Erciyes Med J 2021; 43(6): 548–53 • DOI: 10.14744/etd.2021.67689
ORIGINAL ARTICLE – OPEN ACCESS

The Role of Platelet Count, Platelet Lymphocyte Ratio, and Systemic Immune-Inflammatıon Index in Predicting Lymph Node Metastasis in Colon Cancer

Serhan Yılmaz, Hakan Bölükbaşı, Engin Okan Yıldırım, Aziz Ocakoğlu, Mehmet Abdussamet Bozkurt

ABSTRACT

Objective: This study aimed to evaluate the role of platelet counts, platelet lymphocyte ratio, neutrophil lymphocyte ratio, and systemic immune-inflammation index in predicting lymph node metastasis in preoperative period in patients with colon cancer.

Materials and Methods: This study was conducted between May 2015 and May 2020 at the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital. A total of 130 patients who underwent colon resection for colon adenocarcinoma were evaluated. They were divided into groups via nodal staging using the TNM classification: N0: 0; N1: 1–3; and N2: 4 or more.

Results: A significant difference was observed between the inter-group platelet counts, platelet lymphocyte ratio, and systemic immune-inflammation index. The platelet value was significantly higher in N1 and N2 than in N0. There was also a significant difference between NO and N2 compared with platelet lymphocyte ratio and systemic immune-inflammation index.

Conclusion: Systemic immune-inflammation index, platelet lymphocyte ratio, and platelet count can be used in combination with TNM staging for personalized treatment.

Keywords: Systemic immune-inflammation index, platelet lymphocyte ratio, platelet counts, lymph node metastasis, colon cancer

Cite this article as:
Yılmaz S, Bölükbaşı H, Yıldırım EO, Ocakoğlu A, Bozkurt MA. The Role of Platelet Count, Platelet Lymphocyte Ratio, and Systemic Immune-Inflammatıon Index in Predicting Lymph Node Metastasis in Colon Cancer. Erciyes Med J 2021; 43(6): 548-53.

Department of General Surgery, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Submitted
17.11.2020

Accepted
04.03.2021

Available Online
27.09.2021

Correspondence
Hakan Bölükbaşı, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Department of General Surgery, İstanbul, Turkey
Phone: +90 212 404 15 00
e-mail: hbbolukbasi@gmail.com

INTRODUCTION

Colon cancer can cause a high mortality rate worldwide due to the absence of early symptoms and indecision to perform colonoscopy. A significant number of patients with colon cancer are diagnosed at an advanced stage, with a poor overall survival (1). At present, the TNM (T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body) staging system for colon cancer is the most commonly used predictor of overall survival and recurrence. However, prognostic heterogeneity was observed among patients with similar TNM stage (2). Thus, new biomarkers are needed to see the course of the disease in all types of cancer. For this reason, cheap, simple, and reliable biomarkers have been studied in recent years.

In addition to oncogenic genomic abnormalities, recent studies demonstrated that the body's inflammatory response plays a significant role in carcinogenesis and disease progression (3). The relationship between inflammation and tumor progression has been known for several years. The tumor microenvironment is largely organized by inflammatory cells, which are essential in proliferation, invasion, and metastasis of neoplasm (4). First, Virchow described a link between cancer and inflammation and revealed that lymphocytic infiltrates in the areas of chronic inflammation may reflect the source of cancer (5). Lymphocytes play a critical role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration (6), thus initiating the host immune response to malignancy (7). Laboratory studies have demonstrated that tumor cells may release cytokines that stimulate the recruitment of neutrophils. Within the tumor microenvironment, neutrophils can release cytokines to proliferate tumor cells, activate immunosuppression, and promote tumor angiogenesis (8). Neutrophils can promote adhesion and seeding of distant organ sites through the secretion of circulating growth factors, such as vascular endothelial growth factor and proteases (9).

The relationship between platelets and tumors was first defined by Levin and Conley in 1964 (10). Moreover, few studies have demonstrated that platelets can protect circulating tumor cell from shear stresses during circulation, induce circulating tumor cell epithelial mesenchymal transition, and promote tumor cell extravasation to metastatic sites (11). It has been suggested that the high number of preoperative platelets in colon cancer is associated with poor prognosis (12). Considering these factors, some inflammation and immune-based prognostic scores

have been developed to predict survival and recurrence, such as lymphocyte count, neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) (13).

Systemic immune-inflammation index (SII) measurement is based on platelet, neutrophil, and lymphocyte counts, which are standard laboratory measurements that are routinely performed in clinics. SII was calculated using the formula SII=(P×N) / L, where P, N, and L denote peripheral platelet, neutrophil, and lymphocyte counts, respectively. In the latest studies, the relationship between high levels of SII and poor prognosis has been observed in solid tumors, such as colorectal cancer (14).

This study aimed to evaluate the role of platelet counts, PLR, NLR, and SII in predicting lymph node metastasis in preoperative period patients with colorectal cancer.

MATERIALS and METHODS

Between May 2015 and May 2020, a total of 130 patients over the age of 18 who underwent colon resection for colon adenocarcinoma in tertiary education research hospital were retrospectively evaluated (ethical approval number; KAEK; 24.06.2020/104).

Patients who received emergency operations due to ileus or perforation, received neoadjuvant treatment, were metastatic at the time of diagnosis, were diagnosed with cancer other than adenocarcinoma, and have inflammatory bowel disease-related adenocarcinomas were excluded from the study. Patients with rectal carcinoma were also excluded.

The age and gender of the patients were recorded. The body mass index (BMI) was calculated using the formula weight (kg)/height (m^2); the weight of the patients was measured using the classical scale with calibration and the height using a stadiometer. Postoperative pathology reports of the evaluated patients and TNM tumor staging were made according to the AJCC colorectal cancer classification, 8th edition (15).

Preoperative neutrophils, lymphocytes, and platelet (PLT) counts were recorded. NLR was determined by dividing the number of neutrophils by the number of lymphocytes; PLR was calculated by dividing the number of PLT by the number of lymphocytes. The SII = PLT x Neutrophil / Lymphocyte formula was calculated based on.

Accordingly, carcinoma in situ (Tis) and T4 tumors were excluded from the study. Patients with at least 12 lymph nodes were evaluated in pathology trials to perform lymph node staging due to curative resection.

Statistical Method

The frequency and percentage for categorical variables, average and standard deviation values for continuous variables are given. Variables that show normal distribution were analyzed using one-way ANOVA and Tukey's HSD test. The normality of the variables was controlled using the Shapiro–Wilk test. The Kruskal–Wallis and Bonferroni correction Dunn tests were used for the analysis of non-normal continuous variables. The receiver operating characteristic (ROC) curve was used to determine the optimum cut-off values of statistically significant variables in order to identify positive lymph node. All analyses were conducted using the Statistical Package for the Social Sciences for Windows 22.0 (SPSS Inc., Chicago, Illinois, USA), and the results with a level of $p<0.05$ were significantly accepted.

Table 1. Demographic data of the patients

	n	%
Gender		
Female	42	32.31
Male	88	67.69
BMI (Mean±SD)		
Female	25.69±4.12	
Male	24.30±2.61	
Localization		
Caecum	25	19.23
Descending colon	21	16.15
Hepatic flexure	15	11.54
Transvers colon	8	6.15
Splenic flexure	14	10.77
Ascending colon	15	11.54
Sigmoid colon	26	20.00
Rectosigmoid	6	4.62
T stage		
T1	4	3.08
T2	41	31.54
T3	85	65.38
N stage		
N0	87	66.92
N1	32	24.62
N2	11	8.46

BMI: Body mass index; SD: Standard deviation

RESULTS

A total of 130 patients were included in the study. The mean age was 63.96±12.23. The mean ages of the N0, N1, and N2 groups were 64.20±12.36, 64.18±11.94, and 61.36±12.90, respectively. No significant difference in age was observed between the groups (p=0.765). Among the patients, 32.31% (n=42) were female, and 67.69% (n=88) were male. There was a significant difference in gender between the groups (p=0.282). When the BMI was examined, the mean value was 24.75±3.23. The mean BMI in women was 25.69±4.12 and 24.30±2.61 in men. No significant difference was observed in terms of inter-group BMI (p=0.601). The demographic data of the patients is presented in Table 1.

When the laboratory values of the patients were examined, the mean PLT counts in the N0, N1, and N2 groups were 307.39±109.14, 355.0±62.95, and 471.90±75.48, respectively. The mean PLR ratios in the N0, N1, and N2 groups were 194.38±148.85, 240.81±287.68, and 275.76±93.15, respectively. The mean SII (x109) in the N0, N1, and N2 groups were

Table 2. Laboratory findings

Laboratory value	N0 (n=87)	N1 (n=32)	N2 (n=11)	p
Platelets	307.39±109.14	355.00±62.95	471.90±75.48	**<0.001**
NLR	3.97±3.79	5.57±11.57	3.32±1.37	0.881
PLR	194.38±148.85	240.81±287.68	275.76±93.15	**0.009**
SII (10^9)	1183.60±1021.37	2004.96±4090.03	1547.43±643.32	**0.045**

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; SII: Systemic immune-inflammation index

Table 3. ROC analysis results

Variables	AUC (%95)	Cut-off value	Sensitivity (%)	Specificity (%)
PLT	0.736 (0.652–0.821)	335	76.78	63.22
PLR	0.623 (0.524–0.721)	163.69	72.18	51.74
SII	0.599 (0.499–0.698)	836.88 (x10^9)	72.19	50.65

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; SII: Systemic immune-inflammation index

Table 4. ROC analysis results for N2 patients

Variable	AUC (%95)	Cut-off value	Sensitivity (%)	Specificity(%)
PLT	0.906 (0.852–0.960)	398.50	100	84
PLR	0.758 (0.620–0.896)	211.79	81.82	65.54
SII	0.712 (0.612–0.812)	1068.13 (x10^9)	90.91	58.84

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; SII: Systemic immune-inflammation index

1183.60±1021.37, 2004.96±4090.03, and 1547.43±643.32, respectively. The mean NLR in the N0, N1, and N2 groups were 3.97±3.79, 5.57±11.57, and 3.32±1.37, respectively. A significant difference was observed between the inter-group PLT numbers, PLR, and SII (p<0.001, p=0.009, p=0.045). The PLT value was significantly higher in N1 and N2 compared with N0 (p=0.048, p<0.001). No significant difference was observed between N0 and N1 compared with PLR and SII; between N0 and N1, a significant difference was detected (p=0.003, p=0.018). The laboratory findings are presented in Table 2.

ROC analysis was conducted for PLT, PLR, and SII for lymph node metastasis prediction. The accuracy rates were 0.736–0.623 and 0.599 for PLT, PLR, and SII, respectively. The optimum cut-off values for PLT and PLR were 335 and 163.69, the sensitivities were 76.78% to 72.18%, and the specificities were 63.22% to 51.74% in predicting lymph node metastasis (Fig. 1, 2). The optimum cut-off value for SII was 836.88, the sensitivity was 72.19%, and the specificity was 50.65% in predicting lymph node metastasis (Fig. 3). The results of the ROC analysis are presented in Table 3.

Although a significant difference was observed between the groups in terms of PLR, PLT, and SII, the sensitivity and specificity of these tests in predicting lymph node metastasis were not detected as high as expected. When N2 patients were evaluated, it was found that the PLR, PLT, and SII values increased their sensitivity and specificity in predicting lymph node. The results of the ROC analysis for N2 patients are also presented in Table 4.

DISCUSSION

The pN stage in the TNM classification has become the "gold standard" for lymph node staging of colon carcinomas. Lymph node involvement is directly associated with survival, and disease-free survival is also the most important independent factor affecting mortality rate and prognosis (16). The identification of preoperative lymph node metastasis is one of the most important factors for predicting the possibility of long-term survival. In patients with stage II colon cancer, the 5-year survival is about 80% in non-LN metastasis, but in lymph node metastasis, it is only 50% (17). Because TNM staging is described postoperatively, it is difficult to determine survival prediction and advanced treatment strategies before surgery. As it is known, prognosis is associated not only with the clinicopathologic properties of the tumor but also with the host inflammatory response (18). Inflammatory-based indexes have been considered to be associated with poor prognosis and survival in various malignant solid tumors, including colon cancer (19). An interaction occurs in oncological patients that trigger systemic inflammatory response between the tumor and the host. This condition is associated with cancer progression. Inflammatory response causes the release of a large number of acute-phase reactants, which can also cause complex neuroendocrine changes and cancer progression (3). The patient's inflammatory response can be easily measured using peripheral blood parameters; therefore, many indexes have been developed in recent years using peripheral blood parameters. Our results indicated that the PLT count was

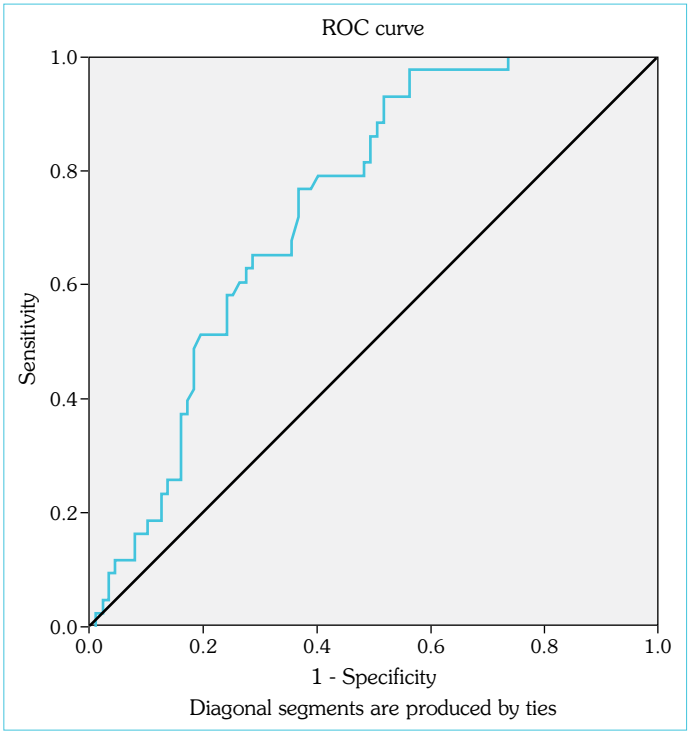

Figure 1. **ROC analysis for platelet count**

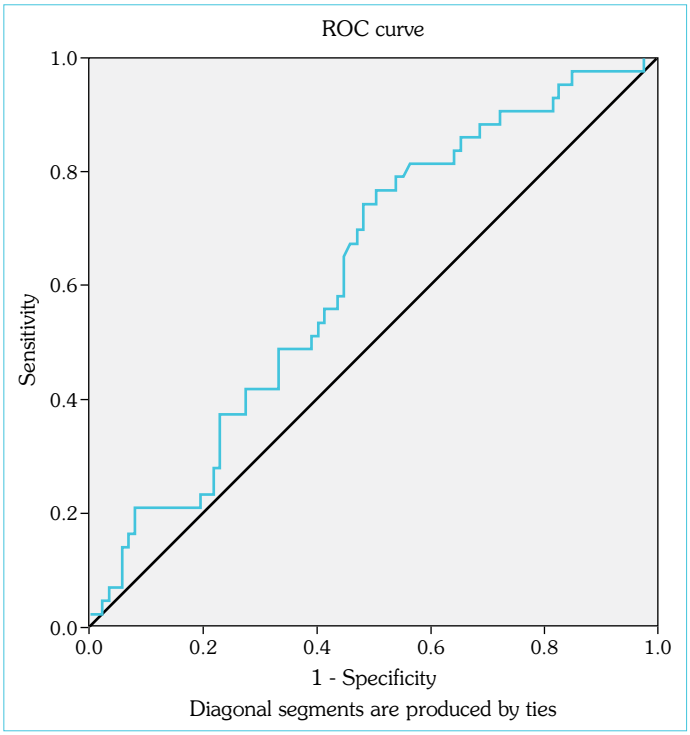

Figure 2. **ROC analysis for PLR**

significantly higher in N1 and N2 compared with N0. Also, PLR and SII can help distinguish N2 disease from N0 disease. The use of these parameters in combination with TNM staging may lead to the emergence of personalized treatment protocols in the future.

While some of the host actors involved in the inflammatory response against cancer play a role in body defense, others help

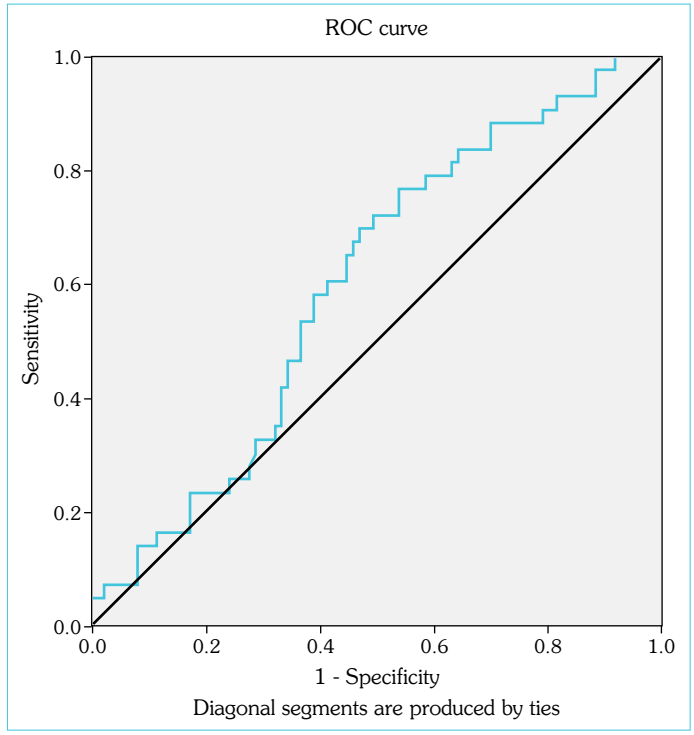

Figure 3. **ROC analysis for SII**

spread cancer. PLTs facilitate the proliferation of tumor cells by separating the tumor from its primary area and masking tumor cells from the immune system. In addition, PLTs facilitate metastasis. When the PLT count was examined in patients with colon cancer, a strong relationship was found between primary tumor and high PLT count (20). The relationship between PLTs and tumors was first defined by Levin and Conley in 1964 (10). Nyasavajjala SM et al. (21), in their study involving 630 patients, claimed that preoperative thrombocytosis is not a prognostic survival value in colorectal carcinoma. Sasaki K et al. (12), in another study of preoperative PLTs, have suggested that it is associated with poor prognosis. In our study, a significant relationship was observed between PLT count and lymph node metastasis ($p<0.001$). With the cut-off value of 335×109, the sensitivity of PLT count in predicting lymph node metastasis was 76.78%, and the specificity was 63.22%. In patients with N2 (lymph node >3), sensitivity and specificity were found to be 100% and 84%, respectively.

PLR has been demonstrated as a prognostic factor in many malignant tumors, including colorectal cancer, stomach cancer, esophageal carcinoma, esophageal epithelial cell carcinoma, and small cell lung cancer (22). There were reviews and meta-analyses of the PLR's effect on survival for colorectal cancer and other tumors. In a meta-analysis of 26 studies by Zhou X et al. (23), which included a total of 13,964 patients, they demonstrated that PLR was a negative predictive factor for overall survival in many types of cancer, including colorectal carcinoma. Gu X et al. (24), in a meta-analysis, reported that a high PLR in colorectal carcinoma is associated with poor prognosis in terms of overall survival and disease-free survival. In another meta-analysis, where 4968 colorectal cancer patients, including 17 different studies, were examined to obtain the clinicopathologic and prognostic values of PLR, Huang X. et al. (25) found that PLR is linked to worse results (overall survival,

disease-free survival, and cancer-specific survival). According to Baranyai Z. et al. (26), in a retrospective study of 336 colorectal cancer and 118 metastatic colorectal cancer patients, PLT count was a valuable prognostic marker for survival in patients in both groups, whereas PLR was not a prognostic factor in both groups. Kwon HC et al. (27), in their retrospective study of 200 colon cancer patients, identified two cut-off values to create three PLR groups (<150, 150–300, and>300) and found that PLR was independently associated with overall survival. Zou ZY et al. (28), in a retrospective study of 216 patients with colorectal cancer, emphasized that PLR with a cut-off value of 246 is an independent prognostic factor. In our study, we found the cut-off value for PLR 163 with a sensitivity of 72.18% and a specificity of 51.74, respectively, in predicting metastatic lymph node. These rates are also compatible with those in the literature. In our study, the PLT counts and PLR values found higher with lymph node metastasis in colon cancer patients, especially when the number of metastatic lymph nodes is more than 3 (N2), more sensitive to predicting (100% sensitivity, 84% specificity - 81.82% sensitivity, 65.54% specificity). A high PLR value can be a promising prognostic biomarker for colorectal carcinoma. Neoadjuvant chemotherapy can be performed by examining the PLT and PLR values in patients with metastatic lymph node.

SII measurement is based on PLT, neutrophil, and lymphocyte counts, which are standard laboratory measurements parameters. Therefore, SII has the potential for use as a marker in the evaluation of tumor recurrence and response to treatment. Patients with high preoperative SII measurements usually exhibit thrombocytosis, neutrophilia, or lymphopenia, which indicate increased inflammation and poor immune response among them. SII, a simple, convenient, easily obtainable, cheap, and noninvasive marker, was first described by Hu et al. (29). Yatabe et al. (30), in a retrospective study involving 733 patients, emphasized that SII may be an independent and significant indicator of worse long-term outcomes after resection in colorectal carcinoma patients. Chen JH et al. (31), in a retrospective study of 1383 patients, demonstrated that SII is a promising tool for predicting the survival outcome of colorectal carcinoma patients and can help identify high-risk patients with the same TNM stage. Passardi et al. (14) in their study of metastatic colorectal patients receiving primary chemotherapy with bevacizumab, found that SII are powerful prognostic and predictive indicators of poor outcome. Our study concluded that the SII values were also significantly different between the groups; thus, it can be a promising preoperative marker for the detection of lymph node metastasis.

Although there are literature indicating that NLR is an independent prognostic factor in colorectal carcinoma (27, 28), our study found no significant difference between the groups in the prediction of lymph node metastasis.

Based on the area under the curve values obtained from the ROC curves in our study, PLT count was found to be the most effective tool for predicting lymph node metastasis compared with SII and PLR. SII, PLR and PLT counts serve as a complement to the TNM classification in the prediction of preoperative lymph node metastasis and overall survival, and also reflect the state of the tumor microenvironment and the preoperative host inflammatory response. Therefore, the use of a combination of parameters reflecting both the tumor characteristics and host systemic inflammatory condition may be very critical to colorectal carcinoma patients to accurately predict both preoperative lymph node metastasis and survival outcome as well as to develop new treatment modalities.

Retrospective nature and the small sample size are the limitations of this study. Thus, further studies are required to verify its results. In addition, the results could not be generalized for all colon cancer patients as only those undergoing radical surgery were included in the study.

CONCLUSION

Systemic immune-inflammation index, platelet lymphocyte ratio, and platelet counts can be used in combination with TNM staging for personalized treatment in future clinical practice. More prospective studies are needed to establish the role of hematological parameters in combination with TNM staging.

Ethics Committee Approval: The Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 24.06.2020, number: KAEK; 24.06.2020/104).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SY; Design – SY, AO; Supervision – MAB; Resource – HB; Materials – EOY, AO; Data Collection and/or Processing – EOY, HB; Analysis and/or Interpretation – SY; Literature Search – EOY, SY; Writing – SY, HB; Critical Reviews – HB.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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