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RESEARCH ARTICLE

Clinical Value of Platelet-to-Lymphocyte Ratio in Predicting Liver Metastasis and Lymph Node Positivity of Colorectal Cancer Patients

Platelet-Lenfosit Oranının Kolon Kanserli Hastalarda Karaciğer Metastazını ve Lenf Nodu Pozitifliğini Öngörebilmedeki Klinik Etkisi

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ABSTRACT

Aim: Colorectal cancer related mortality is still high. The widespread use of colonoscopy, surgical advancements, and standardized use of chemotherapeutic agents has increased survival rates in metastatic cases. Inflammation is the main etiological factor in a variety of cancers. Platelet-to-lymphocyte ratio (PLR), one the most studied biochemical parameters, has been shown as a poor prognostic factor. In this study, our aim was to determine the predictive value of PLR on liver metastasis and lymph node positivity in colorectal patients.

Method: The data of patients who were diagnosed with colorectal cancer and underwent surgery between March 2010 and September 2016 were analyzed retrospectively. Demographic characteristics, preoperative PLR, intraoperative findings, and tumor-node-metastasis stages were recorded. Patients with liver metastasis comprised group 1a and those without liver metastasis were group 1b; patients were also sorted into groups 2a and 2b based on lymph node positivity or negativity, respectively.

Results: A total of 152 patients were included in the study and the male/female ratio was 1.53. Most of patients had rectosigmoid junction tumors. Eight patients had familial history of colorectal cancer and 66 patients had comorbid conditions. Eight patients had early 30-day mortality. Thirty-one patients had liver metastasis. Patients with liver metastasis (group 1a) had significantly higher PLR values when compared to group 1b ($p<0.001$). When age, gender and comorbid diseases were analyzed together, group 1a had significantly higher PLR values ($p<0.001$). The cut-off value of the PLR for liver metastasis was 194.7, giving a sensitivity of 74.2% and specificity of 72.7%. Patients with lymph node positivity (group 2a) had significantly higher PLR ($p<0.001$) than patients in group 2b. The cut-off value of the PLR for lymph node positivity was 163.95, giving a sensitivity of 56.8% and specificity of 56.3%.

Conclusion: As an inexpensive and feasible parameter, PLR could be useful for predicting liver metastasis and even lymph node positivity of colorectal cancers.

Keywords: Platelet, lymphocyte, colon carcinoma, liver metastasis

ÖZ

Amaç: Kolon kanserine bağlı mortalite azalsa da hala yüksektir. Kolonoskopinin artan kullanımı, cerrahi teknolojide ilerlemeler, kemoradyoterapi protokollerinin standardizasyonu metastatik olgularda sağkalımı arttırmıştır. Enflamasyon, birçok kanserin gelişiminde önemli rol oynar. Platelet-lenfosit oranı (PLO) gibi birçok belirteç kanserde kötü prognoz ile ilişkilendirilmiştir. Çalışmamızda preoperatif bakılan PLO'nun kolon kanserli hastalarda karaciğer metastazını ve lenf nodu pozitifliğini öngörebilirliğini saptamayı amaçladık.

Yöntem: Mart 2010 ve Eylül 2016 tarihleri arasında kolorektal kanser tanısı konularak operasyona alınan hastaların dosyaları retrospektif olarak incelendi. Hastaların demografik verileri, preoperatif PLO, intraoperatif bulgular ve postoperatif tümör-nod-metastaz evrelemesine göre histopatoloji raporları kaydedildi. Hastalar karaciğer metastazı saptananlar grup 1a ve saptanmayanlar grup 1b olarak 2 gruba ayrıldı. Aynı şekilde lenf nodu pozitifliği saptananlar grup 2a ve saptanmayanlar grup 2b olarak alt gruba ayrıldı. Sonuçlar SPSS programı ile analiz edildi.

Bulgular: Yüz elli iki hastada erkek/kadın oranı 1,53 idi. En sık rektosigmoid bölgede kanser tespit edildi. Sekiz hastada ailesel kolorektal kanser, 66 hastada komorbid hastalık tespit edildi. Postoperatif 30 günlük dönemde sekiz hastada erken mortalite gözlendi. Otuz bir hastada karaciğer metastazı mevcuttu. PLO'nun gruplar arası karşılaştırmasında, metastaz saptanan grupta PLO değeri, anlamlı şekilde yüksekti ($p<0,001$). Yaş, cinsiyet

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ÖZ

ve komorbid hastalıkların ortak etkisi incelendiğinde, bu üç parametreden bağımsız olarak PLO'nun karaciğer metastazlı hastalarda anlamlı şekilde yüksek olduğu saptandı (p<0,001). PLO'nun karaciğer metastazını öngörmede ROC curve eğrisi ile tespit edilen 194,7 cut-off değeri baz alındığında, %74,2 sensitivite, %72,7 spesifite, %91,7 negatif prediktif değer ve %41,1 pozitif prediktif değerinin olduğu tespit edildi. PLO'nun gruplar arası karşılaştırmasında, lenf nodu pozitifliği saptanan grupta PLO değeri, anlamlı şekilde yüksekti (p<0,001). PLO'nun lenf nodu pozitifliğini öngörmede ROC curve eğrisi ile tespit edilen 163,95 cut-off değeri baz alındığında, %56,8 sensitivite, %56,3 spesifite, %53,3 negatif prediktif değer ve %59,7 pozitif prediktif değerinin olduğu tespit edildi.

Sonuç: Ucuz, kolay uygulanabilir bir belirteç olarak PLO'nun kolorektal bölge kanserlerindeki karaciğer metastazını ve lenf nodu pozitifliğini öngörmede kullanılabileceği kanaatindeyiz.

Anahtar Kelimeler: Platelet, lenfosit, kolon karsinomu, karaciğer metastazı

Introduction

Colorectal cancer is the third most common cancer worldwide. Although mortality rates due to colon cancer have decreased after 1990, it is still the third most common cause of mortality.[1,2] The widespread use of screening tests, primarily colonoscopy, removal of detected premalignant polyps, and the effective and widespread use of neoadjuvant chemoradiotherapy protocols for local advanced-stage tumors have played important roles in the reduction of mortality rates.[3] Distant metastasis is detected at the time of diagnosis in 20% of colorectal cancers, and average life expectancy in stage 4 colorectal cancers ranges from 6 to 8 months even under the best palliative treatment.[4]

Studies conducted since Rudolph Virchow defined the relationship between inflammation and cancer in the 19th century have demonstrated the extensive and significant impact of inflammation on tumor development, progression, and response to treatment.[5] Moreover, many cancers develop from a background of infection, chronic irritation, and inflammation.[6] Although many biochemical parameters have been investigated in terms of their clinical effect on colorectal cancer, the routine clinical use of these tests has been limited by their high cost, a lack of standardization, and unsuitability for widespread use.[7]

Platelet and lymphocyte values, which are among the most commonly analyzed parameters in peripheral blood, are inexpensive to measure and are suitable for routine use, and are therefore the most commonly investigated inflammation markers. The platelet-to-lymphocyte ratio (PLR) has been associated with poor prognosis in many cancers, including colorectal cancer.[6,8,9] Previous studies have focused on changes in PLR at different stages of colon cancer and its effect on prognosis, response to chemotherapy, and recurrence time.[4,5,6,7,8,9,10]

In this study, we aimed to determine the utility of PLR at time of admission in predicting hepatic metastasis and lymph node positivity in patients who have undergone colorectal surgery.

Materials and Methods

After receiving approval from the Kafkas University Faculty of Medicine, Local Ethics Committee (Approval number: 80576354-050-99/87, date: 11.01.2017), we retrospectively reviewed the medical records of patients who were diagnosed with colorectal cancer and operated after being admitted to the general surgery and emergency departments of our hospitals between March 2010 and September 2016 with complaints of abdominal pain, gas, inability to defecate, and blood in stool. The patients' age, sex, medical history, preoperative PRL determined at time of admission, intraoperative findings, and data from postoperative histopathological reports regarding tumor, lymph node involvement, and metastasis [tumor-node-metastasis (TNM) staging] were recorded from their records. The PLR was measured from the complete blood count. The Beckman Coulter R Gen-S System® (Beckman Coulter Diagnostic System Laboratories, Inc., Texas, USA) device was used for hematological analysis. Patients were grouped based on those with hepatic metastasis (group 1a) and those without (group 1b) and as those with lymph node positivity (group 2a) and those without (group 2b).

Thirty-five patients were excluded from the study because they had a hematologic disease or active infection within the past week, their records were not accessible, or they had a history of blood transfusion within the last 10 days.

Statistical Analysis

SPSS version 22 for Windows (Chicago, Illinois, USA) software package was used for statistical analyses. Distribution normality of continuous variables was determined using the Kolmogorov-Smirnov test. Descriptive statistics were reported as continuous variables, mean ± standard deviation, or median or range, depending on the context and relevance. Categorical variables were expressed as case numbers and ratios. Differences between groups were compared using student's t-test for mean values and the Mann-Whitney U test for median values. Pearson's chi-square test was used for categorical variables. Sensitivity, specificity, positive

predictive value (PPV), and negative predictive value (NPV) were compared using ROC curve analysis. P values <0.05 were accepted as statistically significant.

Results

The male/female ratio among the 152 patients included in the study was 1.53. Tumors were most commonly located in the rectosigmoid region of the colon (73.7%). Eight patients had a family history of colorectal cancer and 66 patients had a history of comorbid disease. Pulmonary embolism, anastomotic leakage, and early mortality due to comorbid diseases were observed in 8 patients (5.3%) in the postoperative 30-day period. In 31 patients, a mass lesion consistent with liver metastasis was detected intraoperatively, metastasectomy was performed, and the mass was confirmed as adenocarcinoma in histopathologic examination. The demographic characteristics of the patients are given in Tables 1 and 2.

The groups were homogenous in terms of both sex and age distribution (p=0.357 and p=0.240, respectively) (Table 3).

Table 1. Demographic characteristics of the patients

Sex	Number	Percentage (%)
Female	60	39.5
Male	92	60.5
Family history	**Number**	**Percentage (%)**
No	144	94.7
Yes	8	5.3
Mortality	**Number**	**Percentage (%)**
No	144	94.7
Yes	8	5.3
Comorbid disease	**Number**	**Percentage (%)**
No	85	55.9
Yes	66	43.4

Tumor location was not associated with liver metastasis (p=0.596).

Mean PLR value was significantly higher in the group with metastasis (232.4; range, 79.4-837.5) than in the nonmetastatic group (159.7; range, 57.4-289.3) (p<0.001). The PLR distribution graph for the two groups is shown in Figure 1.

When the common effect of age, sex, and comorbid diseases was examined, it was found that the PLR value was significantly higher in patients with liver metastasis independent of these three parameters (p<0.001).

Based on the 194.7 cut-off value determined using the ROC curve, PLR was found to have 74.2% sensitivity, 72.7% specificity, 91.7% NPV, and 41.1% PPV in predicting liver metastasis (Figure 2).

Mean PLR value was significantly higher in the group exhibiting lymph node positivity (p<0.001) (Figure 3).

Based on the 163.95 cut-off value determined using the ROC curve, PLR had 56.8% sensitivity, 56.3% specificity, 53.3% NPV, and 59.7% PPV in predicting lymph node positivity (Figure 4).

Discussion

Liver metastases of colon cancer pose a major clinical problem.[11] Because lymphatic drainage of the colon occurs primarily through the portal vein, the first locations of metastasis are the regional lymph nodes, liver, lung, and

Table 2. Distribution of patients by affected colon segment

Colon segment	Number	Percentage (%)
Ascending colon	32	21.1
Transverse colon	4	2.6
Descending/sigmoid colon	31	20.4
Rectum	81	53.3
Anal canal	1	0.7
Total colon	3	2.0

Table 3. Age and sex distribution of the patient groups

	Sex	M0	M1	Total		
	Female	50	10	60		
	Male	71	21	92		
	Total	121	31	152		
Age (years)	**Mean**	**Standard deviation**		**Minimum**	**Maximum**	**Median**
M0	61.21	12.934		24	85	63.00
M1	64.23	12.412		32	88	65.00
Total	61.82	12.847		24	88	63.00

M0: No liver metastasis; M1: Liver metastasis

peritoneum, in that respective order.[12] Treatment options for cases of colon cancer with liver metastasis include adjuvant chemotherapy protocols as well as surgical resection, local tumor ablation, radiofrequency ablation, regional intraarterial chemotherapy, chemoembolization, and radiotherapy. Of these methods, only surgery has been reported to prolong survival. For this reason, with recent advances in surgical techniques and technology, the criteria for operability have been expanded in cases with liver metastasis.[11,13]

In contrast to previous studies investigating the prognostic value of PLR in cancer, in the present study we also aimed to determine the utility of earliest preoperative PLR in predicting lymph node positivity and hepatic metastases confirmed by postoperative pathology reports in patients with colon cancer. The retrospective nature of our study

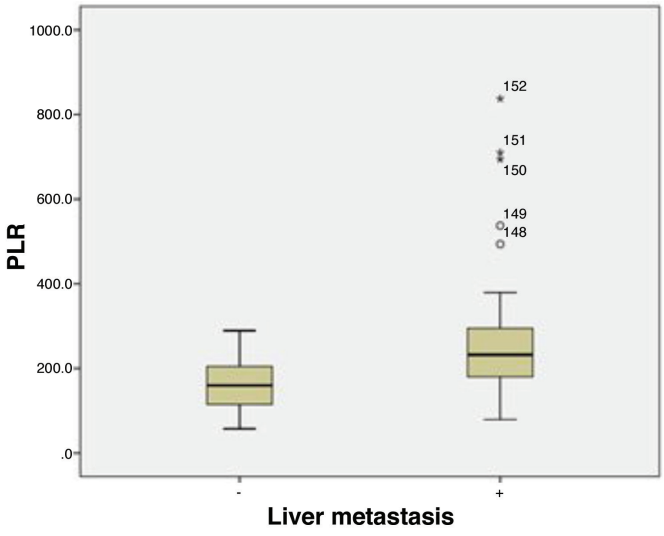


Figure 1. Platelet-to-lymphocyte ratio distribution graph for patients with and without liver metastasis (group 1a and 1b, respectively)
PLR: Platelet-to-lymphocyte ratio

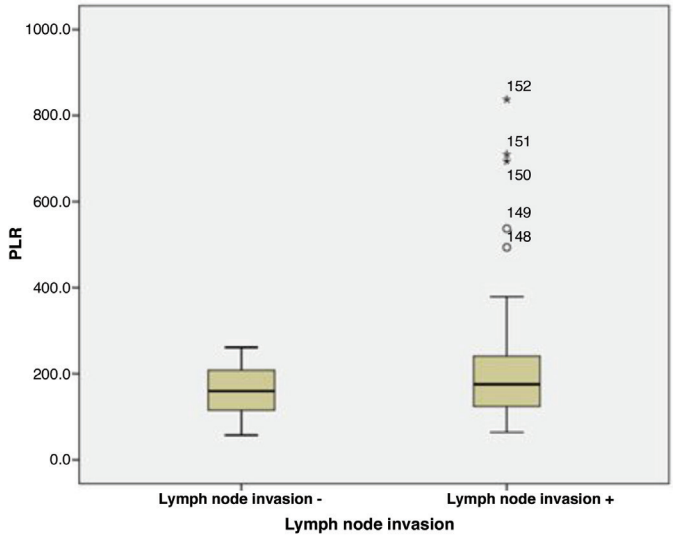


Figure 3. Platelet-to-lymphocyte ratio distribution graph for patients with and without lymph node involvement (group 2a and 2b, respectively)
PLR: Platelet-to-lymphocyte ratio

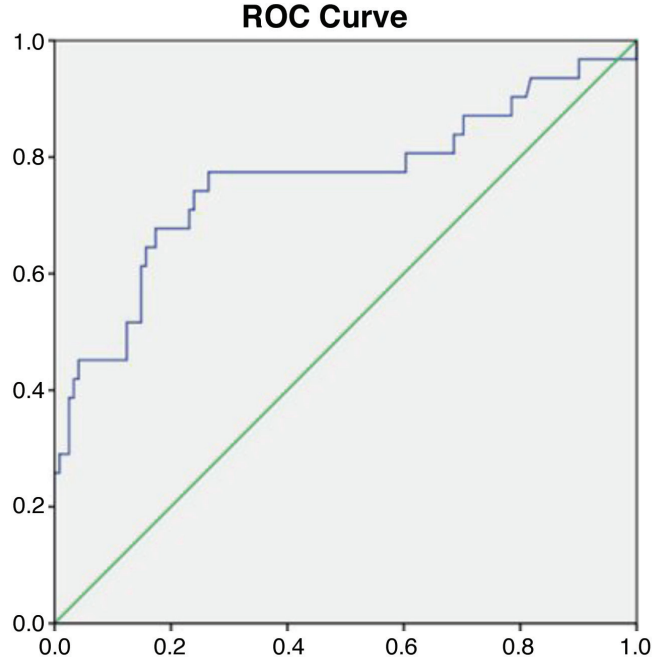


Figure 2. ROC curve analysis for patients with and without liver metastasis (group 1a and 1b, respectively)

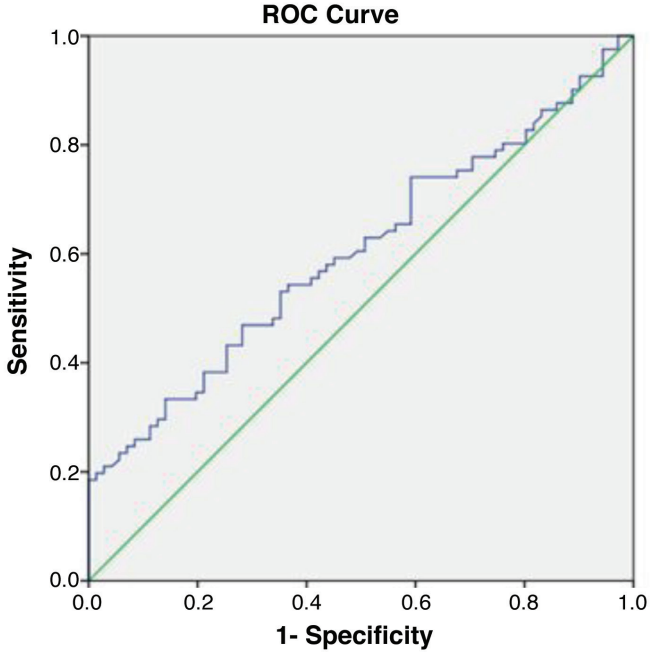


Figure 4. ROC curve analysis for patients with and without lymph node involvement (group 2a and 2b, respectively)

and the relatively low number of patients are among the fundamental limitations of our study.

Platelets play an important role in hemostasis and thrombosis, and they also positively affect the growth, spread, and neovascularization processes of tumor cells. Platelets aggregated by the tumor lead to cancer-related thrombosis. Tumor growth is also induced by platelet-derived growth factor and tissue growth factor, which are mainly secreted from the platelets.[5,14] In many studies, significant PLR elevation has been associated with poor prognosis in many types of cancer.[14,15,16,17]

The male/female ratio in our study showed a predominance of males, in accordance with the literature. Similarly, consistent with the literature, the rectosigmoid region was the colon segment most commonly affected.[1] Eight patients had a family history of colorectal cancer and 66 patients had comorbid diseases. Pulmonary embolism, anastomotic leakage, and early mortality due to comorbid diseases were observed in 8 patients (5.3%) in the postoperative 30-day period. Liver metastasis was detected intraoperatively in 20.3% of the patients, in accordance with the literature.[4]

When sex and age distributions between groups were examined, both were observed to be homogeneous (p=0.357 and p=0.240). Reports in the literature indicate that mortality is 25% higher among males than females and that colorectal cancers are located more proximally in females.[18]

Our analysis of colon segment involvement showed that tumor location was not associated with liver metastasis (p=0.596). We did not encounter any findings on this subject in the literature.

Mean PLR value was significantly higher in the group with metastasis (232.4; range, 79.4-837.5) than in the nonmetastatic group (159.7; range, 57.4-289.3) (p<0.001). This finding is important because it shows that tumor load is related to PLR. In many studies in the literature, higher PLR values have been shown to be a marker of poor prognosis, especially in colorectal cancer. Hypercoagulability induced by cytokines secreted by malign solid tumors produces reactive thrombocytosis. Interleukin-6 in particular leads the transformation of megakaryocytes into platelets in the bone marrow. Other important factors include the increase of platelet-associated inflammatory reactions, decreased antitumor response due to relative scarcity of lymphocytes, and tumoral growth and spread induced by various epithelial and endothelial growth factors secreted by circulating active platelets.[4,5,6,7,8,9,10]

When the common effect of age, sex, and comorbid diseases was examined, it was found that PLR was significantly higher in patients with liver metastasis independent of these three parameters (p<0.001). The most important prognostic marker in colon cancer is cancer stage, and liver metastasis detected preoperatively corresponds to a more advanced stage. The average 5-year survival rate is 35-58%, even in resectable cases. In addition to prognostic studies, the increase in PLR was also found to be significantly higher in more advanced stages of colorectal cancer, significantly affecting the T aspect of TNM staging.[9] In another study, it was reported that an increased PLR value after surgical therapy could be a statistically significant indicator of disease recurrence in stage 2 and 3 patients.[7] Another use of PLR in colorectal cancers is to evaluate response to chemotherapy. In a study conducted with metastatic colorectal cancer patients, Wu et al.[10] reported that normalization of PLR value is a marker of good prognosis in the assessment of response to chemotherapy.

There is only one study in the literature evaluating liver metastases of colorectal cancers and PLR. In that study, PLR was found to be a significant and independent factor indicating overall survival and disease-free survival in patients with colorectal cancer who underwent curative liver resection after neoadjuvant chemotherapy and only had liver metastasis. In addition, preoperative PLR value was found to be superior to neutrophil-to-lymphocyte ratio (NLR) as a negative indicator in these cases.[19]

In the present study, we also evaluated lymph node positivity and found that this parameter was able to predict involvement in patients with statistically high PLR values. However, the sensitivity and specificity levels were not as high as those for PLR in predicting liver metastasis. In our review of the literature, we did not find any studies in which PLR predicted lymph node involvement in colon cancer. However, Özgehan et al.[20] examined the effect of NLR on tumor staging in colon cancer and reported that NLR was significantly high in patients with lymph node positivity. This is important in that it demonstrates the importance of PLR, which is another inflammatory marker like NLR.

In their study conducted in the northeastern Anatolia region of Turkey in 2015, Çakmur et al.[21] reported that colorectal cancer patients were diagnosed late in Turkey, which is not consistent with the literature. They emphasized the importance of screening tests, especially in the context of preventive health services.[21] Considering these data in light of our results, we believe that PLR can be used as an inexpensive, convenient, universal, and non-invasive marker to predict liver metastases in newly diagnosed cases of colorectal cancer.

Ethics

Ethics Committee Approval: The study was approved by the Kafkas University Local Ethics Committee (Approval number: 80576354-050-99/87, Date: 11.01.2017).

Informed Consent: The study was designed retrospectively, and consent form was obtained from all patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.A., A.C.Y., Concept: T.A., Design: T.A., Data Collection or Processing: T.A., A.C.Y., Analysis or Interpretation: T.A., A.C.Y., Literature Search: T.A., A.C.Y., Writing: T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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