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The value of inflammatory indexes in colorectal cancers

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Abstract

In recent years, a relationship has been established between inflammatory indexes and the prognosis of many cancers. Although there are many studies investigating their relationship with colorectal cancers (CRC), there is a serious difference between the results in the related literature. The present study aimed to share our own experience with inflammatory indexes in CRC patients. Patients with a diagnosis of CRC who underwent surgery between January 2019 and June 2022 were retrospectively scanned. Exclusion criteria were as follows; being in a septic state before surgery, accompanying hematological disease, receiving neoadjuvant chemotherapy/radiotherapy, being diagnosed with recurrent CRC, undergoing emergency surgery, receiving immunosuppressive or anti-inflammatory treatment. Therefore, the study was conducted with 52 patients. Demographic information, tumor localization, stages and pathology data of the patients were examined. The relationship between these variables and the systemic immune-inflammation index (SII), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) was investigated. A significant correlation was found between pathological T stages and SII ($p=0.008$), NLR ($p<0.001$) and PLR ($p=0.035$). No correlation was found between inflammatory indexes and Age, Tumor Diameter, N Stage, Total Lymph Node Count, Metastatic Lymph Node Count. In our study, inflammatory indexes were found to be associated only with the T stage. Considering our results together with the variable results in the literature, more evidence is needed for the safe and active use of SII, NLR and PLR as markers of colorectal cancers.

Keywords: Colorectal cancer, systemic immune-inflammation index, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio

Introduction

CRC, responsible for approximately 9% of cancer-related deaths, is the third most prevalent cancer in males and the second most frequent cancer in women [1]. While the 5-year survival is around 90% in the early stage, it decreases to 13% as the stage progresses [2]. Markers such as RAS mutation, microsatellite instability and BRAF mutations have prognostic value [3]. However, the fact that these tests require invasive intervention, special equipment and high costs limit their use. As a result, several research have been done to identify less expensive and more accessible prognostic indicators.

It is known that inflammation stimulates tumor development, metastasis and progression by creating mutations or triggering epigenetic mechanisms [4]. Therefore, various related studies have been designed and conducted to study the association between inflammation and cancer [5,6]. Some of the mediators secreted by neutrophils stimulate the proliferation of tumor cells, tumoral invasion, angiogenesis, and lymph node or distant organs metastasis [7,8]. Platelets help free-circulating tumor cells to escape from the immune system and also stimulate proliferation and angiogenesis through mediators [9,10]. When the number of monocytes grows, so does the number of tumor-associated

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macrophages, promoting tumor growth and metastasis [11]. Lymphocytes may trigger cytotoxic cell death, as well as impede tumor cell growth and migration, so contributing to the immune response to cancer [12,13]. For this reason, the balance between these cells directly influences tumor formation.

With a complete blood count, immune-inflammatory elements (neutrophils, lymphocytes and platelets) levels can be easily measured. Several immunological measures, such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and Systemic immune-inflammation index (SII), have been developed in recent years [14-16]. While there are studies showing that these indexes, especially SII, are significant prognostic factors in CRC, there are also studies that have come to the opposite conclusion [17-19]. In our study, we aimed to share our own results on this subject, which has controversial results in the literature.

Material and Methods

Patients who were operated on with the diagnosis of CRC at Ondokuz Mayis University Faculty of Medicine General Surgery Department between January 2019 and June 2022 were retrospectively scanned. The study criteria were determined as follows; having a pathologically confirmed diagnosis of CRC, undergoing surgical resection, staging with preoperative cross-sectional imaging, and preoperative complete blood count result. Exclusion criteria were as follows; being in a septic state before surgery, having accompanying hematological disease, receiving neoadjuvant chemotherapy/radiotherapy, being diagnosed with recurrent CRC, undergoing emergency surgery, receiving immunosuppressive or anti-inflammatory treatment. Patients' age, gender, tumor localization (right-transverse / left-rectosigmoid), distant metastasis, pathological diagnosis, tumor differentiation, presence of lymph node metastasis, TNM stage, tumor diameter, total number of lymph nodes removed at surgery, number of metastatic lymph nodes, complete blood count results (neutrophil, lymphocyte and platelet) were analyzed.

Formulas used in calculating indexes;

PLR=platelet count / lymphocyte count

NLR=neutrophil count / lymphocyte count

SII=PLR × neutrophil count

This study was conducted with the permission of Ondokuz Mayis University Clinical Research Ethics Committee (January 30, 2023, 2022/586). Informed consent was obtained from the patients.

IBM SPSS V23 was used to evaluate the data. The Shapiro-Wilk test was used to assess conformity to the normal distribution. Pearson's correlation was employed for normally distributed data and Spearman's rho correlation analysis for non-normally distributed data in the investigation of the association between quantitative data and PLT, SII, NLR, and PLR. To compare normally distributed data by matched groups, an independent two-sample t-test was performed. The Mann Whitney U test was used to compare data from matched groups that were not regularly distributed. For quantitative data, the findings were reported as mean, standard deviation, and median (minimum - maximum), and for categorical data, as frequency and %. The significance threshold was set as p=0.050.

Results

There were 124 patients who underwent surgery for CRC. Thirty-six patients were excluded because of neoadjuvant chemoradiotherapy, 33 patients due to emergency surgery, and 3 patients because of their second primary cancer. Therefore, the study was conducted with 52 patients, 65.4% of whom were male, 32.7% had a right localized tumor, 3.8% had distant metastases, 40.4% had lymph node metastases, 55.8% were stage I-II. When the pathological diagnoses of the patients were examined, it was observed that adenocarcinoma was the most common with 86.5% and neuroendocrine tumor was the rarest with 1.9% (Table 1).

Table 1. Descriptive statistics of categorical variables

	Frequency (n)	(%)
Gender		
Male	34	65.4
Female	18	34.6
Tumor Location		
Right/Transvers	17	32.7
Left/Rectosigmoid	35	67.3
TNM stage		
I-II	29	55.8
III-IV	23	44.2
T Stage		
I	4	8
II	12	23
III	24	46
IV	12	23
N Stage		
0	31	60
I	11	21
II	10	19
M Stage		
0	50	96.2
I	2	3.8
Pathological Diagnosis		
Adenocarcinoma	45	86.5
Mucinous Adenocarcinoma	6	11.6
Neuroendocrine Tumor	1	1.9
Tumor Differentiation		
Well differentiated	23	44.2
Moderately differentiated	26	50.0
Poorly differentiated	3	5.8
Lymph Node Metastasis		
Presence	21	40.4
Absence	31	59.6

TNM: American Joint Committee on Cancer, TNM staging classification for colon cancer 8th edition, T: Primary Tumor, N: Regional Lymph Nodes, M: Distant Metastasis

Descriptive statistics of quantitative variables are summarized in Table 2. Platelet count and age had a statistically significant negative and modest connection (r=-0.366; p=0.008). SII and problematic T stage had a statistically significant positive and modest connection (r=0.363; p=0.008). NLR and pathological T stage were shown to have a statistically significant positive and moderate connection (r=0.484; p=0.001). PLR and diseased T stages were shown to have a statistically significant positive

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and modest connection (r=0.293; p=0.035). No statistically significant association was found between any quantitative data and PLT, SII, NLR, or PLR (p>0.050) (Table 3).

Table 2. Descriptive statistics of quantitative variables

	Mean±S.D	Median (Min.-Max.)
Platelet count	280423.08±88841.20	274500 (88000-546000)
SII	823.17±531.82	682 (197-3063)
NLR	2.56±1.76	2 (1-9)
PLR	192.25±90.20	182 (54-539)
Age	63.10±13.52	62.5 (31-94)
Tumor Diameter (mm)	48.02±22.99	40 (15.00-130)
Total Lymph Node Count	21.65±14.91	18.5 (0-73)
Metastatic Lymph Node Count	2.42±6.03	0 (0-38)

SII: Systemic Immune-Inflammation Index, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio

No statistically significant difference was found between genders in platelet count (p=0.402), SII (p=0.110), or PLR (p=0.082). There was a statistically significant variation in median NLR levels based on gender (p=0.027). Men had a median NLR value of 2.5, whereas women had a median NLR score of 2. No statistically significant difference was found between tumor localization and platelet count (p=0.899), SII (p=0.074), NLR (p=0.166), and PLR (p=0.429). According to lymph node metastasis, no statistically significant difference was found in platelet count (p=0.285), SII (p=0.661), NLR (p=0.275), or PLR (p=0.608). Table 4 shows no statistically significant difference in platelet count (p=0.386), SII (p=0.235), NLR (p=0.074), and PLR (p=0.412) values based on TNM stage I-II or III-IV (p=0.412).

Table 3. The relationship between quantitative data and PLT, SII, NLR, PLR

	PLT		SII		NLR		PLR	
	r	p	r	p	r	p	r	p
Age	-0.366**	**0.008**	-0.021*	0.882	0.268*	0.055	-0.137*	0.334
Tumor Diameter (mm)	0.273*	0.050	0.271*	0.052	0.228*	0.105	0.201*	0.152
T Stage	-0.083*	0.557	0.363*	**0.008**	0.484*	**<0.001**	0.293*	**0.035**
N Stage	-0.151*	0.287	0.084*	0.555	0.158*	0.265	0.094*	0.508
Total Lymph Node Count	0.113**	0.426	-0.026*	0.853	-0.135*	0.339	-0.028*	0.843
Metastatic Lymph Node Count	-0.131*	0.355	0.08*	0.446	0.169*	0.230	0.122*	0.390

*r: Spearman's rho correlation coefficient, **Pearson's correlation coefficient SII: Systemic Immune Inflammation Index, NLR: Neutrophil to Lymphocyte Ratio, PLR : Platelet to Lymphocyte Ratio, N: Regional Lymph Nodes, M: Distant Metastasis

Table 4. The relationship between PLT, SII, NLR, and PLR according to categorical variables

		Platelet (10^9/L)	SII	NLR	PLR
Gender					
Male		272±92	850±476	2.8±1.7	199.9±81.2
		259 (88-546)	726 (197-2438)	2.50 (1-9)	193.5 (54-489)
Female		294±81	771±634	2±1.7	177.7±106
		296 (147-412)	597 (293-3063)	2 (1-8)	137.5 (90-539)
	Test st.	t=0.845	U=223	U=195	U=215.5
	p	0.402	0.110	**0.027**	0.082
Tumor Location					
Left/Rectosigmoid		279±81	761±546	2.3±1.6	190±96.7
		280 (88-446)	641(197-3063)	2 (1-8)	177 (54-539)
Right/Transvers		282±104	950±491	2.9±1.9	196.6±77.5
		269 (98-546)	797 (368-2180)	2 (1-9)	196 (90-361)
	Test st.	t=0.128	U=206	U=229	U=257
	p	0.899	0.074	0.166	0.429
Lymph Node Metastasis					
Absence		291±79	852±614	2.4±1.6	195±104.4
		297 (147-446)	641 (197-3063)	2 (1-8)	177 (54-539)
Presence		264±100	780±389	2.8±1.9	188.3±65.9
		253 (88-546)	714 (282-2180)	2 (1-9)	195 (77-361)
	Test st.	t=1.080	U=302	U=269	U=298
	p	0.285	0.661	0.275	0.608
TNM stage					
I-II		290±81	816±618	2.2±1.6	194.3±107.9
		297 (147-446)	629 (197-3063)	2 (1-8)	173 (54-5390)
III-IV		268±97	831±410	2.9±1.8	189.6±63.3
		266 (88-546)	722 (282-2180)	3 (-9)	195 (77-361)
Test st.		t=0.874	U=269	U=240	U=289
p		0.386	0.235	0.074	0.412

t: Two independent samples t test statistic, U: Mann-Whitney U test statistic, mean±s. deviation, median (minimum – maximum). SII: Systemic Immune-Inflammation Index, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, TNM: American Joint Committee on Cancer TNM Staging Classification for Colon Cancer

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Discussion

Hu et al. discovered SII in hepatocellular cancer. They found a possible relation between the computed preoperative SII with free-circulating tumor cells [20]. Elevation of SII was found to be a poor prognostic factor in patients with hepatocellular carcinoma, gastric cancer, esophageal squamous cell carcinoma, urinary system cancer, small cell lung cancer, non-small cell lung cancer, and acral melanoma in the meta-analysis of 22 studies and 7657 patients by Yang et al., but it was found to be unrelated to prognosis in CRC patients [21]. Similar to SII, NLR and PLR are calculated with different combinations of systemic inflammatory parameters [22,23]. Passardi et al. discovered a relation between elevated SII, NLR, and PLR levels and a poor prognosis in CRC patient [24].

According to our findings, there was a negative association between platelet count and age (p=0.008), and a statistically significant link between pathological T stage and SII (p=0.008), NLR (p=0.001), and PLR (p=0.035) (Table 3). Also, males had greater NLR than females (p=0.027). The findings of the research in the literature differ greatly. 240 individuals with metastatic CRC were evaluated retrospectively by Xie et al. In individuals with metastatic CRC, a high SII level independently predicts poor clinical outcomes. Moreover, contrary to our findings, they discovered that, while SII was related with the N stage, it was not connected with the T stage [25]. Although all the patients in their trial were in stage IV, just two of the patients in our study were in stage IV. Tao et al. observed that SII is linked with prognosis in their research of 118 individuals with CRC. Similar to our study, they did not find a relationship with age, gender and tumor localization [26]. In Chen et al.'s retrospective study of 1383 CRC patients, they found a significant relationship between SII, NLR and PLR levels and T stage, similar to our results, but different from us, they concluded that there was a significant relationship with tumor diameter, N, M and TNM stages. They did remark, however, that there is a link between SII, NLR, and PLR and prognosis, and that SII is a more potent tool for predicting survival result than NLR and PLR [17]. Dong et al. discovered that SII elevation was related with poor prognosis in a meta-analysis of 12 studies, and they, like us, did not identify a connection with gender, tumor site, lymph node metastases, or age [3]. Contrary to other studies, Sato et al.'s study on 86 obstructive CRC patients found a correlation between low preoperative SII and PLR values and poorer relapse-free survival [27]. It should be noted, however, that all the patients in this research were diagnosed with obstructive CRC, which may have resulted in alterations in neutrophil, lymphocyte, and platelet counts. The reason for the different results in the literature may have been resulting from their highly variable study designs. On the other hand, the parameters used in the calculation of these indexes are also affected by non-cancer reasons. Neutrophil, lymphocyte and platelet counts can be affected by many factors; viral or bacterial infections, inflammation, use of drugs such as steroids or heparin, asplenia, hypersplenia, chronic liver disease, exercise, trauma, stress, obesity, hematological malignancies, solid malignancies, thymoma, chemotherapeutics, autoimmune diseases, alcoholism [28-38]. The fact that the parameters used are affected by many factors may prevent the standardization of studies.

Conclusion

In our study, a significant relationship was established between T stage and SII, NLR and PLR. However, the usefulness of the relationship that can only be established with the T-stage in daily practice is debatable. Considering our results together with the variable results in the literature, we think that more evidence is needed for a safer and more active use of SII, NLR and PLR as markers in colorectal cancers.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was conducted with the permission of Ondokuz Mayis University Clinical Research Ethics Committee (January 30, 2023, 2022/586).

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