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Predictive value of hematological parameters in colonoscopy patients with colon involvement on PET/CT

PET/CT'de kolon tutulumu olup kolonoskopi yapılan hastalarda hematolojik parametrelerin kolon tutulumunu öngörü değeri

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Background and Aims: *This study aimed to evaluate the findings of patients who underwent colonoscopy due to colon involvement in positron emission tomography/computed tomography, as incidental 18-fluoro-2-deoxyglucose uptake can be detected during tumor imaging.* ***Materials and Methods:*** *A total of 84 patients were included in this prospective study. Hematological parameters and their effects on malignancy were examined in patients who underwent colonoscopy. Demographic characteristics and positron emission tomography/computed tomography involvement sites were compared with laboratory parameters.* ***Results:*** *The gastrointestinal system maximum standardized uptake value was important in predicting cancer before endoscopy (area under curve: 0.738, p = 0.001). The neutrophil to lymphocyte ratio also predicted cancer before endoscopy (area under curve: 0.659, p = 0.033), as did the platelet to lymphocyte ratio (area under curve: 0.657, p = 0.035). All three diagnostic tests showed clinical predictivity, with the gastrointestinal system maximum standardized uptake value having the highest distinctiveness power. Logistic regression analysis revealed that an increase in the gastrointestinal system maximum standardized uptake value increased the probability of cancer by 1.179 times (p = 0.004), while an increase in the neutrophil to lymphocyte ratio value increased the probability of cancer by 1.108 times (p = 0.007).* ***Conclusion:*** *This research demonstrated the predictive potential of gastrointestinal system maximum standardized uptake value, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio in premalignant/malignant colon pathologies.*

Key words: *PET/CT, colon cancer, SUVmax, NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio)*

Giriş ve Amaç: *Bu çalışmada, tümör görüntüleme sırasında tesadüfen 18-floro-2-deoksiglukoz tutulumu tespit edilebildiğinden, kolon tutulumu nedeniyle kolonoskopi yapılan hastaların pozitron emisyon tomografi/bilgisayarlı tomografideki bulgularının değerlendirilmesi amaçlandı.* ***Gereç ve Yöntem:*** *Bu prospektif çalışmaya toplam 84 hasta dahil edildi. Kolonoskopi yapılan hastalarda hematolojik parametreler ve bunların maligniteye etkileri incelendi. Demografik özellikler ve pozitron emisyon tomografi/bilgisayarlı tomografi tutulum bölgeleri laboratuvar parametreleriyle karşılaştırıldı.* ***Bulgular:*** *Endoskopi öncesi kanseri öngörmede gastrointestinal sistem maksimum standardize tutulum değeri önemliydi (eğri altında kalan alan: 0.738, p = 0.001), Nötrofil/lenfosit oranı (eğri altında kalan alan: 0.659, p = 0.033), trombosit/lenfosit oranı (eğri altında kalan alan: 0.657, p = 0.035) aynı zamanda endoskopi öncesi kanseri öngördü. Her üç tanısal test de klinik öngörücülüğü gösterdi; gastrointestinal sistem maksimum standardize tutulum değeri en yüksek ayırt etme gücüne sahipti. Lojistik regresyon analizi, gastrointestinal sistem maksimum standardize tutulum değerindeki artışın kanser olasılığını 1.179 kat (p = 0.004), nötrofil lenfosit oranı değerindeki artışın ise kanser olasılığını 1.108 kat (p = 0.007) artırdığını ortaya koydu.* ***Sonuç:*** *Bu araştırma, premalign/malign kolon patolojilerinde gastrointestinal sistem maksimum standardize tutulum değeri, nötrofil lenfosit oranı ve trombosit/lenfosit oranı 'nin öngörü potansiyelini ortaya koymuştur.*

Anahtar kelimeler: *PET/BT, kolon kanseri, SUVmax, NLR (nötrofil lenfosit oranı), PLR (Trombosit lenfosit oranı)*

INTRODUCTION

Colorectal cancers are the third most common cancer among newly diagnosed cancer patients, after prostate and lung cancers in men and breast and lung cancers in women (1). Metastases are detected in approximately half of colorectal cancer patients within the first five years after diagnosis. In addition to anatomical methods such as ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging, and positron emission tomography/computerized tomography (PET/CT) have been widely used in the detection of these metastases in recent years (2,3). Based on the increased use of glucose in malignant tissues, 18-fluoro-2-deoxyglucose (FDG) PET/CT is used as a non-invasive method in the follow-up of treatment response, as well as diagnosis and staging (4). However, since FDG is not a tumor-specific agent, it is known that it can also be involved in benign conditions, and this situation may cause diagnostic confusion (5).

Positron emission tomography (PET) is a non-invasive functional imaging technique that investigates the presence of malignant tumors. Fluorodeoxyglucose and PET play an active role in determining the diagnosis, staging, and response to treatment, revealing tumor aggressiveness, and detecting the radiotherapy area. FDG is retained in higher concentrations in tumors than in normal tissue and is easily detected as high-count foci in FDG-PET images (5,6). Although it varies from person to person, there may be physiologically diffuse or segmental colon involvement in the intestines. Due to the high sensitivity of PET examination performed for a different purpose, focal or nodular hypermetabolic lesions detected in the gastrointestinal system (GIS) have been reported to have a high probability of premalignant/malignant lesions such as a hyperplastic polyp, villous adenoma, or carcinoma. Therefore, colonoscopic evaluation of incidentally detected focal or nodular lesions is recommended (7).

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As 18-fluorodeoxyglucose PET/CT scans the whole body apart from becoming a frequently used method for tumor imaging, staging, and follow-up, it can incidentally detect malignities. Incidental FDG uptake was detected in 3.6% of the patients in PET/CT to evaluate non-gastrointestinal system diseases. False positive involvements were detected in approximately 9.3% to 63% of patients. Rigault et al. detected at least one lesion on colonoscopy in 46 of 70 patients with incidental focal colorectal FDG uptake (8). Kunawudhi et al. reported the positive predictive value of PET/CT as 48% for colon neoplasms (9). Putora et al. detected colonoscopic lesions in 44 of 51 patients with colonic involvement (10).

Within the scope of this research, we aimed to evaluate the findings of patients who underwent colonoscopy due to colon involvement in PET/CT.

MATERIALS and METHOD

In this study, hematological parameters were monitored in patients who underwent colonoscopy due to colon involvement in PET/CT, and their effects on malignancy were examined. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 14/465-18, and informed consent has been obtained from all participants.

Hematological laboratory parameters of the patients were collected. Demographic characteristics of the patients (age, gender, comorbid disease) and involvement sites in PET/CT were compared with laboratory parameters.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences) program was used to evaluate the data. Descriptive statistical methods (mean, standard deviation) and the quantitative data of normal distribution were compared with the Student's t-test-the Mann-Whitney U-test was utilized for non-normally distributed parameters. Pearson correlation analysis was conducted for parametric measures and Spearman correlation analysis for non parametric values to determine the relationship.

Student T Test, Mann Whitney U Test, and Spearman Correlation Analysis were used during univariate analysis of patients with and without cancer in order to predict malignancy before colonoscopy. In multivariate analysis, the independent variables in predicting cancer using possible factors were analyzed using logistic regression analysis. The Hosmer-Lemeshow test was performed for model fit. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 84 patients have been enrolled in this prospective study. The patients were analyzed according to the presence of cancer; 23.8% (n = 20) were cancer patients, and 76.2% (n = 64) did not have cancer. The mean age of 84 patients was 67.8 ± 9.5 years (43 – 92 years), with no statistically significant difference (Table 1).

The mean maximum standardized uptake (SUV_{max}) value of the patients (pleural mass) was 10.42 ± 6.63 (0 - 27.2), with no significance between cancer patients and other individuals. The median gastrointestinal system (GIS) SUV_{max} value of cancer patients was 10.85 [interquartile range (IQR) = 6.92], while the median GIS SUV_{max} value of the other subjects was 7.65 (IQR = 4.65), and there was a statistically significant difference (p = 0.001).

The white blood cell (WBC) of the cancer patient group was 8.08 ± 2.95 x 1000/µl (4.4 - 13.9), and the mean WBC of the other group was 7.67 ± 2.88 x 1000/µl (3.7 - 15.20). There was no statistically significant difference between the mean of the two groups. The neutrophil count of the cancer patients was 5.85 x 1000/µl (IQR = 4.67) and 5.97 x 1000/µl (IQR = 3.52), with no difference between the two groups. The lymphocyte count of the cancer patient group was 0.44 x 1000/µl (IQR = 0.43), and the lymphocyte count of the other group was 0.91 x 1000/µl (IQR = 0.76), and the difference was statistically significant (p < 0.05). The neutrophil to lymphocyte ratio (NLR) of the cancer patient group was 11.55 (IQR = 25.07), and the median of the other individuals was 7.11 (IQR = 9.81), with a statistical significance. The platelet to lymphocyte ratio (PLR) of cancer patients was 461.66 (IQR = 437.2), and the PLR of the other group was 283.59 (IQR = 285.73) (p = 0.035).

There was no significant difference between the two patient groups regarding endoscopy findings by gender. On the other hand, endoscopy findings were clinically different according to the type of involvement (p < 0.001). The cancer rate of those with diffuse involvement was higher than those with focal involvement (52.4% and 14.3%, respectively). The presence of adenomatous polyps or hyper polyps was similar between the groups (Table 2).

As a result of the receiver operating characteristic (ROC) analysis, it has been observed that the GIS SUV_{max} value is important in predicting cancer before endoscopy [area under curve (AUC): 0.738, 95: 0.626 - 850, p = 0.001]. NLR predicted cancer before endoscopy (AUC: 0.659, 95: 0.523 - 0.795, p = 0.033). The PLR was important in predicting cancer before endoscopy (AUC: 0.657, 95: 0.523 - 0.791, p = 0.035). All three diagnostic tests were important in terms of clinical predictivity. However, since the area of the GIS SUV_{max} value was bigger than the others, its distinctiveness power was higher. However, it is used as a diagnostic with high specificity and sensitivity to rule out other situations (Table 3) (Figure 1).

Table 1. Group comparisons of variables.

		N	Mean	SD	Minimum	Maximum	Median	IQR	P-value
Age	Cancer	20	66.90	10.49	53	92	65.00	15	
	No cancer	64	68.08	9.24	43	86	69.50	13	0.631
	Total	84	67.80	9.50	43	92	68.50	12	
Main lung mass SUV_{max}	Cancer	20	12.54	5.36	1.4	20.65	13.1	8.7	
	No cancer	64	9.75	6.87	0.00	27.20	9.35	9.9	0.100
	Total	84	10.42	6.63	0.00	27.20	10.07	10.52	
GIS SUVmax	Cancer	20	13.003	6.627	6.6	35	10.85	6.92	
	No cancer	64	9.02	4.81	2.78	26.41	7.65	4.65	**0.001**
	Total	84	9.97	5.53	2.78	35.00	8.60	5.79	
WBC	Cancer	20	8.08	2.95	4.4	13.9	7.55	5.43	
	No cancer	64	7.67	2.88	3.70	15.20	7.35	3.75	0.583
	Total	84	7.77	2.89	3.70	15.20	7.40	4.13	
Neutrophil	Cancer	20	6.47	2.69	3	11.8	5.85	4.67	
	No cancer	64	6.41	2.62	2.00	13.65	5.97	3.52	0.979
	Total	84	6.42	2.62	2.00	13.65	5.87	3.9	
Lymphocytes	Cancer	20	0.54	0.356	0.1	1.34	0.44	0.43	
	No cancer	64	0.83	0.41	.08	1.65	0.91	0.76	**0.009**
	Total	84	0.76	0.42	.08	1.65	0.76	0.75	
Hemoglobin	Cancer	20	10.68	1.05	9	12.4	10.55	1.68	
	No cancer	64	10.97	1.75	6.40	14.20	10.90	2.95	0.370
	Total	84	10.90	1.61	6.40	14.20	10.70	2.55	
Platelets	Cancer	20	206.52	60.02	140.4	366.8	190	92.3	
	No cancer	64	239.82	87.35	82.40	420.00	246.00	132.3	0.116
	Total	84	231.89	82.58	82.40	420.00	240.40	100.75	
MPV	Cancer	20	9.54	1.12	7.2	12	9.2	1.48	
	No cancer	64	9.39	1.53	6.40	13.00	9.45	2.28	0.713
	Total	84	9.43	1.44	6.40	13.00	9.40	1.8	
Monocyte	Cancer	20	0.1032	0.09	0	0.32	0.09	0.16	
	No cancer	64	0.18	0.22	0.00	1.00	0.11	0.23	0.452
	Total	84	0.16	0.20	0.00	1.00	0.10	0.18	
Albumin	Cancer	20	30.68	5.62	22	42	30	8.6	
	No cancer	64	32.30	6.71	16.60	46.00	32.40	9.73	0.334
	Total	84	31.91	6.47	16.60	46.00	32.00	10	
Total protein	Cancer	20	59.58	11.93	28	78	62	18.5	
	No cancer	64	63.91	8.29	40.00	76.60	64.60	12.1	0.143
	Total	84	62.88	9.39	28.00	78.00	64.60	12.35	
AST	Cancer	20	58.65	22.99	14	104	57	29.5	
	No cancer	64	52.92	29.98	11.00	136.00	45.00	38	0.157
	Total	84	54.29	28.45	11.00	136.00	46.00	36	
ALT	Cancer	20	58.95	23.77	14	110	58	32.5	
	No cancer	64	57.34	32.33	12.00	146.00	48.00	38	0.366
	Total	84	57.73	30.38	12.00	146.00	51.00	36	
LDH	Cancer	20	209.55	58.36	130	320	195	103	
	No cancer	64	206.41	102.43	112.00	782.00	168.00	99.5	0.248
	Total	84	207.15	93.51	112.00	782.00	187.00	100	
NLR	Cancer	20	22.14	24.8	4.33	92	11.55	25.07	
	No cancer	64	11.61	12.51	1.61	87.25	7.11	9.81	**0.033**
	Total	84	14.12	16.74	1.61	92.00	7.70	10.24	
PLR	Cancer	20	573.42	394.34	163.68	1520	461.66	437.2	
	No cancer	64	465.81	597.80	72.35	4335.00	283.59	285.73	**0.035**
	Total	84	491.43	555.86	72.35	4335.00	335.11	410.98	

SD: Standart deviation; IQR: Interquartile range; SUV: Standardized uptake value; GIS: Gastrointestinal system; WBC: White blood cell; MPV: Mean platelet volume; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

Table 2. Involvement, adenomatous polyp, hyper polyp according to endoscopy findings

			Endoscopy Findings Cancer (+)	Cancer (-)	Total	P-value
Involvement	Diffuse	n	11	10	21	**0.000**
		%	52.4%	47.6%	100.0%	
	Focal	n	9	54	63	
		%	14.3%	85.7%	100.0%	
Adenomatous polyp	No	n	20	60	80	**0.568**
		%	25.0%	75.0%	100.0%	
	Yes	n	0	4	4	
		%	0.0%	100.0%	100.0%	
Hyperpolyp	No	n	20	61	81	**1.000**
		%	24.7%	75.3%	100.0%	
	Yes	n	0	3	3	
		%	0.0%	100.0%	100.0%	

Table 3. GIS SUVmax, MPV, NLR, and PLR values of the study population

	GIS SUV_{max}	MPV	NLR	PLR
N	84	84	84	84
Mean	9.97	9.43	14.12	491.43
Standard deviation	5.53	1.44	16.74	555.86
Minimum	2.78	6.40	1.61	72.35
Maximum	35.00	13.00	92.00	4335.00
Median	8.60	9.40	7.70	335.11
IQR	5.79	1.80	10.24	410.98

GIS: Gastrointestinal system; SUV: Standardized uptake value; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; IQR: Interquartile range.

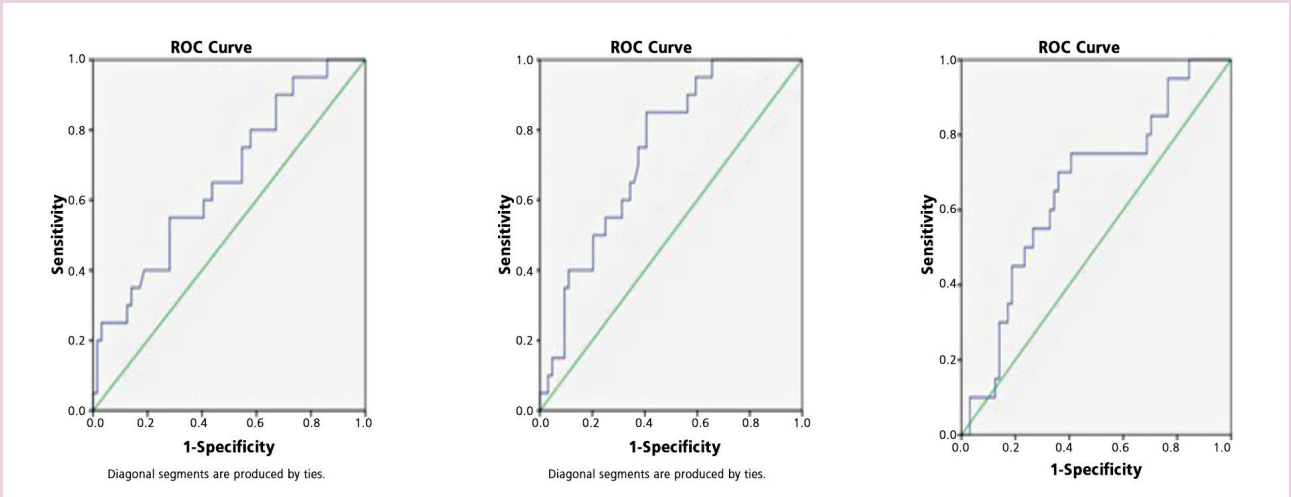

Figure 1. The sensitivity and specificity of GIS SUVmax value, NLR and PLR.
GIS: Gastrointestinal system; SUV: Standardized uptake value; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

A total of 84 patients (20 cancer, 64 control) were included in the study. In the logistic regression analysis, the p-value of the GIS SUV_{max} value was significant (p = 0.004), and one unit increase in the GIS SUV_{max} value increased the probability of cancer by 1.179 times. The p-value of the NLR (p = 0.007) was significant, and one unit increase in the NLR value increased the probability of cancer 1.108 times.

Table 4. Logistic regression model variables table

	AUC	P-value	Sensitivity %	Specifity %	Cut-off value	95% CI	Positive Predictive Value %	Negative Predictive Value %
GIS SUVmax	0.738	**0.001**	0.85	0.594	8.55	0.626-0.850	39.5	92.7
MPV	0.513	**0.862**				0.380-0.646		
NLR	0.659	**0.033**	0.55	0.719	11.1859	0.523-0.795	37.9	83.6
PLR	0.657	**0.035**	0.75	0.594	336.33	0.523-0.791	36.6	88.4

AUC: area under the ROC curve; CI: Confidence interval; GIS: Gastrointestinal system; SUV: Standardized uptake value; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

In the logistics regression analysis (LRA), the model created with only constant predicted 76.2% of the observed values correctly; hence, our model provided significant coefficients and the correct estimation of 78.6% of the observed values (Table 4).

DISCUSSION

The accuracy of preoperative staging in colorectal cancer (CRC) is very important in guiding the treatment. Therefore, imaging methods are expected to fully evaluate the localization, borders, and local and distant metastasis (11). Patients with CRC present with 20% metastases at the time of diagnosis, and these patients should be evaluated for distant metastases covering the whole body. However, imaging methods currently can only meet some of these expectations among the anatomical imaging methods. FDG-PET allows whole-body imaging in a single session. There is an increase in glucose consumption due to anaerobic glycolysis in malignant cells. This increase can be transferred to radiolabeled glucose imaging methods (12). Especially in patients with CRC who are followed up for recurrence, the tumor size can be detected with FDG-PET before it reaches the dimensions that conventional imaging methods can detect, and the patient's chance of curative resection increases (13).

However, it should be kept in mind that images with high metabolic properties detected in PET/CT, especially in metabolic terms, are not always specific to malignancy, and similar images can be obtained in the presence of inflammation and infection. It is also known that PET/CT may give false negative results, especially in malignancies with lower grades and low proliferation rates. For this reason, PET/CT results should be evaluated together with the patient's tumor type and clinical presentation by the clinician (14). In our study, the median GIS SUVmax value of cancer patients was 10.85 (IQR = 6.92), while the median GIS SUV_{max} value of the other subjects was 7.65 (IQR = 4.65), and there was a statistically significant difference. As a result of the ROC analysis, it has been observed that the GIS SUV_{max} value is important in predicting cancer before endoscopy. In the logistic regression analysis, the p-value of the GIS SUV_{max} value was significant, and one unit increase in the GIS SUV_{max} value increased the probability of cancer by 1.179 times. However, since the area of the GIS SUV_{max} value was bigger than NLR and PLR, its distinctiveness power was higher.

Changes in peripheral blood, such as neutrophilia, lymphopenia, and thrombocytosis, were evaluated in response to systemic inflammation. Since the physiological response of leukocytes to stress causes an increase in the number of neutrophils and a decrease in the number of lymphocytes, the ratio of these two subgroups to each other is used as an inflammatory marker. Thrombocytosis occurs as a result of proinflammatory cytokines stimulating megakaryocytes (15). In this context, studies on new parameters obtained from routine complete blood count, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) have been frequently conducted in various cancer types recently. These parameters depend on the complex relationship between the tumor's local environment and the host's inflammatory response and may predict early tumor relapse and mortality (16). Some studies have focused on the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio, which are considered among the markers of the systemic inflammatory response, and it has been shown that there is a relationship between these markers and the progression of the disease in patients with operated colorectal cancer. In other studies, a preoperative neutrophil/lymphocyte ratio of more than 4 or 5 in ovarian and lung cancers other than colorectal cancer has been found to be associated with an unfavorable prognosis, and an increase in the platelet/lymphocyte ratio is shown as a negative prognostic factor (17).

Other studies on CRC have reported that low NLR is associated with better disease-free survival (DFS) outcomes compared with patients with higher rates. In contrast, high NLR is associated with an independent prognostic factor and poor prognosis (18-20).

Kwon et al. reported that in preoperative NLR and PLR in colorectal cancers, preoperative elevated PLR reflected increased inflammatory response in response to more aggressive tumor biology (21). Smith et al. showed that high preoperative serum carbohydrate antigen (CA) 19-9 level and

increased PLR in cases with pancreatic adenocarcinoma indicate a poor prognosis at one-year survival (22).

Systemic inflammation triggers lymphopenia and causes an increase in NLR levels. NLR levels may be a prognostic determinant factor for cancer, and the use of anti-inflammatory drugs in the perioperative period may yield good results in terms of prognosis (16). In a previous study, NLR values in CRC patients were significantly higher than in the control group. These findings were consistent with the literature. The cut-off value for the NLR value was 5 (23). Halazun et al. stated that the cut-off value was accepted as 5 for the NLR value in 440 patients with liver metastasis of colorectal cancer (24). Chiang et al. found a cut-off value of 3 for the NLR value in 3857 colorectal cancer patients. It is thought that this difference may be due to factors such as geography, nutrition, environment, and genetics, which are thought to play a role in the development of CRC, and the data that each patient's immune response to cancer cells is different (25). In our study, NLR and PLR predicted cancer before endoscopy. One unit increase in the NLR value increased the probability of cancer 1.108 times.

This research elaborated on the predictivity potential of GIS SUVmax, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio in premalignant/malignant colon pathologies. All three diagnostic tests, GIS SUVmax, NLR, and PLR, were important in clinical predictivity. However, since the area of the GIS SUVmax value was bigger than NLR and PLR, its distinctiveness power was higher.

Ethics: *This study protocol was approved by Ethics Committee of Ankara Keçiören Keçiören Training and Research Hospital (Date: 22.06.2021, and number KAEK –14/465-18.). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all participants.*

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