

Are Inflammatory Markers Useful in Determining The Anatomic Localization of Colorectal Cancer? Immature Granulocytes and Red Cell Distributon Width

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Abstract

Background: There are embryological, clinicopathological, and prognostic differences between right and left colon tumours. The aim of this study was to investigate the diagnostic benefit of inflammatory markers in the differentiation of right and left colon cancers.

Methods: Two groups of patients were formed as 71 (33.8%) with right colon cancer (RCC) and 139 (66.2%) with left colorectal cancer (LCRC). The groups were compared in respect of clinical characteristics, hemoglobin, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune inflammation index (SII), immature granulocyte count (IGC), immature granulocyte percentage (IG%), and red blood cell distribution width percentage (RDW%).

Results: The TNM grade, and NLR, PLR, SII, IGC, and IG% values were similar in both groups. In the RCC group, hemoglobin was determined to be lower than in the LCRC group (11.35 [6.40-16.40] vs. 13.00 [6.00-17.00] mg/dl), and RDW was higher (14.80% [11.90-27.90] vs. 13.70% [11.00-37.10]) (p=0.001, p=0.005, respectively). In ROC analysis, hemoglobin (AUC:0.640, p<0.001) and RDW% (AUC:0.621, p=0.004) were determined to be significant.

Conclusion:Inflammatory markers such as NLR and PLR, which have been previously investigated, and SII and IGC, promising and examined for the first time, are insufficient to show the anatomic localization of CRC. However, differences were observed in RDW and hemoglobin and these may be associated with subclinical bleeding, which is frequently seen in RCC.

Keywords: Colorectal Cancer, Colorectal Cancer Localization, Inflammatory markers, Immature Granulocytes, Red Cell Distribution Width

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer in both males and females (1). Important advances have been made in the screening, diagnosis, and treatment of CRC in recent decades. Nevertheless, a very limited decrease has been seen in the incidence and mortality rates of CRC, even in western countries (2). When colorectal cancer is examined in two groups according to localization as right-side colon cancer (RCC) (ascending colon and transverse colon) and left-side colorectal cancer (LCRC) (splenic flexura, descending colon, sigmoid colon and rectum), it can be seen to have different embryological roots (3). LCRC is seen more often than RCC (4). RCC is seen more in females than LCRC, is generally more advanced at the time of diagnosis, and has a poorer prognosis (5, 6). Significant differences have been shown between right and left colon cancers in terms of molecular markers, and this is reflected in treatment protocols (7). The epidermal growth factor receptor antagonist, cetuximab, is more effective in LCRC than in RCC (8). RCC presents more often with anemia due to subclinical bleeding, and LCRC with hematochesia and changes in defecation habits (9).

Together with the formation of malignancy, inflammatory cytokines and growth factors are expressed from tumour cells, and inflammation develops in the tumour micro-environment (10). There is prolonged inflammation together with cancer, and inflammatory cells play an important role in tumour pathogenesis. Neutrophils cause oncogenesis whereas lymphocytes slow down tumour maturation (11). Bone marrow activity increases because of the proinflammatory activity of tumour cells (12). The over-activation of bone marrow causes immature cells to pass into the serum. In inflammatory conditions, an increase is seen in dimensional blood cell indexes, which signifies an increase in red blood cell and platelet production, such as RDW and PDW (13).

There are differences between right and left colon tumours in respect of embryology, epidemiology, clinicopathology, molecular markers, and prognosis (14). Therefore, there is clinical importance to the differentiation of RCC and LCRC. The Fecal Occult Blood Test (FOBT) is less sensitive and specific in the diagnosis of RCC than LCRC (15). The sensitivity of colonoscopic examination for RCC is lower due to technical reasons, morphologic features of polyps and sometimes inadequate cleaning of the proximal colon (16). Therefore, inflammatory markers, which are easily accessible, low-cost, and obtained from routinely used tests, may be

useful in the identification of the localization of colorectal cancer. In the literature there are some studies of NLR and PLR related to colorectal cancer localization, and a limited number of studies of SII and RDW (17-20). Immature granulocytes and PDW have not been investigated to date. The aim of this study was to investigate the diagnostic benefit of inflammatory markers in the differentiation of right and left colon cancers.

MATERIALS AND METHODS

The study is a methodological research using retrospective data screening method. Based on the paper with a similar subject and method, an effect size of 0.43 was calculated in the power analysis for the mann Whitney U test, which is the test used in the manuscript (21). The minimum sample size required to be included in the study for a level of error of 0.05 and a power of 0.80 were $n=176$. Sample size estimation was performed using G*Power 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany. The hospital database was screened for the data of patients who underwent surgery because of CRC in the General Surgery Clinic of a tertiary-level hospital between 01.06.2023 and 30.04.2024. The patients included in the study were those aged >18 years who underwent colon resection because of colorectal cancer, and had hematological blood tests before surgery or medical treatment. The study exclusion criteria were defined as colectomy performed because of benign disease, emergency colon surgery because of perforation or obstruction in the colon, colectomy due to colon involvement of another malignancy, the presence of synchronous colon tumour, familial adenomatous polyposis, Gardner syndrome, Lynch syndrome, a simultaneous other malignancy, hematological disease, pregnancy, another inflammatory disease that could change the results of the hematological test, or unavailability of the pre-treatment hematological test results.

The patients were separated into two groups of right colon cancer (ascending colon and transverse colon) and left colorectal cancer (splenic flexura, descending colon, sigmoid colon, and rectum). A record was made for each patient of age, gender, tumour localization, tumour differentiation, and tumour grade.

The full blood count taken before the first treatment (surgical or medical) of the patients was used for the hematological markers. Peripheral venous blood samples were

taken and the samples were centrifuged for 15 minutes at room temperature. Measurements were taken using a Sysmex XN series analyzer (Sysmex, Kobe, Japan). Comparisons were made between the two groups of the parameters of neutrophil count, lymphocyte count, platelet count, hemoglobin value, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune inflammation index (SII) (platelet x neutrophil count / lymphocyte count), immature granulocyte count (IGC), immature granulocyte percentage (IG%), platelet distribution width (PDW), and red blood cell distribution width percentage (RDW%).

Approval for the study was granted by the Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK-2024-238, dated: 20.03.2024). All the study procedures were in compliance with the Helsinki Declaration and local ethics criteria.

Data obtained in the study were analyzed statistically using SPSS vn. 26.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc vn. 22.023 (Medcalc software, Ostend, Belgium). The distribution of numerical variables was examined with visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were stated as mean \pm standard deviation (SD) values for continuous variables showing normal distribution, and as median, minimum and maximum values for those not showing normal distribution. Categorical variables were stated as number (n) and percentage (%). In the comparisons between groups, the Student's t-test was used for normally distributed data, the Mann Whitney U-test for data not normally distributed, and Pearson's Chi-square test was applied to categorical data. Receiver Operating Curve (ROC) analysis was performed to determine the sensitivity and specificity of the inflammatory markers for colorectal cancer localization, and cutoff values were determined with Yuoden index. About the AUC, a value of 0.5 indicates that the test provides no information to distinguish between groups, while a value of 1.0 indicates that all patients and healthy people were correctly classified.

RESULTS

Evaluations were made of a total of 210 patients with colorectal cancer, as 71 (33.8%) in the RCC group and 139 (66.2%) in the LCRC group, with a mean age of 66.50 years (range, 25 - 90 years). The clinical characteristics

of the patients are shown in Table 1. The numerical data of the comparisons of the clinical characteristics and inflammatory parameters of the groups are shown in Table 2. No significant difference was determined between the groups in respect of age, gender, and tumour grade.

Table 1. Demographic and Oncologic Characteristics of All Patients

Variable	Value
Age*	66.50 (25.00 – 90.00)
Gender	
Male	126 (60.0 %)
Female	84 (40.0 %)
Tumour Localization	
Ascending Colon	52 (24.8 %)
Transverse Colon	19 (9.0 %)
Descending Colon	24 (11.4 %)
Sigmoid Colon	60 (28.6 %)
Rectum	55 (26.2 %)
T stage	
T1	15 (7.1 %)
T2	30 (14.3 %)
T3	118 (56.2 %)
T4	47 (22.4 %)
N Stage	
N0	117 (55.7 %)
N1	54 (25.7 %)
N2	39 (18.6 %)
M Stage	
M0	183 (87.1 %)
M1	26 (12.4 %)
Tumour Differentiation	
Good	29 (13.8 %)
Mild	130 (61.9 %)
Poor	18 (8.6 %)

*median (min – max)

Table 2. Clinical, Demographic and Laboratory Characteristics of Patients According to Tumor localization

Value	Right Colon Cancer n=71 (33.8 %)	Left Colorectal Cancer n=139 (66.2 %)	p Value
Age*	68.00 (35.00 – 90.00)	65.00 (25.00 – 89.00)	0.125 ^d
Gender (male)	39 (54.9 %)	87 (62.6 %)	0.284 ^e
Tumour Stage			0.352 ^e
Stage 1	10 (14.1 %)	29 (20.9 %)	
Stage 2	27 (38.0 %)	48 (34.5 %)	
Stage 3	22 (31.0 %)	48 (34.5 %)	
Stage 4	12 (16.9 %)	14 (10.1 %)	
Tumour Stage			0.651 ^e
Stage 1-2	37 (52.1 %)	77 (55.4 %)	
Stage 3-4	34 (47.9 %)	62 (44.6 %)	
Neutrophyl* ^a	4.74 (1.89 – 16.93)	4.88 (1.65 – 12.13)	0.908 ^d
Lymphocyte* ^a	1.86 (0.95 – 5.47)	1.99 (0.31 – 4.78)	0.319 ^d
Platelet** ^a	306.50 ± 83.18	304.19 ± 109.54	0.873 ^f (CI: 24.52 - 28.84)
Hemoglobin* ^b	11.35 (6.40 – 16.40)	13.00 (6.00 – 17.00)	0.001 ^d
NLR*	2.54 (0.81 – 10.14)	2.47 (0.89 – 21.06)	0.493 ^d
PLR*	151.82 (52.10 – 405.93)	143.30 (2.23 – 564.89)	0.230 ^d
SII*	731.71 (187.38 – 4612.66)	714.48 (11.99 – 4112.43)	0.489 ^d
IG count* ^a	0.03 (0.00 – 0.15)	0.03 (0.01 – 0.14)	0.902 ^d
IG %*	0.40 (0.00 – 1.60)	0.40 (0.10 – 1.70)	0.815 ^d
PDW* ^c	11.10 (9.10 – 17.90)	11.50 (7.60 – 18.60)	0.653 ^d
RDW %*	14.80 (11.90 – 27.90)	13.70 (11.00 – 37.10)	0.005 ^d

*median (min – max), **mean ± standart deviation, ^a103/μL, ^bgr/dl, ^cfL, ^d Mann Whitney U test, ^e Pearson's Chi-square test, ^f Student's t test, NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; IG Count: Immature Granulocyte Count; IG%: Immature Granulocyte Percentage; PDW: Platelet Distribution Width; RDW: Red Blood Cell Distribution Width

When the neutrophil, lymphocyte, platelet, and PDW measurements were compared according to tumour localization, there were seen to be no significant differences ($p=0.908$, $p=0.319$, $p=0.873$, $p=0.653$, respectively). The NLR, PLR, and SII index values were similar in both groups ($p=0.493$, $p=0.230$, $p=0.489$, respectively). The median (min-max) IGC and IG% values were almost the same in the two groups; RCC: 0.03(0.00 – 0.15) 103/ μ L and 0.40%(0.00 – 1.60), LCRC: 0.03(0.01 – 0.14) 103/ μ L and 0.40% (0.10 – 1.70) ($p=0.902$, $p=0.815$, respectively). Hemoglobin was determined to be statistically significantly lower in the RCC group than in the LCRC group (11.35 (6.40 – 16.40) vs 13.00 (6.00 – 17.00) mg/dl) ($p=0.001$). The RDW % was determined to be statistically significantly higher in the RCC group than in the LCRC group (14.80 %(11.90 – 27.90) vs. 13.70% (11.00 – 37.10) ($p=0.005$)).

A ROC curve was drawn and the Area Under the Curve (AUC) values were calculated to determine the diagnostic value of the inflammatory parameters in colorectal cancer localization (Table 3, Figure 1). In parallel with the results of the paired comparisons, the NLR, PLR, SII, IGC, and IG% showed no significance in the ROC analysis. There was determined to be a significant difference in respect of hemoglobin and RDW%, with AUC >0.6 ($p<0.001$, $p=0.004$, respectively). A cutoff value of <12.7 mg/dl for hemoglobin in the differentiation of RCC from LCRC showed sensitivity of 74.6%, specificity of 54.0%, and AUC of 0.640. A cutoff value of >15.4 % for RDW% was found to have 44.8% sensitivity, 77.7% specificity, and AUC 0.621.

Table 3. ROC Analysis Results of Variables According to Tumor Localization

Valuable	Cut-Off Value	AUC	p	Sensitifty	Specificity
Hemoglobin	<12.7	0.604	<0.001	74.6 %	54.0 %
NLR	>2.35	0.529	0.491	61.9 %	48.2 %
PLR	>195.86	0.551	0.222	38.0 %	75.5 %
SII	>403.49	0.529	0.484	88.7 %	23.0 %
IG count	>0.02	0.505	0.904	59.2 %	47.5 %
IG %	≤ 0.4	0.510	0.820	70.4 %	23.7 %
RDW %	>15.4	0.621	0.004	44.8 %	77.7 %

AUC: Area Under the Curve; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; IG Count: Immature Granulocyte Count; IG%: Immature Granulocyte Percentage; RDW: Red Blood Cell Distribution Width

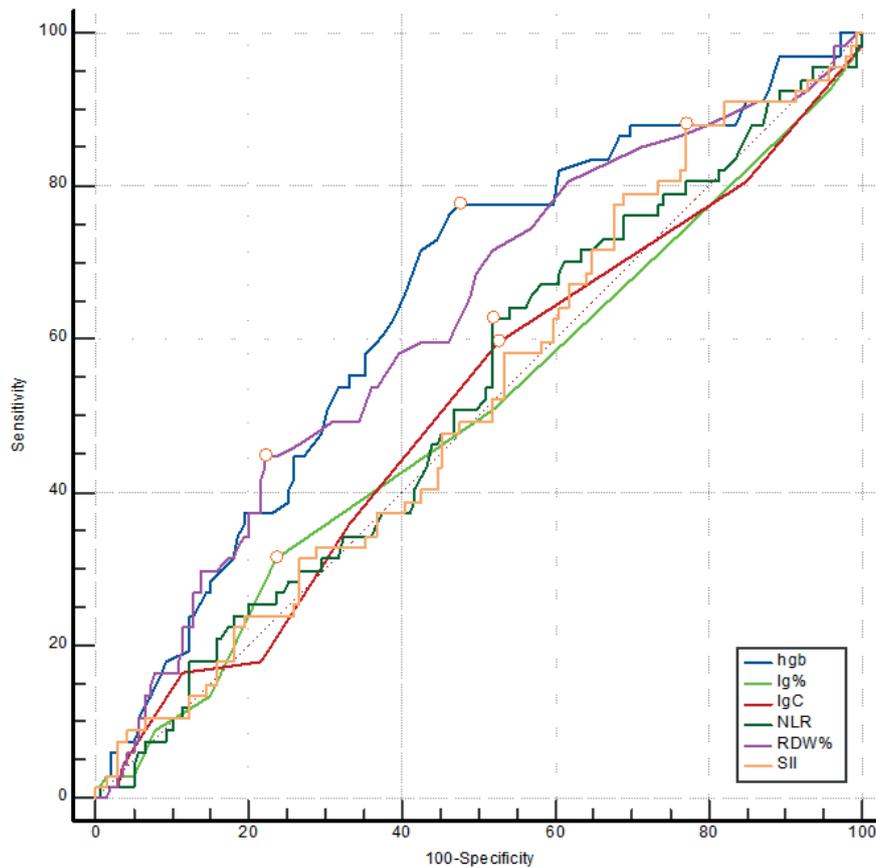


Figure 1: ROC-AUC Curve of Variables by Diagnosis of Right Colon Cancer.

DISCUSSION

There are embryological, epidemiological, clinicopathological, prognostic and even molecular differences between right and left colorectal cancer (22). Therefore, the need to evaluate RCC and LCRC as two different clinical entities has been advocated by some authors (17). There is known to be a strong association between cancer and inflammation (23, 24). This has led to recent frequent investigation of the use of inflammatory markers obtained from the full blood count in the diagnosis of malignancies.

The inflammatory markers first examined in this field are NLR and PLR, and although some previous studies have reported significant results related to CRC localization, there are also conflicting results (17, 18, 25). In the current study, NLR and PLR were determined to be higher in RCC, but not at a significant level. From the

encouraging results of NLR and PLR, researchers defined the SII, which they believed would have greater diagnostic power. The SII is obtained by multiplying the neutrophil and platelet counts, then dividing by the lymphocyte count (26). The SII is an important prognostic marker in CRC, but there is a limited number of studies on the prediction of CRC localization (27). In two recent studies, the SII was reported to be diagnostic for RCC in one, whereas the other study showed no significant difference (28, 29). The current study results showed no benefit of SII in the evaluation of CRC localization.

Immature granulocytes (IG) seen in peripheral blood indicate an increase in bone marrow activation (30). This emerges in infections and other inflammatory conditions. In studies of the severity of inflammation, significant results have been obtained for IG (31). When the relationship of cancer with inflammation is taken into

consideration, IG as a predictive factor of cancer has been the subject of previous studies. It has been evaluated as a predictive factor for renal cell carcinoma, thyroid malignancy, and axillary metastasis of breast cancer (12, 32, 33). In a recent study, IG was shown to be significant in the differentiation of metastatic colorectal cancer from non-metastatic colorectal cancer (34). Therefore, the value of IG in determining the anatomic localization of CRC was investigated in the current study as it has not been focused on previously. However, no significant difference could be determined in either the paired tests or in the ROC analysis. The benefit of IG has been demonstrated in the diagnosis of renal cell carcinoma, breast cancer, and thyroid cancer, as well as in the staging of colon cancer. However, it does not provide significant information regarding the localization of colorectal cancer. We believe that this may be due to the similar impact of inflammatory processes on colorectal cancer development, regardless of whether it occurs on the right or left side.

When hemoglobin values in CRC have been compared according to anatomic localization, hemoglobin has been observed to be lower in RCC (9, 19). One of the two markers for which a difference was found in the current study was hemoglobin. RDW is a marker that reflects the heterogeneity of erythrocyte volume, and is defined as increased anisocytosis. It has been used for a long time to obtain information about the types of anemia (20). RDW has been shown to be increased in some chronic and inflammatory conditions (35). In two previous studies of the differentiation of RCC from LCRC, high sensitivity and specificity values were reported for RDW (19, 20). In the current study results, RDW was seen to be significant in the determination of the anatomic localization of CRC. The right colon (especially the cecum) is wider than the sigmoid colon and the rectum. Tumours developing in the right colon can remain silent and grow for a long time without causing obstruction. A mass growing asymptotically in the right colon becomes ulcerated and progresses to subclinical chronic bleeding. This chronic slow bleeding can then cause iron deficiency and microcytic anemia (22). This is thought to be the pathogenesis of increased RDW and low hemoglobin in RCC.

The TNM grades were similar in the two groups of the current study, so the comparisons of the inflammatory

markers were independent of the tumour grade. The fact that some previous papers have reported significant results for NLR, PLR, and SII in the determination of anatomic localization can be considered to be due to the correlation between tumour grade and inflammatory markers. As the tumour grades of the current study groups were similar, there was no difference in the NLR, PLR, and SII values. Although hemoglobin and RDW were found to be significant in the determination of anatomic localization, this could have been due to subclinical chronic bleeding. IG has recently been viewed as a parameter showing inflammation, and there are cancer-related results in a few studies. To the best of our knowledge, the current study is the first in literature to have examined IG in CRC anatomic localization, and therefore we were hopeful, however this inflammatory marker was not statistically significant.

In addition to the previously frequently examined parameters of NLR, PLR, and SII, this study also included the rarely studied RDW, and IG, which has not been previously investigated. The investigation of recently considered inflammatory parameters together in a single study can be considered a strong aspect of this research. However, there were also some limitations to this study, primarily the single-centre, retrospective design, the relatively low number of patients (total 210), and that molecular markers were not investigated.

In this study of CRC localization in patient groups with similar TNM grades, no difference was observed in the inflammatory markers of NLR, PLR, SII, and IG, and a significant difference was determined only in hemoglobin and RDW. This suggested that the inflammatory markers were not sufficient to determine tumour localization and the significant parameters could have been due to subclinical hemorrhage.

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Abbreviations list

CRC: colorectal cancer
 RCC: right colon cancer
 LCRC: left colorectal cancer
 NLR: neutrophil-lymphocyte ratio
 PLR: platelet lymphocyte ratio
 SII: systemic immune inflammation index
 IG: Immature granulocytes
 IGC: immature granulocyte count
 IG%: immature granulocyte percentage
 RDW%: red blood cell distribution width percentage
 PDW: platelet distribution width
 FOBT: Fecal Occult Blood Test
 ROC: receiving operatin curve
 AUC: Area Under the Curve

Ethics approval and consent to participate

All authors declare that the study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of Türkiye. Approval was granted by the Ethics Committee of Ankara Etlik City Hospital (Date: 20.03.2024, No: AEŞH-BADEK-2024-238).

Consent for publication

This study was designed as a retrospective review of hospital data; thus, ethics committee approval was obtained, while patient informed consent was not deemed necessary.

Availability of data and materials

The study data are digitally archived in the personal repositories of the authors.

Competing interests

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.

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Authors' contributions

Idea/Concept: ÜÖ. Design: ÜÖ. Control/Supervision ÜÖ, NTB. Data Collection And/Or Processing: ÜÖ, NTB. Analysis And/Or Interpretation: ÜÖ. Literature Review: ÜÖ. Writing The Article: ÜÖ. Critical Review: NTB. References And Fundings: ÜÖ. Materials: NTB. Other: ÜÖ.

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