ORIGINAL RESEARCH

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The Diagnostic Importance of RDWLR, PDWLR, and Immature Granulocytes in Colorectal Cancer

Ümit ÖZDEMIR[1], Abdurrahman ÖZKUBAT[2]

[1] Ankara Etlik City Hospital, Department of General Surgery, Section of Gastroenterogical Surgery, Ankara, Türkiye
[2] Ankara Etlik City Hospital, Department of General Surgery, Ankara, Türkiye

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Abstract

Objective

A complex inflammatory response forms against the local effects of malignancy. In the differentiation of colorectal cancer from benign colorectal polypoid lesions, inflammatory biomarkers such as platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and Red Cell Distribution Width (RDW) have previously provided promising results. This study aimed to investigate the results of immature granulocytes (IG) and as yet unstudied biomarkers such as nucleated red blood cells (NRBC), platelet distribution width (PDW), and Mean Platelet Volume (MPV) with new inflammatory indexes such as the RDW-lymphocyte ratio (RDWLR) and the PDW-lymphocyte ratio (PDWLR).

Material and Method

The hematological biomarkers were compared between 269 patients with colorectal benign polyps and 57 patients with colorectal adenocarcinoma. To determine the sensitivity and specificity of the biomarkers related to the neoplastic characteristics of the colorectal polyps, the Receiver Operating Characteristics (ROC) curve analysis was performed.

Results

The mean NRBC count, IG count, and rates were similar in both groups. In the colorectal carcinoma group, PDW was lower (p=0.004) and RDW was higher (p=0.018). The NLR, PLR, RDWLR, and PDWLR values were significantly higher in the colorectal carcinoma group (p<0.001, p<0.001, p<0.001, p=0.003, respectively). In the ROC analysis for the differential diagnosis of colorectal cancer from colorectal polyp, the AUC values of NLR, PLR, and RDWLR were determined to be higher (0.714, 0.719, 0.720) with sensitivity and specificity of 73.68% and 64.31%, 64.91% and 72.75%, and 69.09 and 69.78%, respectively. The AUC value of PWDLR was determined to be 0.625, with a sensitivity of 73.21% and specificity of 52.81%.

Conclusion

The diagnostic importance of NLR and PLR in colorectal cancer was confirmed, and RDWLR is a promising new parameter. IG has no significant diagnostic value.

Keywords: Colorectal cancer, colorectal polyp, immature granulocyte, red cell distribution width to lymphocyte ratio, platelet distribution width to lymphocyte ratio, diagnosis

Correspondence: Ü.Ö. / uozdemir2001@yahoo.com
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ORCID IDs of the Authors: Ü.Ö: 0000-0001-5681-7421; A.Ö: 0009-0000-4980-6070

Introduction

Colorectal cancer is the third most frequently seen cancer, but the cure rates have increased significantly with early detection (1). Colorectal polypoid lesions are precursors of colorectal adenocarcinoma. The incidence of colon adenomatous polyps in individuals aged >50 years is estimated to be 24-50% (2). Colorectal cancers develop from a polyp, but malignancy is present in less than 1% of colon polyps (3). Therefore, the morphological and histopathological identification of colorectal polyps is important. Currently, colorectal cancer screening is performed using colonoscopy, and polyps that do not have a morphologically obvious malignant appearance can only be distinguished with polypectomy and histopathological examination. However, colonoscopy cannot be used as a routine screening program as it is both costly and troublesome for the patient. The fecal occult blood test, which is used in colorectal cancer screening, has low sensitivity (4). Moreover, patients who have undergone polyp excision with colonoscopy require more frequent colonoscopy follow-up afterwards (5). Therefore, there is a clear need for a new, easily accessible, low-cost method that can be widely used in the differential diagnosis of colorectal cancer and colorectal benign polyps.

A complex inflammatory response forms against the local effects of malignancy. This inflammatory response is known to have been observed at the initial stage of the tumour, and in progression or recurrence (6, 7). Biomarkers such as platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and Red Cell Distribution Width (RDW) have been studied in the differentiation of colorectal cancer from benign colorectal polypoid lesions, and promising results have been shown in the literature (8, 9).

RDW is a reflection of the heterogenity of red blood cell size (10, 11). Immature granulocytes (IG) refer to an increase in the ratio of immature granulocytes in circulation (12, 13). Mean Platelet Volume (MPV) is a marker of the mean thrombocyte volume, and is accepted as a differentiating characteristic of the rate and stimulation of thrombocyte production. In destructive thrombocytopenia, there are high MPV levels, and in hypoproliferative thrombocytopenia, there are low MPV levels (14). Platelet distribution width (PDW) is a marker of variation in thrombocyte size (14). There is increasing information that all these parameters show reactive characteristics in inflammation.

Hemogram is an accessible, low-cost test that can be performed in every centre. However, questions have arisen about biomarkers such as IG, nucleated red blood cells (NRCB), PDW, and MPV, which are routinely studied in the hemogram in the differentiation of colorectal cancer from colorectal polypoid lesions (8, 15). This study aimed to support the information related to biomarkers such as PLR, NLR, and RDW in the differential diagnosis of colorectal invasive carcinoma and colorectal benign polyps, and to contribute to the medical literature with the results of as yet unstudied biomarkers such as immature granulocytes (IG), NRBC, PDW, and MPV and new inflammatory indexes such as the RDW-lymphocyte ratio (RDWLR) and the PDW-lymphocyte ratio (PDWLR).

Material and Method

The study included 326 patients diagnosed with colorectal polyps during colonoscopy in the Endoscopy Unit of a tertiary-level hospital between 01.01.2023 and 31.12.2023. The data were screened retrospectively by examining the patient files in the hospital information system. From the results of the histopathological examination of the colorectal polyps, the cases were separated into two groups as Group A, containing patients with colorectal benign polyps, and Group B, containing patients with colorectal adenocarcinoma. The hematological biomarkers were compared between these two groups. Patients were excluded from the study if they had a current diagnosis of or a history of colorectal cancer, or a history of inflammatory bowel disease or hereditary polyposis syndromes. Other study exclusion criteria were defined as a current malignancy other than colorectal cancer, pregnancy, the use of anti-aggregants or anticoagulants, a recent history of blood transfusion, the presence of any gastrointestinal, inflammatory, hepatobiliary, cardiac, pulmonary, or hematological disease determined during colonoscopy, or age <18 years.

The full blood count taken routinely before colonoscopy examination was used for the hematological biomarkers. Peripheral venous blood samples were obtained from the patients for the full blood count, and the samples were centrifuged for 15 minutes at room temperature. Using a Sysmex XN series analyzer (Sysmex, Kobe, Japan), measurements were taken of white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, hemoglobin value (g/dl), immature granulocyte count and ratio, platelet distribution width (PDW), red cell distribution width (RDW), nucleated red blood cell count (NRBC), and mean platelet volume (MPV).

The neutrophil lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, the platelet lymphocyte ratio (PLR) by dividing the platelet count by the lymphocyte count, the RDW lymphocyte ratio (RDWLR) by dividing the RDW by the lymphocyte count, and the PDW lymphocyte ratio (PDWLR) by dividing the PDW by the lymphocyte count.

Approval for the study was granted by the Ankara Etlik City Hospital Ethics Committee Ethics Committee (decision no: AEŞH-BADEK-2024-195, dated: 28.02.2024). All the study procedures complied with the Helsinki Declaration and local ethics criteria.

Data obtained in the study were analyzed statistically using SPSS v. 26.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc v. 22.023 (MedCalc software, Ostend, Belgium). Conformity of numerical variables to normal distribution was examined with visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were stated as mean±standard deviation (SD) values for continuous variables with normal distribution and as median (minimum-maximum) values for those not showing normal distribution. Categorical variables were stated as numbers (n) and percentages (%). The Student's t-test was applied to data with normal distribution, the Mann-Whitney U-test to data not normally distributed, and the Pearson Chi-square test to categorical data. A value of $p<0.05$ was accepted as statistically significant. To determine the sensitivity and specificity of the biomarkers related to the neoplastic characteristics of the colorectal polyps, Receiver Operating Characteristics (ROC) curve analysis was performed, and cut-off values were determined.

Results

Evaluation was made of a total of 326 patients as 269 (82.5%) in the colorectal benign polyp group (Group A) and 57 (17.5%) in the colorectal carcinoma group (Group B). The comparisons of the clinical characteristics and inflammatory parameters of the patients are shown in Table 1. The mean age of the colorectal carcinoma group (66.28±10.49 years) was determined to be significantly older than that of the benign polyp group (59.81±11.36 years) ($p<0.001$). The gender distribution was similar in the two groups, with more males in both groups.

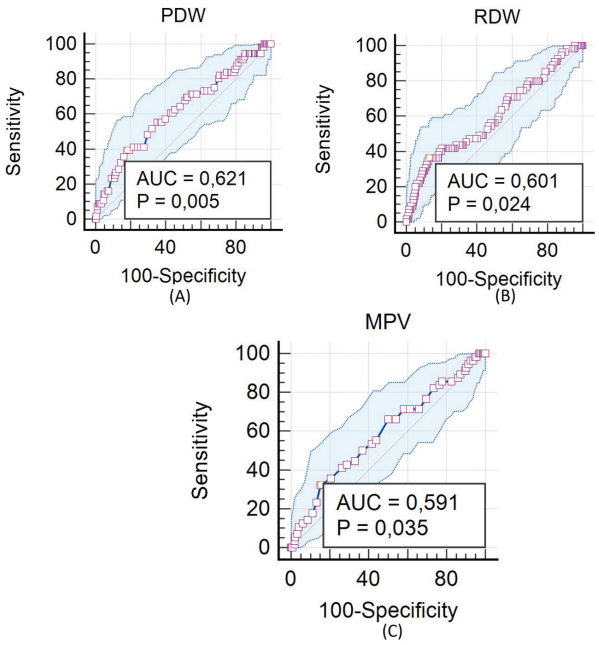

Figure 1
(A) ROC curve and AUC of PDW, (B) ROC curve and AUC of RDW, (C) ROC curve and AUC of MPV

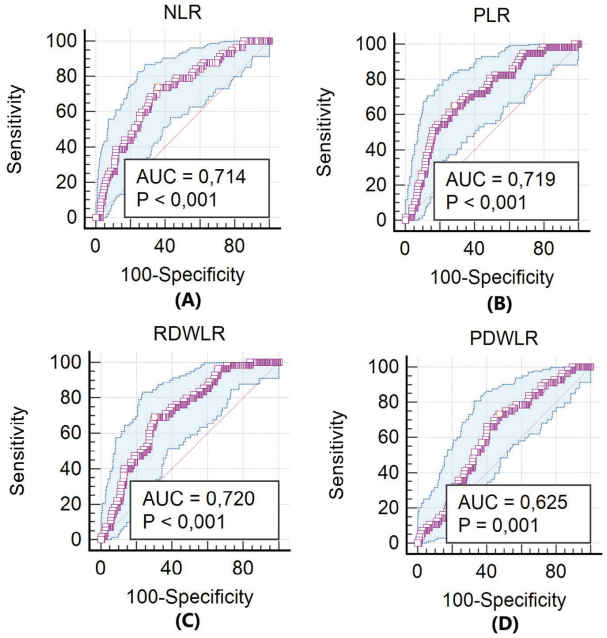

Figure 2
(A) ROC curve and AUC of NLR, (B) ROC curve and AUC of PLR, (C) ROC curve and AUC of RDWLR, (D) ROC curve and AUC of PDWLR

Colorectal benign polyps were seen more often in the rectum (40.9%), and colorectal carcinomas were seen more often in the left colon (descending+sigmoid colon) (43.9%) ($p=0.038$). No statistically significant difference was determined between the two groups in respect of WBC and neutrophil count ($p=0.800$,

Table 1 The comparisons of the clinical characteristics and inflammatory parameters of the patients

	Colorectal Benign Polyp n=269 (82,5 %) (Group A)	Colorectal Carcinoma n=57 (17,5 %) (Group B)	P value	Confidence interval of difference
Age	59,81 ± 11,36	66,28 ±10,49	**<0,001**	-9,68 to -3,24
Gender (male)	150 (55,8%)	34 (59,6)	0,591	
Polyp localization			**0,038**	
Ascendent	61 (22,7%)	12 (21,1%)		
Transverse	29 (10,8%)	3 (5,3%)		
Descendent + sigmoid	69 (25,7%)	25 (43,9%)		
Rectum	110 (40,9%)	17 (29,8%)		
WBC	7,60 (2,74 – 20,00)	7,34 (3,46 – 12,86)	0,800	
Neutrophil	4,28 (0,48 – 13,64)	4,66 (2,12 – 10,70)	0,067	
Lymphocyte	2,34 ± 0,85	1,81 ± 0,56	**<0,001**	
Platelet	263,00 (59,00 – 576,00)	276,00 (147,00 – 649,00)	0,132	
HGB	14,00 (6,60 – 18,60)	12,25 (8,70 – 16,30)	**<0,001**	
Immature granulocytes	0,02 (0,00 – 0,53)	0,02 (0,01 – 0,13)	0,914	
immature granulocytes %	12,20 (11,70 – 22,50)	14,10 (11,60 – 26,80)	0,352	
PDW	12,10 (8,30 – 20,30)	11,20 (8,40 – 16,60)	**0,004**	
RDW	43,90 (32,20 – 73,80)	44,50 (38,90 – 77,30)	**0,018**	
NRBC	0,00 (0,00 – 2,00)	0,00 (0,00 – 0,30)	0,841	
P-LCR	29,25 ± 7,33	26,66 ± 7,33	**0,017**	0,46 to 4,70
MPV	10,52 ± 0,91	10,24 ± 0,89	**0,037**	0,01 to 0,54
NLR	1,91(0,19 – 15,86)	2,66 (1,24 – 8,82)	**<0,001**	
PLR	113,22 (25,11 – 787,50)	171,42 (52,69 – 600,93)	**<0,001**	
RDWLR	19,02 (7,72 – 119,50)	26,39 (13,74 – 107,31)	**<0,001**	
PDWLR	5,36 (1,87 – 28,75)	6,62 (3,44 – 23,27)	**0,003**	

HGB: hemoglobin, PDW: platelet distribution width, RDW: Red Cell Distribution Width, NRBC: nucleated red blood cells, P-LCR: platelet larger cell ratio, MPV: Mean Platelet Volume, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, RDWLR: RDW-lymphocyte ratio, PDWLR: PDW-lymphocyte ratio

p=0.067, respectively). The mean lymphocyte count was determined to be statistically significantly greater in the colorectal benign polyp group (2.34 ± 0.85 10^3/μL vs. 1.81 ± 0.56 10^3/μL; p<0.001). The mean platelet counts were similar in both groups. The median hemoglobin value was determined to be statistically significantly lower in the colorectal carcinoma group [14.00 (6.60-18.60) g/dl vs. 12.25(8.70-16.30) g/dl] (p<0.001).

The median NRBC count and the IG count, and the ratio were similar in both groups. In the colorectal carcinoma group, PDW was lower (p=0.004) and RDW was higher (p=0.018). The platelet large cell ratio (P-LCR) and MPV, which are parameters related to the measurements of platelet size, were determined to be statistically significantly lower in the colorectal carcinoma group (p=0.017, p=0.037, respectively). Statistically stronger p-values were determined for the inflammatory parameters when

Table 2 ROC-AUC analyses and Cut-off values of inflammatory biomarkers evaluated by complete blood count

	ROC-AUC	Cut-off Value	sensitivity	spesifity	P value
PDW	0,621 (0,566 to 0,674)	≤10,5	39,29	82,02	0,0050
RDW	0,601 (0,545 to 0,655)	>48,2	36,36	86,94	0,0241
MPV	0,591 (0,535 to 0,645)	≤9,6	32,14	84,64	0,0353
NLR	0,714 (0,662 to 0,763)	>2,25	73,68	64,31	<0,0001
PLR	0,719 (0,666 to 0,767)	>140,42	64,91	71,75	<0,0001
RDWLR	0,720 (0,668 to 0,768)	>23,35	69,09	69,78	<0,0001
PDWLR	0,625 (0,570 to 0,678)	>5,57	73,21	52,81	0,0008

PDW: platelet distribution width, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, RDWLR: RDW-lymphocyte ratio, PDWLR: PDW-lymphocyte ratio

the values were proportional to the lymphocyte count. The NLR, PLR, RDWLR, and PDWLR values were determined to be statistically significantly higher in the colorectal carcinoma group ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.003$, respectively).

ROC analysis was performed to investigate the diagnostic value of the parameters that showed a significant difference in the paired comparisons between the two groups (Table 2). PDW, RDW, and MPV were significant parameters in the paired comparisons. The results of the ROC analysis showed that the area under the curve (AUC) values of NLR, PLR, and RDWLR were higher (Figures 1 and 2). A cutoff value of >2.25 for NLR had an AUC of 0.714 with 73.68% sensitivity and 64.31% specificity (Figure 2A). A cutoff value of >140.42 for PLR had an AUC of 0.719 with 64.91% sensitivity and 72.25% specificity (Figure 2B). A cutoff value of >23.35 for RDWLR had an AUC of 0.720 with 69.09% sensitivity and 69.78% specificity (Figure 2C). A cutoff value of >5.57 for PDWLR had an AUC of 0.625 with 73.21% sensitivity and 52.81% specificity (Figure 2D).

Discussion

Colorectal cancer usually occurs with dysplasia of colorectal polyps over time and transformation to malignant processes (16). The incidence of polypoid lesions in the colon increases with advancing age (2). However, malignancy is present in less than 1% of colon polyps (3). Patients who have undergone colonoscopy polypectomy are at risk of again developing colonic polyps or malignancy, and therefore, colonoscopy follow-up must be more frequent than for patients at average risk (5, 17, 18). Moreover, colonoscopy is not an easily accessible method as it is high-cost, requires specialist personnel, and patient compliance with colon cleaning before the procedure (9). The fecal occult blood test has low sensitivity (19). Therefore, there is a need for new, easily accessible, low-cost methods with high patient compliance that can be used in the differential diagnosis of colon polyps from colon adenocarcinoma.

During the development of cancer, inflammatory cytokines and growth factors are expressed from malignant cells, and at the same time, an inflammatory response against the malignancy forms in the host (20, 21). Prolonged inflammation is present together with malignancy. The relationship between colorectal cancer and some inflammatory markers has become a matter of debate in some studies (15, 22, 23).

Malignant cells cause neutrophilia by releasing granulocyte colony-stimulating factor (23). Neutrophils then cause extracellular matrix remodelling, angiogenesis, and mutagenesis, and suppress the T-lymphocyte response (24, 25). All these effects lead to tumour growth and the development of metastasis. Lymphocytes prevent tumour maturation and are responsible for the cytotoxic effect directed at malignant cells (8, 26). The NLR shows the balance between the pro-tumour inflammatory status and the anti-tumour immune status, and an elevated NLR disrupts the oncological results and decreases survival. With an increase in NLR, poor oncological results are seen in intestinal malignancies such as colon, pancreas, and stomach cancers (8, 23, 27-29). In the current study, the lymphocyte count was

determined to be lower in the colorectal cancer group, and in parallel with the literature, the NLR had high sensitivity and specificity in the ROC analysis.

By passing the submucosal barrier, malignant cells create a systemic inflammatory response, and many pro-inflammatory cytokines are released (30). Platelets are both carriers of these cytokines and are affected by them, and an increase in the number. As in many other malignancies, PLR is elevated in patients with colorectal cancer compared to healthy individuals, and the current study results support this finding (23, 31). MPV is a marker of mean platelet volume and shows the change in inflammation status. In literature, MPV is high in different cancer types such as gastric cancer and hepatocellular cancer (32, 33). However, in colorectal cancer, low MPV has been associated with malignancy and decreased survival, and the current study results were consistent with this (30, 34, 35).

The PDW value is obtained with the measurement of variation in thrombocyte size, immature thrombocytes in inflammation, and there is increased destruction of mature thrombocytes at the same time. The relationship between PDW and cancer has not been able to be fully clarified. In parallel with the current study, there are studies in the literature showing low PDW in colorectal cancer (30, 36). However, just as there are studies showing that low PDW is associated with better survival, there are other studies stating that there is no diagnostic significance (34, 37). The PDWLR was evaluated for the first time in the current study. It was determined to be higher in the colorectal carcinoma group, but a high ROC-AUC value did not emerge. The low PDW and high PDWLR in the current study colorectal carcinoma group can be attributed to the significantly low lymphocyte count. The ratio of the two parameters, which were low in the colorectal carcinoma group, can be considered to have prevented the emergence of a diagnostic parameter. Therefore, there is a need for further, more detailed studies of the value of PDW and PDWLR in the differential diagnosis of colorectal cancer and colorectal benign polyps.

RDW is a parameter for which high values are measured in inflammatory processes. Since the diagnostic importance was shown in solid tumours, there have been few studies showing that it could be useful in the differentiation of colorectal cancer from colon polyps (38). In parallel with the literature, RDW in the current study was determined to be high in the colorectal cancer group, but the AUC value of 0.621 in the ROC analysis was not satisfactory. Therefore, proportioning with the lymphocyte count, which was shown to be low in colorectal cancer, was considered. The RDWLR value was determined to be higher in the colorectal cancer group than in the colon polyp group, and a satisfactory diagnostic value of AUC 0.720 was obtained in the ROC analysis. The diagnostic value of RDWLR has been investigated in only one previous study. Huang et al. reported that there was diagnostic importance (9). There is one study related to the prognostic importance of RDWLR, and the results of that study showed significance in the prediction of 3-year disease-free survival (39). It can be said that RDWLR is a remarkable parameter in the diagnosis of colorectal cancer, but further studies of larger series are.

The immature granulocyte count is a parameter in the full blood count, and its diagnostic importance in inflammation has been shown. It is elevated in inflammatory conditions such as sepsis, pancreatitis, and appendicitis (13). Except for bladder and breast cancer, there are no data related to its diagnostic importance in solid organ cancers (40, 41). According to the results of our study, there was no diagnostic significance of IG in the differentiation of colorectal cancer from colorectal benign polyps. This is the first and only study on this subject in the literature.

There were some limitations to this study. A group of healthy individuals could not be included for comparison because of the retrospective nature of the research. A second limitation was that the number of patients in the colorectal cancer group was lower than that of the colorectal benign polyp group, and this could have reduced the statistical power of the results.

Conclusion

The results of this study confirmed the diagnostic importance of NLR and PLR in colorectal cancer. RDWLR is a promising new parameter in the differential diagnosis of colorectal cancer from colon polyps. However, IG was not found to have any significant diagnostic value. There remains a need for further investigation of these findings with larger series.

Conflict of Interest Statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical Approval

Approval for the study was granted by the Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-

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Availability of Data and Materials
Data available on request from the authors.

Artificial Intelligence Statement
The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions
ÜÖ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

AÖ: Investigation; Data curation; Formal analysis; Writing- review & editing.

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