR and NLR in early diagnosis and prognostic prediction in patients with resectable GC. Preoperative PLR and NLR levels were significantly higher in GC patients compared to healthy subjects. Low preoperative PLR and NLR levels correlated with better clinicopathological features, including decreased depth of invasion, less lymph node metastasis, and early tumor stage. Kaplan-Meier plots illustrated that patients with higher preoperative NLR and PLR had decreased OS and disease-free survival. Thus, PLR and NLR measurements can provide important diagnostic and prognostic results in patients with resectable GC.

In the current study, neutrophil count, NLR, and PLR were found to be significantly higher in patients with GC when compared to the control group. NLR and PLR were found to be significantly higher in patients with stage IV cancer compared to those with stage III, while lymphocyte counts were found to be

significantly lower in patients with stage IV compared to stage III in both types of cancer. As in our study, others have shown that a high NLR is clinically significant in GC patients [20-22]. Mellor et al. [23] showed that NLR is an important prognostic indicator associated with both OS and disease-free survival after R0 resection of GC, but the critical level is confusing. Similarly, an increased NLR was associated with tumor aggressiveness in patients with CRC [24–27]. Zhou et al. [24] indicated that these measurements may be used as a cost-effective way to evaluate the systemic inflammatory response. NLR may provide available information in the differential diagnosis of CRC, adenomatous polyps, and healthy people. Palin et al. [25] reported that preoperative NLR is an inexpensive, easily performed, and useful clinical tool to aid in the prediction of outcome in emergency CRC patients. Silva et al. [26] evaluated the prognostic value of nutritional status and NLR in CRC patients and determined that NLR, weight loss, and body mass index assessments are promising prognostic indicators of CRC. Eto et al. [27] reported that preoperative NLR appears to be a useful predictor of bowel obstruction as a result of CRC growth.

Similarly, recent studies have shown that elevated PLR predicted poor prognoses and clinicopathological characteristics in CRC and that PLR is a convenient and low-cost blood-derived prognostic marker for CRC [28, 29]. However, the clinical significance of PLR in CRC is controversial and has not been confirmed [30-34]. Azab et al. [35] evaluated patients with stages I-IV categorized into an equal tertile based on PLR, and results showed that PLR was significantly related to tumor stage. Other researchers have shown a significant association between PLR and tumor stage and pT category [36, 37]. Emir et al. [38] showed that there was no significance of NLR between those with neoplastic colorectal polyps and healthy individuals. Further studies are needed to assess the clinical significance of PLR in CRC using optimal multivariable analysis or adjustment [39].

We found that a high PLR was more important in GC risk increase and a high NLR was more important in CRC risk increase. We also found that high NLR and PLR together increased the risk of both GC (12.86 fold) and CRC (14.23 fold). The fact that the risk increases significantly shows that NLR and PLR can be used as evaluation criteria by being included in routine tests. Systemic and local immune response indexes allow stratification of patients in different OS and recurrence-free survival risk groups.

This study has some limitations. First, the study population is relatively small. Second, this study is retrospective in design, thus some important clinical features could not be recorded. Third, since there were no survival data included in the study, we could not use prognostic values.

The results of the study suggest that lymphocyte count was decreased, and neutrophil count, NLR, and PLR were elevated in patients with GC and CRC. Platelets play an important role in inflammatory conditions related to cancer. Chronic inflammation is also known to induce platelet activation. Platelet function may be modified by the systemic inflammation associated with GC and CRC. A low lymphocyte count can be used as a negative acute phase reactant in the evaluation of cancer. NLR and PLR may be significant predictive biomarkers in GC and CRC.

In conclusion, NLR and PLR could be used as simple, feasible, inexpensive, and useful parameters to predict clinical significance in patients with GC and CRC. These results should be validated in further large-scale studies in clinical practice.

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