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Platelet-lymphocyte ratio predicts poor prognosis in stage II / III colon and rectum cancer

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ABSTRACT

Objective: There is an increasing number of studies in the literature reporting that serum platelet/lymphocyte ratio (PLR) can provide useful prognostic data for various cancers. In the present study, the effects of platelet-lymphocyte ratio on survival in stage II/III colorectal cancers (CRC) were examined.

Material and Method:A total of 106 Stage II/III CRC patients who underwent curative surgery 2015-2020 were included in the study. Emergency cases and patients diagnosed with other than adenocarcinoma were excluded from the study. The demographic data of the patients, preoperative imaging and laboratory results, postoperative pathology reports, and patient follow-up examination data were obtained from hospital records. The relations between demographic, histopathological, hematological values and the prognosis was analyzed in terms of statistical significance.

Results:Among the 106 patients, 62 (58.5%) were male and 44 (41.5%) were female. The mean age was 64.3±12.01 (23-89). The mean follow-up period was calculated as 24.6±15.8 (2-63) months. When the pathology reports were reviewed, it was found that the mean tumor diameter was 5.3±2.33 cm (2-17) and the mean metastatic lymph node was 1.8±2.4 (0-10). The PLR ratio was determined as a poor prognostic factor affecting survival in the cox regression analysis, in which preoperative complete blood count, c-reactive protein and albumin values, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and PLR were compared, and was separated from other variables (P=0.002 CI= 95%). When variables such as age, clinical stage, and tumor diameter were included in the model, PLR was similarly found to be an important predictive variable (P= 0.002). When only NLR, LMR, and PLR were evaluated, PLR again came to the forefront with a significance value of P=0.01. Also, high neutrophil count, increased platelet distribution volume (PDW), advanced age, and perineural invasion (PNI) were found to be significant factors in predicting poor prognosis.

Conclusions: High PLR is a poor prognostic factor for CRC patients. For this reason, it may be necessary to follow a more aggressive strategy in the management of postoperative treatment in patients who have high PLR.

Keywords: Platelet/Lymphocyte Ratio, adjuvant chemotherapy, colorectal cancer, Stage II/III, prognostic factor.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer on a global scale after lung cancer excluding gender-specific prostate and breast cancer. Stage II-III CRCs are the most common patient group in daily practice (1,2). In many previous studies, parameters such as biological characters such as tumor stage, histological grade, lympho-vascular invasion (LVI), peri-neural invasion (PNI), and the number of metastatic lymph nodes, obstruction, perforation, serum carcinoembryonic antigen (CEA) levels were defined as clinicopathological prognostic factors for CRC (3-7). Although these factors are guiding in the choice of treatment, there are still many uncertainties in terms of the treatment modality. Different biological features in tumors may cause resistance in treatment, and patients at the same stage may show different clinical outcomes (8,9). On the other hand, although the benefit of adjuvant chemotherapy in stage III CRC was demonstrated in many studies, it is still a matter of debate to which patient group it should be given in stage II CRC. For this reason, standardized and reliable prognostic biomarkers are needed to identify high-risk patients especially in stage II-III CRCs (10-13).

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It was shown in various studies that cells that are involved in inflammation play important roles in many stages such as carcinogenesis, tumor progression, invasion, and metastasis. It is considered that these cells, especially platelets, lymphocytes, neutrophils, and macrophages can provide useful data on the biological behaviors of the tumor by helping the traditional pathological staging classifications. These cells were used individually or in various combinationsin the literature (14,15).

It was documented that the lymphocytes in the tumor microenvironment can recognize abnormally expressed neoantigens, attack cancer cells, and play roles in regression. In previous studies, various factors such as platelet derived growth factor (PDGF), platelet factor-4, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and thrombospondin that are secreted from platelets are involved in the proliferation of tumor cells, growth of tumor mass, and metastasis. It was also reported that the platelet/lymphocyte ratio (PLR) is a poor prognostic factor in various cancers such as ovarian, breast, lung, and pancreas, and is associated with decreased survival rates (16-20).

However, there are some difficulties in making use of these parameters in the clinical practice. For example, there are many different opinions regarding the evaluation methods and cut-off values. There are also inconsistencies in the results because of the limited number of studies on combinations between inflammatory cells and heterogeneous patient groups. In the present study, the relations between preoperative serum platelet-lymphocyte ratio (PLR) and survival were investigated in stage II-III CRC patients who were given adjuvant chemotherapy after curative surgery.

MATERIAL AND METHOD

This study was approved by Tekirdağ Namık Kemal University Non-interventional Clinical Research Ethics Committee (Date: 25.01.2022, Decision No: 2022.05.01.05). The study was conducted in line with the ethical standards of the Institutional/National Research Committee and 1964 Helsinki Declaration.

Data Sources

The study was conducted in Tekirdağ Namık Kemal University, Department of General Surgery. The data of 230 patients who underwent curative surgery for CRC between 2015 and 2020 were analyzed retrospectively in the study. The demographic data of the patients, preoperative imaging and laboratory results, postoperative pathology reports, and patient follow-up examination data were obtained from the archives of Tekirdağ Namık Kemal University. A total of 106 patients who met the criteria were included in the study.

Patient Population

All 106 patients who had data integrity were patients with stage II-III colorectal adenocarcinoma, and each received systemic chemotherapy in the postoperative period. Exclusion criteria were listed as follows; patients who were operated on under emergency conditions, patients who underwent laparoscopic-robotic surgery, cases diagnosed other than adenocarcinoma, patients who died in the early postoperative period (in 1 month), cases who died because of reasons not related to the disease, stage I and stage IV patients, patients not receiving chemotherapy, and cases with chronic inflammatory comorbidities.

Hematological Examination

The blood samples collected preoperatively in standard tubes containing ethylenediaminetetraacetic acid (EDTA) were analyzed by using an automated hematology analyzer (BeckmanCoulter, CA, the USA) and evaluated by an experienced biochemist. The platelet (x103/μL), lymphocyte (x109/L), and other blood parameter counts, NLR, LMR, and PLR were calculated. Systemic inflammation score (SIS), modified glasgow prognostic score (mGPS), albumin-NLR score, and prognostic nutritional index (PNindex) scores are shown in **Table 1**.

Table 1. Prognostic scoring systems

SIS	0	LMR ≥3.8	and	Albumin ≥39.75 g/l
	1	LMR <3.8	or	Albumin <39.75 g/l
	2	LMR <3.8	and	Albumin <39.75 g/l
MGPS	0	CRP ≥10 mg/l		
	1	CRP <10 mg/l	and	Albumin ≥3.5 g/dl
	2	CRP <10 mg/l	and	Albumin <3.5 g/dl
Albumin-NLR	0	Albumin ≥39.75 g/l	and	NLR <2.39
	1	Albumin <39.75 g/l	or	NLR ≥2.39
	2	Albumin <39.75 g/l	and	NLR ≥2.39
PN index	10×Albumin g/dl + 0.005×Total Lymphocyte mm³			

SIS : SystemicInflammationScore, MGPS: Modified Glasgow PrognosticScore, PN index: PrognosticNutritionalIndex

Histopathologic Evaluation

The slides and paraffin blocks of the patients were evaluated again by an experienced pathologist by using a conventional light microscope (Nikon Eclipse E600, Nikon AG Instruments, Switzerland) and x10-x20 objective. The grade, presence of LVI, and presence of PNI were verified. The tumor sizes and metastatic lymph node ratios were scanned retrospectively.

Follow-up

Regarding the overall survival (OS), the time between the date of primary surgery and the date of disease-related death was calculated. The patients were contacted by using the contact numbers in the hospital records to determine these data. The patients were seen every 3 months for the first 2 years, every 6 months for the next 3 years, and then

annually. A complete physical examination was performed and tumor markers and biochemical tests were evaluated in the patient follow-up examinations. Control colonoscopy was performed 1 year after the surgery. If no pathological condition was detected, the second colonoscopy was performed 3 years later at the earliest. Chest flat film was performed every 3 months for the first 2 years. Abdominal computed tomography scans were performed every 6 months for the first 2 years. The patients were followed as of the date of surgery until February 2021 and the survival time was determined.

Statistical Evaluation

The Cox Regression Analyzes were performed to calculate the effects of the independent variables on survival. When survival groups were compared multivariately, a 95% Confidence Interval and a Hazard Ratio (HR) of 1.0 were used to identify the independent prognostic factors. The Log-Rank Test was used to compare the survival groups univariately, and survival curves were presented with the Kaplan-Meier Method. The area under the curve (AUC) was calculated by performing ROC analysis for significant laboratory values. The cut-off values were calculated based on the highest true positive and lowest false negative rates for the variables with AUC > 50%. The mean, range, standard deviation, and percentages were used to note the descriptive variables. The distributions of the independent variables were analyzed with the Shapiro-Wilk Test. The Pearson Correlation Tests were preferred for parametric data and the Spearman Correlation Tests were preferred for non-parametric data. The IBM SPSS statistics ver. 22 was used for all statistical analyses.

RESULTS

Among the 106 patients, 62 (58.5%) were male, and 44 (41.5%) were female. The mean age was 64.3±12.01 (23-89). The mean follow-up period was calculated to be 24.6±15.8 (2-63) months. When the pathology reports were reviewed, it was found that the mean tumor diameter was 5.3±2.33 cm (2-17) and the mean metastatic lymph node was 1.8±2.4 (0-10). It was determined at the end of the follow-up period that 81 patients, 25 of whom died, continued to survive. Tumor localizations and numbers were; cecum 9, ascending colon 13, hepatic flexure 6 (right colon 28), transverse colon 4, splenic flexure 5, descending colon 6, sigmoid colon 26, recto-sigmoid region 10, rectum 24, and synchronous tumor 3, respectively. As a result of the re-evaluation of paraffin blocks and slides, the presence of LVI was found in 69 patients and the presence of PNI in 36 patients. The number of Grade 1-2-3 tumors was 17, 83, and 6, respectively. When the pathological stages were classified, the number of stage 2A-2B-3A-3B and 3C patients were found to be 32, 10, 11, 34, and 19, respectively.

The demographic characteristics of the patients, biological characteristics of the tumor, preoperative blood count, serum albumin and CRP levels, NLR, LMR and PLR ratios,and mGPS, SIS, and albumin-NLR scores were evaluated by using the Backward Method in Cox Regression Analysis. PLR rate was separated from other variables as a poor prognostic factor affecting survival (P=0.002 CI= 95%). It was calculated that one-unit increase in PLR value increased the risk of death 1.028 times. In the Chi-Square Analysis, a PLR value of 197 and above was found to be linearly related to deaths (P=0.005). The variables that were found to be significant in predicting poor prognosis are shown in **Table 2**. The cut-off values of PLR, neutrophil, PDW, and age were found as; 197, 4.74, 19.75, and 72.5, respectively. The ROC Analysis and survival curves are shown in **Figure 1**. **Table 3** summarizes the relations between PLR and other variables.Among scoring systems such as albumin -NLR, SIS, mGPS, and PN index, albumin-NLR score (the worst prognosis =2, the best prognosis=0) was determined as the most important predictive factor (P=0.039).

Table 2. Significant factors predicting poor prognosis for OS

Variables	P Value	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Age	0.015	1.108	1.020	1.205
PNI	0.008	13.633	1.967	94.490
PDW	0.005	1.438	1.114	1.858
NEU	0.004	3.344	1.479	7.561
PLR	0.002	1.028	1.010	1.046

OS: Overall survival, Exp(B): Exponentiation of the B coefficient. PNI: Peri-neural invasion, PDW:Plateletdistributionwidth, NEU: Neutrophil, LYM: Lymphocyte, PLR: Platelet/Lymphocyte Ratio

Table 3. Association between PLR and other variables

Variables		PLR>197	PLR<197	P value
Gender	Female	15 (34.1%)	29 (65.9%)	0.84
	Male	20 (32.3%)	42 (67.7%)	
Age	<72.5	25 (30.9%)	56 (69.1%)	0.39
	>72.5	10 (40%)	15 (60%)	
Localization	Right	10 (35.7%)	18 (64.3%)	0.72
	Others	25 (32.1%)	53 (67.9%)	
T Stage	2-3	29 (31.2%)	64 (68.8%)	0.28
	4	6 (46.2%)	7 (53.8%)	
Grade	1	3 (17.6%)	14 (82.4%)	0.14
	2-3	32 (36%)	57 (64%)	
LVI	+	25 (36.2%)	44 (63.8%)	0.33
	-	10 (27%)	27 (73%)	
PNI	+	13 (36.1%)	23 (63.9%)	0.62
	-	22 (31.4%)	48 (68.6%)	
N Stage	0	15 (32.6%)	31 (67.4%)	0.59
	1	16 (37.2%)	27 (62.8%)	
	2	4 (23.5%)	13 (76.5%)	
Clinical Stage	2	9 (21.4%)	33 (78.6%)	0.04 (OR=2.50)
	3	26 (40.6%)	38 (59.4%)	
Survival	Ex	14 (56%)	11 (44%)	0.05(OR=3.63)
	Alive	21 (25.9%)	60 (74.1%)	

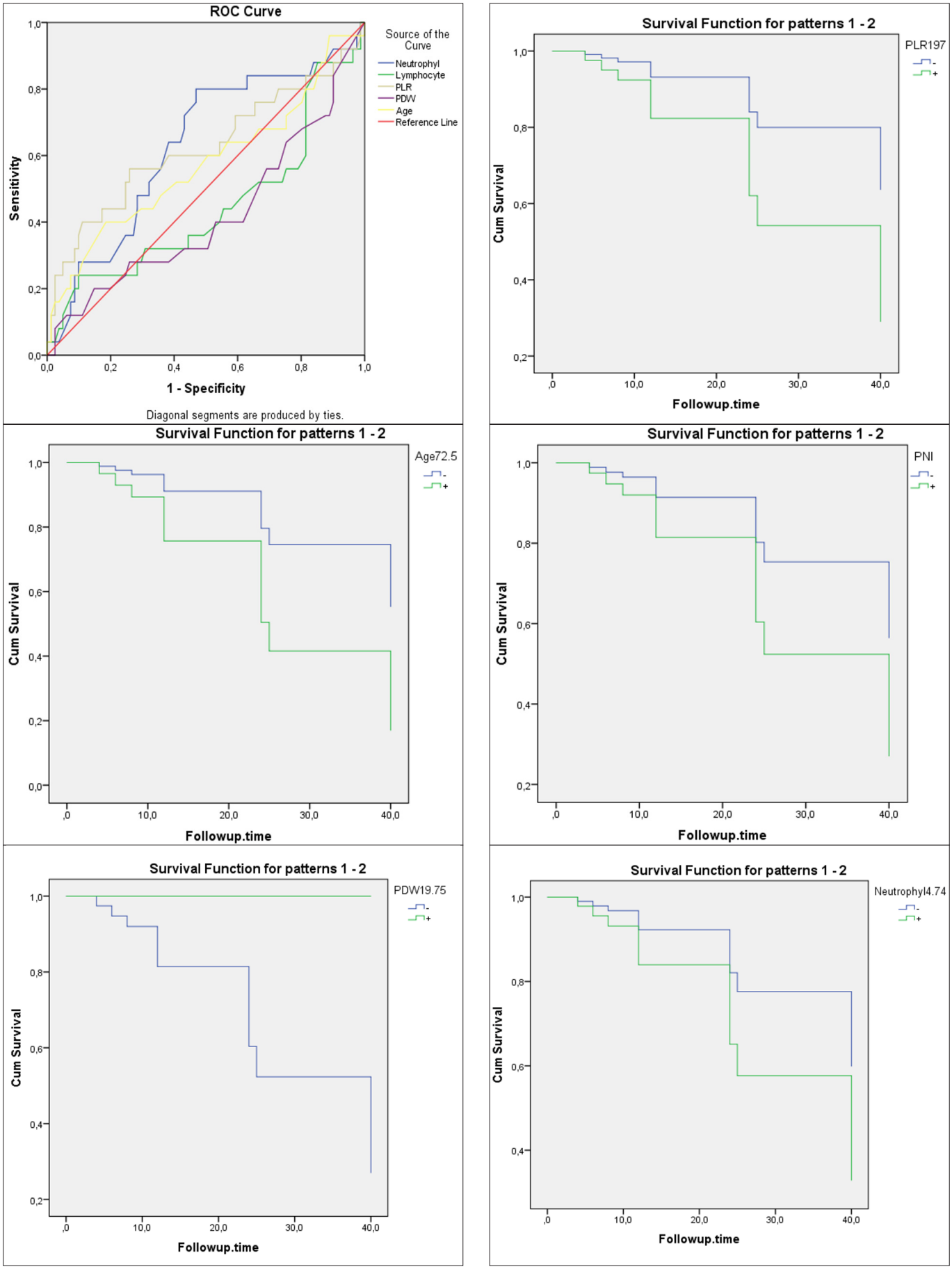

Figure 1. ROC analysisandsurvivalcurves of poorprognosticpredictors (for PLR: AUC=0.622 Cut-off: 197).

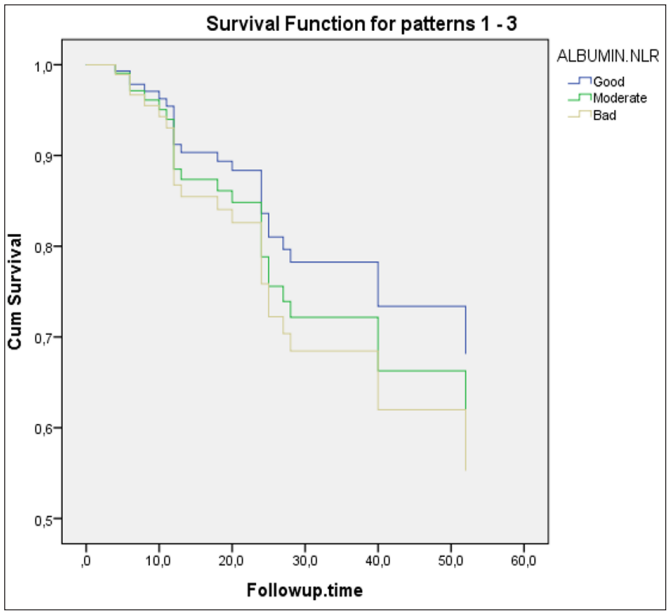

Figure 2. Albumin-NLR Survivalcurve

DISCUSSION

Many genetic and environmental risk factors play roles in the development of CRC (21). In the present study, it was shown that advanced age, high neutrophil count, PNI, high PDW, and high PLR were associated with poor prognosis and decreased survival.

The age is an important risk factor for CRC. The incidence begins to increase at significant levels after the age of 50; and 90% of CRC cases are seen after this age (22). The most common age group is the 6th and 7th decades. CRC is the most common type of cancer in individuals who are over 75 years of age in the USA with an incidence similar between men and women (23). In the present study, the incidence of CRC was found to be higher in elderly patients, in line with the literature data.

The relations between inflammation and cancer were first described by Rudolf Virchow in 1863. He detected the presence of neoplastic tissues and leukocytes in the regions where chronic inflammation occurred and observed that cancer cells developed from these regions. In their study, Balkwill and Mantovani (14, 15) reported that inflammation is an important factor for the development of solid tumor malignancies, and some solid organ malignancies can trigger an intrinsic inflammation to form the basis of the inflammatory microenvironment with pro-tumorigenic effects with a critical role in tumor resistance. De Visser et al. (24) showed that the tumor microenvironment includes macrophages, neutrophils, mast cells, natural killers, dendritic cells, T and B lymphocytes, fibroblasts, endothelial cells, pericytes, and mesenchymal cells in different types of inflammation. These different cells communicate with each other in different ways. As a result, they also affect the tumor control and growth with autocrine and paracrine products. Lin and Karin (25) showed that different mediators that are released from these different cell types determine whether inflammation will have a tumor-initiating effect or anti-tumor activity. It was reported previously that inflammation plays roles in carcinogenesis and disease progression.

Lymphocytes are essential components of the cancer microenvironment contributing to carcinogenesis (26). In a study by Own by HE et al. (27) it was reported that the host, lymphocytes are primarily responsible for the anti-tumor immune response against tumor cells, lymphocytes cause cytotoxic cell death and cytokine production, inhibit the proliferation and metastatic activities of tumor cells, and the number of lymphocytes in the peripheral blood has important effects on the prognosis of breast cancer and the survival of the patient. It was shown in another study that in case of a decrease in the number of lymphocytes in the peripheral blood, an immune-tolerant microenvironment is formed around the tumor, and for this reason, lymphopenia has a poor prognostic effect (28).

In a study conducted by Ku GY et al.(29) it was found that the median survival of patients with a lymphocyte value above a thousand cells per ml in those receiving treatment for malignant melanoma was higher than those with a lymphocyte value below a thousand cells per ml. In an article that was published by Zhang GQ et al. (30) in March 2015, it was shown that the overall survival time is increased in patients with gastric cancer who are given activated autologous lymphocyte counts, and it was proven that the development of lymphopenia is directly related to the suppression of the immune system and is associated with a poor prognosis in many cancers.

Almost one third of cancer patients have thrombocytosis at diagnosis, and it was shown that abnormal activation of platelets is associated with CRC(31,32). Martin et al. (16) reportedin their studies that platelets play roles in tumor angiogenesis and invasion. They also reported that pro-inflammatory cytokines (IL-1, IL-2 and IL-6) increased platelet release after stimulating megakaryocytes in cancer patients. High platelet counts may be an indicator of exaggerated systemic inflammatory response in cancer patientsas an indicator of poor prognosis. Similar to neutrophils, platelets are also responsible for the release of various growth factors such as PDGF, PlateletFactor-4, TGF-B, VEGF and thrombospondin. These factors are involved in mitogen activation, proliferation of tumor cells, fusion of tumor cells, and growth and metastasis of the tumor mass. Platelets can release numerous growth factors to facilitate cancer growth and spread. Fidler et al. (33, 34) showed that platelets play important roles in tumor development and metastasis. They initiate tumor development by inducing angiogenesis via VEGF. They also reported that tumor cells adhere to other tumor cells

and platelets in their circulation. They argued that this may have important roles in tumor cell aggregation and tumor cell survival.

Orellana et al. (35) cultivated ovarian cancer cells with human platelets, and found that platelet-cancer interactions contributed to the formation of metastatic foci. Also, blocking key platelet receptors attenuated ovarian cancer metastasis. Templeton AJ et al. (36) published a meta-analysis of 20 studies in 2014, examined the relations between PLR-survival in different solid tumor types, and showed that high PLR level was associated with poor survival in pancreatic, colorectal, gastroesophageal, hepatocellular and ovarian cancer.

In the present study, no relations were found between lymphocyte count alone and prognosis. However, high platelet-lymphocyte ratios were found to be a poor prognostic factor. It was also found that a one-unit increase in PLR value increased the risk of death approximately one-fold.

Platelet size correlates with platelet activity, with larger platelets having more granules and secretory capacity. A relationwas detected between the platelet volume index and hematological diseases, thromboembolism, vascular diseases and some inflammatory diseases(37,38).

There are different opinions about the prognostic value of PDW in the literature. Zhang et al. and Huang et al. showed increased PDW as a poor prognostic factor in larynx and breast cancers, and other studies showed that decreased PDW is associated with a poor prognosis (39-42). It was shown in a study by Günaldı M, et al. (43) that increased PDW is associated with metastasis in gastric cancers. In our study, high platelet counts and PDW were associated with poor prognosis.

It was shown in a study showing that increased neutrophil count is associated with poor prognosis that cytokines responsible for hematopoiesis produced by tumor cells cause an increase in neutrophils in the peripheral blood, and this increase is also an indicator of aggressive tumor biology in neutrophils. It was shown that increased neutrophils cause remodeling in the extracellular matrix, initiate tumor development, play roles in metastasis, and suppress the T cell response by regulating the release of reactive oxygen products, nitric oxide and arginase (44). Consistent with this study, it was observed that survival was lower in our patients with high neutrophil counts.

PNI and LVI are the most evaluated prognostic parameters in pathology reports of various cancers. It was studied mostly in gastric and pancreatic cancers and was found to be associated with poor prognosis (45,46). Studies on colorectal cancer have shown that PNI is associated with poor prognosis (47,48). The relations of the scoring systems such as mGPS, SIS and PN Index with prognosis was investigated in many studies (49-51). In our study, the relations of these parameters with survival was not found to be statistically significant. In a study conducted by Wang F, et al. (52) in 2018, it was shown that the albumin-NLR inflammation score predicted the prognosis in CRC better than both SIS and mGPS. It was observed in our study that the prognosis of patients with low albumin value and high NLR value was worse.

There are some limitations in the present study. Being retrospective may cause some prejudices. The serum samples taken were not according to a certain standardization due to being retrospective. The small sampling size was another limitation. The inclusion of all colon and rectal cancers resulted in heterogeneity, and the recurrence rate was not given.

CONCLUSION

As a result, it is important to determine the risky stage II CRC patient group for which adjuvant chemotherapy will be beneficial. Currently, adjuvant chemotherapy is given to some risky stage II patient groups. However, it is not certain which stage II patient group will be given adjuvant chemotherapy and for how long. More study is needed. In the study, it was shown that PLR is a poor prognostic factor. We think that it would be more beneficial to administer adjuvant chemotherapy in the stage II CRC patient group with high PLR, and to give 6-month regimens instead of 3-month regimens in the stage III patient group.

Abbreviations: PLR: platelet-lymphocyte ratio, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width, PNI: perineural invasion, LVI: lymphovascular invasion H&E: hematoxylinandeosin, IHC: immunohistochemistry, CRC: colorectal cancer, LMR: lymphocyte-monocyte ratio, MPGS: modified glasgow prognostic score, SIS: systemic inflammation score, PNindex: prognostic nutritional index

ETHICAL DECLERATIONS

Ethics Committee Approval: This study was approved by Tekirdağ Namık Kemal University Non-interventional Clinical Research Ethics Committee (Date: 25.01.2022, Decision No: 2022.05.01.05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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