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Diagnostic significance of systemic inflammatory biomarkers in colorectal cancer: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV)

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide with early detection being crucial for improving survival rates. Systemic inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) have gained attention as potential diagnostic tools in CRC.

This study aimed to evaluate the diagnostic value of NLR, PLR, MPV, red blood cell distribution width (RDW), hemoglobin (HB), white blood cell (WBC), platelet (PLT) in CRC screening.

Materials and Methods: A retrospective, single-center study was conducted on 1,090 patients who underwent colonoscopy between January 2020, and January 2024. Patients were categorized into malignant, premalignant, and control groups. Hematological parameters including NLR, PLR, MPV, RDW, hemoglobin (HB), white blood cell (WBC), platelet (PLT) counts were analyzed. ROC curve analysis was performed to determine diagnostic cut-off values sensitivity, and specificity.

Results: NLR and PLR values were significantly higher in the malignant and premalignant groups compared to the control group ($p<0.001$). NLR demonstrated the highest diagnostic performance, with an AUC of 0.629, sensitivity of 50.56%, and specificity of 73.13%. PLR had lower diagnostic accuracy (AUC: 0.579, sensitivity: 40.42%, specificity: 37.04%). MPV was significantly elevated in the premalignant group but lacked strong diagnostic value due to its susceptibility to systemic diseases. RDW levels were significantly elevated in both the malignant and premalignant groups but were not sufficient as standalone diagnostic markers.

Conclusion: NLR emerged as the most reliable biomarker for CRC screening, while PLR demonstrated weaker diagnostic accuracy. MPV showed limited value in CRC diagnosis, and RDW, despite its statistical significance, was influenced by other systemic factors, limiting its diagnostic utility.

Keywords: Biomarkers, colorectal cancer, diagnosis, mean platelet volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red blood cell distribution width

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Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide accounting for approximately 10% of all cancer cases.[1] The majority of CRCs arise through a sequential pathway in which normal-appearing mucosa progresses to adenoma, dysplasia, and carcinoma.[2] The most important determinant of disease-related survival is the early detection of the disease. However, most patients are still diagnosed at an advanced stage.[3] While the 5-year survival rate for patients with early-stage colon cancer is 90%, it drops to 11.7% for patients with metastatic colon cancer.[4] This underscores the importance of colorectal cancer screening programs. The most commonly used screening tests for CRC are the fecal occult blood test (FOBT) and the fecal immunochemical test (FIT). These tests are influenced by several dietary factors and have low sensitivity for CRC screening.[5] Colonoscopy is the most effective method for detecting CRC; however, its use as a screening tool is limited due to the discomfort it causes patients.[6] Recent studies have shown that inflammation plays a crucial role in the process of carcinogenesis. Various biomarkers such as mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), are currently used to measure systemic inflammation.[7] Elevated levels of these biomarkers are known to have poor prognostic value in CRC.[8] However, there are limited studies on their diagnostic value. In particular, there is evidence supporting the diagnostic value of NLR and PLR in CRC screening.[9]

In our study, we aimed to comprehensively analyze the diagnostic value of NLR and PLR in CRC and additionally to evaluate the diagnostic significance of other biomarkers such as MPV, RDW, and platelet count.

Materials and Methods

Our study was retrospective, single-centered and conducted in a tertiary healthcare institution. A total of 8,240 patients who underwent colonoscopy between January 2020, and January 2024 were reviewed. Patients who had a complete blood count performed within 0–30 days prior to the procedure without distant organ metastasis for malignant cases and who underwent a colonoscopy that reached the cecal base were included in the study. Patients with inflammatory bowel disease, rheumatic diseases, liver cirrhosis, end-stage renal disease, active gastrointestinal bleeding, active colitis, those using nonsteroidal anti-inflammatory drugs (NSAIDs), and those with polyps smaller than 1 cm were excluded from the study. A total of 1,090 patients were included.

The demographic characteristics, age, gender and laboratory test results of the patients were recorded in a database. Laboratory data including hemoglobin (HB), mean corpuscular volume (MCV), red blood cell distribution width (RDW), platelet count, white blood cell (WBC), mean platelet volume (MPV), absolute neutrophil, lymphocyte and monocyte counts were measured using the Advia 2120 (Siemens Healthcare Diagnostics) device. The neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count while the platelet-to-lymphocyte ratio (PLR) was calculated as the platelet count divided by the absolute lymphocyte count.

Informed consent was obtained from all patients prior to the colonoscopy procedure. Based on the colonoscopy results, patients were divided into three groups: premalignant (adenomatous polyps, serrated polyps, hyperplastic polyps), malignant (adenocarcinoma) and control (normal colonoscopy). The diagnostic sensitivity of PLR, NLR, MPV, WBC, platelet count and other parameters was compared among these three groups.

Colonoscopy Procedure

All patients followed a three-day colonoscopy diet. On the day before the procedure, patients consumed Monobasic Sodium Phosphate 21.6 g and Dibasic Sodium Phosphate 8.1 g (Fleet Phospho-soda 45 ml) solutions at 06:00 PM and 09:00 PM. Additionally, patients administered Sodium Dihydrogen Phosphate + Disodium Hydrogen Phosphate enema (B.T enema enema 135 cc) rectally at 08:00 PM the night before and at 07:00 AM on the morning of the procedure. The procedure was performed under sedation with the patient in the left lateral decubitus position. A Fujinon EC-530WL colonoscope was used for all procedures.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS (Statistical Package for the Social Sciences) version 25.0 software package. Categorical variables were summarized as frequencies and percentages while continuous variables were expressed as mean and standard deviation (or median and minimum-maximum values where necessary). The Chi-square test was used for comparisons of categorical variables. The Kolmogorov-Smirnov test was applied to assess whether the parameters followed a normal distribution. For parameters that did not show normal distribution, the Man-

n-Whitney U test was used for pairwise group comparisons and the Kruskal-Wallis test was used for multiple group comparisons. Sensitivity and specificity values of WBC, HB, RDW, platelet count, MPV, NLR, and PLR were calculated based on the malignant variable. Additionally the area under the ROC curve (AUC) was analyzed, and a cutoff value was determined. A p-value of less than 0.05 was considered statistically significant for all tests.

Results

A total of 1,090 patients were included in the study. The cases were divided into three groups: malignant, premalignant, and control. In the malignant group, there were 240 patients of whom 165 (68.7%) were male and 75 (31.3%) were female. In the premalignant group, there were 381 patients of whom 208 (54.6%) were male and 173 (45.4%) were female. In the control group which had normal colonoscopy findings, there were 469 patients, of whom 176 (37.5%) were male and 293 (62.5%) were female. The higher proportion of males in the premalignant and malignant groups compared to the control group was statistically significant (p<0.001). The mean age was 60.5±10.7 years in the premalignant group, 64.5±12.1 years in the malignant group, and 54.9±12.2 years in the control group. The mean age in the premalignant and malignant groups was statistically significantly higher than in the control group (p<0.001). Among the malignant group, 110 patients (45.8%) had rectal cancer and 130 patients (55.2%) had colon cancer. The tumor localization in colon cancer cases was distributed as follows: 27 (20.7%) in the cecum, 13 (10%) in the ascending colon, 10 (7.6%) in the hepatic flexure, 11 (8.5%) in the transverse colon, 5 (4%) in the splenic flexure, 13 (10%) in the descending colon and 51 (39.2%) in the sigmoid colon. Tumor cell differentiation was categorized as well-differentiated in 76 patients (31.6%), moderately differentiated in 89 patients (37%) and poorly differentiated in 75 patients (31.4%) (Table 1).

Table 1. Comparison of clinical characteristics and laboratory parameters of cases

	Premalign (n=381) n (%)	Malign (n=240) n (%)	Control (n=469) n (%)	p
Sex				
Female	173 (45.4)	75 (31.3)	293 (62.5)	<0.001
Male	208 (54.6)	165 (68.7)	176 (37.5)	
Tumor Localization				
Rectum	110 (45.8)			
Colon	130 (54.2)			
Tumor Differentiation				
Good	76 (31.6)			
Moderate	89 (37)			
Bad	75 (31.4)			
	Med±Ss (Med)	**Med±Ss (Med)**	**Med±Ss (Med)**	**p**
Age	60.5±10.7 (62)	64.5±12.1 (65)	54.9±12.2 (55)	<0.001
WBC	7.82±2.1 (7.3)	7.68±2.6 (7.28)	7.18±1.8 (6.9)	<0.001
HB	13.5±1.9 (13.6)	11.7±2.3 (11.8)	13.2±1.7 (13.3)	<0.001
RDW	14.3±2.0 (13.7)	15.7±3.2 (14.65)	13.9±1.99 (13.5)	<0.001
Platelet	266246.7±77406.8 (261000)	310830.4±130036.2 (292000)	265816.6±67779.2 (252000)	<0.001
MPV	9.73±1.2 (9.7)	9.44±1.6 (9.7)	9.45±0.9 (9.4)	<0.001
NLR	2.30±1.5 (2.0)	3.53±2.6 (2.7)	1.99±0.99 (1.78)	<0.001
PLR	129553.7±73631.1 (113373.9)	213393.5±156636.9 (161945.6)	124484.2±53310.9 (11846.2)	<0.001

WBC: White blood cell; HB: Hemoglobin; RDW: Red blood Cell distribution width; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platet-to-lymphocyte ratio.

As shown in Table 1, compared to the control group, the mean values of WBC, RDW, NLR, and PLR were significantly higher in the malignant and premalignant groups (p<0.001, p<0.001, p<0.001, p<0.001). In the malignant group, hemoglobin levels were significantly lower compared to the premalignant and control groups (p<0.001).

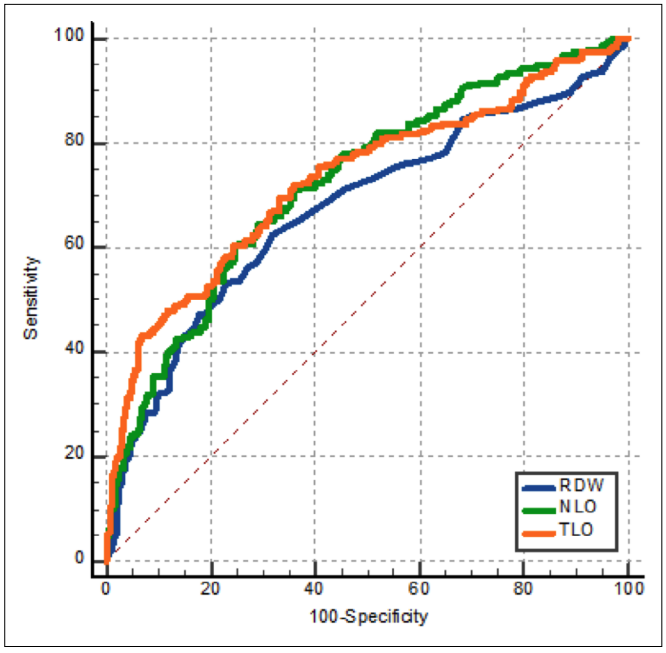

Figure 1. Diagnostic values of RDW, NLR, and PLR.
RDW: Red blood Cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platet-to-lymphocyte ratio.

In the premalignant group, the mean MPV value was statistically significantly higher than in the other groups (p<0.001) (Table 1).

The diagnostic performance of WBC, HB, RDW, PLT, MPV, NLR, and PLR in predicting malignancy was assessed using the ROC curve test and the cut-off values were determined (Fig. 1). According to the analysis, the cutoff values for WBC, HB, RDW, PLT, MPV, NLR, and PLR were found to be >8.06, <11.3, >14, >268,000, >8.9, >2.29, and >147,852.8, respectively. NLR was identified as the best diagnostic test for predicting malignancy, with an AUC of 62.9%, sensitivity of 50.56%, and specificity of 73.13% (Table 2).

Discussion

The role of systemic inflammation in the process of carcinogenesis has been demonstrated in large-scale studies.[10] Inflammatory factors such as neutrophils, lymphocytes, platelets, and monocytes promote tumor cell formation, migration and dissemination.[11] Therefore, ratios representing systemic inflammatory responses such as NLR and PLR, are considered potential diagnostic biomarkers for colorectal cancer (CRC).

In our study, NLR and PLR were shown to be significantly higher in the malignant group compared to the premalignant and control groups. The growing number of stud-

Table 2. Evaluation of the ability of inflammatory indices to predict the malignant group using ROC curve analysis

	p	Cut-Off	AUC (%95 CI)	Sensitive (%95 CI)	Spesifite (%95 CI)	PPV (%95 CI)	NPV (%95 CI)
WBC	<0.001	>8.06	0.567 (0.537-0.597)	39.61 (35.7-43.6)	73.77 (69.5-77.7)	66.7 (62.5-70.5)	48 (45.9-50.1)
HB	0.010	<11.3	0.545 (0.514-0.574)	24.48 (21.1-28.1)	90.62 (87.6-93.1)	77.6 (71.6-82.5)	48.5 (46.2-48.9)
RDW	<0.001	>14	0.610 (0.580-0.639)	47.83 (43.8-81.5)	73.35 (69.1-77.3)	70.4 (66.7-73.8)	51.5 (49.2-53.8)
Platelet	0.021	>268000	0.540 (0.510-0.570)	51.37 (47.4-55.4)	59.49 (54.9-64)	62.7 (59.5-65.7)	48 (45.3-50.5)
MPV	0.001	>8.9	0.568 (0.538-0.598)	76.49 (73-79.8)	34.97 (30.7-39.5)	60.9 (59-62.8)	52.9 (48.2-57.5)
NLR	<0.001	>2.29	0.629 (0.600-0.658)	50.56 (46.6-54.6)	73.13 (68.9-77.1)	71.4 (67.8-74.7)	52.8 (50.4-55.2)
PLR	<0.001	>147852.8	0.579 (0.549-0.608)	37.04 (33.2-41)	81.66 (77.9-85.1)	72.8 (68.3-76.9)	49.5 (47.6-51.3)

AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; WBC: White blood cell; HB: Hemoglobin; RDW: Red blood Cell distribution width; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platet-to-lymphocyte ratio.

ies on the diagnostic value of NLR and PLR in CRC has attracted considerable attention. In a study by Kılıncalp et al.[12], NLR was reported to have diagnostic value in CRC while PLR was noted for its prognostic significance. Similarly, Stojkovic et al.[6] emphasized the diagnostic importance of NLR in their study. Peng et al.[9] demonstrated that PLR could be used as an early diagnostic marker in CRC patients. In our study, NLR had the largest AUC (0.629) with a sensitivity of 50.56% and a specificity of 73.13%, making it the most statistically significant diagnostic test for predicting malignancy. Conversely, PLR had a lower AUC (0.579), sensitivity (40.42%), and specificity (37.04%) compared to NLR. Our results indicate that NLR is a strong diagnostic biomarker while PLR is weaker in this regard.

MPV is used as an inflammatory biomarker in cardiovascular, cerebrovascular, and rheumatological diseases.[13] Additionally, there is evidence supporting its use in the early diagnosis of gastric, pancreatic, hepatocellular and colorectal cancers.[14] In our study, MPV levels were significantly higher in the premalignant group compared to the malignant and control groups. However, given that MPV is influenced by numerous systemic diseases including obesity we do not consider our findings in the premalignant group to have strong diagnostic validity. In the literature, Wiesner et al.[15] demonstrated that elevated MPV could serve as a diagnostic biomarker in CRC. In contrast, Kılıncalp et al.[12] in agreement with our findings showed that MPV has low diagnostic value in CRC.

RDW is associated with anisocytosis in erythrocytes and increases in the presence of inflammation. Elevated RDW is an inflammatory biomarker linked to ischemic heart disease, atherosclerosis, vascular obstructive disease, hypertension and rheumatological diseases. There are limited studies on the use of elevated RDW as a potential biomarker in the early diagnosis of CRC.[16] In our study, RDW levels were significantly higher in the premalignant and malignant groups compared to the control group. However, no significant difference was observed between the premalignant and malignant groups. In a retrospective study by Cengiz et al.,[17] RDW was found to be elevated in malignant patients but they concluded that it was unsuitable as a standalone diagnostic biomarker. Since our study excluded patients with chronic diseases related to systemic inflammation, RDW elevation in the malignant and premalignant groups carries diagnostic value. Although the sensitivity (47.8%) and specificity (73.3%) of RDW are significant, its susceptibility to numerous systemic diseases remains its major limitation.

Limitations of the Study

Our study has several limitations. Firstly, it is retrospective and single-centered. Secondly, in the premalignant group, the histological characteristics of the polyps were not homogeneously distributed, introducing a risk of bias. However, including patients without distant metastasis and/or local invasion in the malignant group and patients with polyps larger than 1 cm in the premalignant group enhances the validity of our findings for CRC screening programs. Additionally, excluding patients with chronic diseases associated with systemic inflammation strengthens the relationship between the biomarkers we analyzed and CRC.

Conclusion

NLR and PLR are biomarkers with high sensitivity in colorectal cancer screening. Although, RDW is elevated in the malignant group its susceptibility to various systemic diseases limits its utility as a CRC biomarker. On the other hand, MPV does not have diagnostic value in CRC screening.

Disclosures

Ethichs Committee Approval: The study received approval from the Koşuyolu Higher Specialization Training and Research Hospital Local Ethics Committee (Date: 03.12.2024; Approval No: 2024/21/965).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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