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Comparison of colorectal neoplastic polyps and adenocarcinoma with regard to NLR and PLR

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Abstract. – OBJECTIVE: Cancer-related inflammation affects many aspects of malignancy, including proliferation and survival of malignant cells, angiogenesis, and therapeutic response. Some biomarkers representing the degree of systemic inflammation, such as the Glasgow prognostic score, NLR and PLR, have been shown to have prognostic value in many kinds of cancer patients. Aim of this study to investigate to compare neutrophil/leukocyte (NLR) and platelet/lymphocyte (PLR) ratios of the patients with colorectal neoplastic polyps and colorectal cancer (CRC) and tried to determine whether this could be used as a biomarker in follow up of the patients with neoplastic polyps.

PATIENTS AND METHODS: A total of 100 colorectal polyps, 113 colorectal cancers and 124 healthy controls were included in the study. Exculusion criteria were endocrinologic or metabolic diseases, acute or chronic diseases, hypertension and atherosclerotic heart diseases, renal diseases. Blood count parameters of the patients were measured. The NLR was calculated as a simple ratio between the absolute neutrophil and the absolute lymphocyte counts. The PLR was defined as the platelet counts to lymphocyte ratio.

RESULTS: A statistically significant difference was not detected between Group A and C with regard to NLR and PLR. NLR and PLR were found statistically significantly high in Group B (CRC), Group A (colorectal polyp) and Group C (healthy individuals) ($p < 0.001$ and $p < 0.001$). Our study showed that the optimum NLR cut-off point for neoplastic polyps was 2.28 (sensitivity: 68.7%, specificity: 42.3%). When the sensitivity and specificity levels of the PLR were assessed, they were 68.7% and 46.5% for neoplastic polyps, 80% and 68.9% for colorectal cancer.

CONCLUSIONS: NLR and PLR may be used for follow up conversion of colonic and rectal neoplastic polyps to invasive tumor.

Key Words:
Biomarker, Colorectal cancer, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio.

Introduction

Colorectal cancer (CRC) is the third leading cancer type among all cancers. In addition, it is also one of the important causes of cancer-related deaths in both gender and it is the most curable cancer type among gastrointestinal cancers[1]. All factors which may play a role in diagnosis and follow up gain importance as early diagnosis and appropriate treatment significantly improve survival and quality of life of the patients.

Adenomas consist approximately 30% of all colon polyps and carry the risk for malignity. Adenomatous polyps are seen in the ratio of 25-40% of general population above 50 years in USA. However most of the adenomas detected in 1/3 of these subjects has minimum risk for CRC and they are 1 or 2 tubular adenomas smaller than 1 cm. Less than 1% of these polyps are malignant. Adenomas are morphologically defined as dysplastic clonal proliferations of colonic epithelium. Microscopically, adenomas are categorized architecturally as tubular, tubulovillous and villous[2]. Cancer-related inflammation affects many aspects of malignancy, including proliferation and survival of malignant cells, angiogenesis, and therapeutic response[3]. Systemic inflammatory state can be measured by using a wide spectrum of biochemical and haematological markers[4-6]. Some biomarkers representing the degree of systemic inflammation, such as the Glas-

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gow prognostic score, neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR), have been shown to have prognostic value in many kinds of cancer patients[7]. The NLR, a measure of the relative difference of the baseline neutrophil and lymphocyte counts, has recently been discovered to be a strong prognostic factor for CRC[8,9]. Thrombocytosis is caused by the stimulation of megakaryocytes by proinflammatory mediators[10], and it commonly associated with malignant disease and has been suggested to be a poor prognostic indicator in gastric cancer patients[11]. Mean platelet volume is a widely used laboratory marker associated with platelet function based on inflammatory conditions[12,13]. There was a report that PLR is a significant prognostic indicator in resected pancreatic cancer[14]. In this study, it was aimed to NLR and PLR of the patients with colorectal neoplastic polyps and CRC and tried to determine whether this could be used as a biomarker in follow up of the patients with neoplastic polyps.

Patients and Methods

Our study group was consisted of the patients who underwent colonoscopy in Endoscopy Unit of our hospital and diagnosed with neoplastic colorectal polyp (Group A), colorectal cancer (Group C) and healthy individuals (Group C). A total of 100 colorectal polyps, 113 colorectal cancers and 124 healthy controls were included in the study. The patients who had any endocrinologic or metabolic diseases, acute or chronic diseases, hypertension and atherosclerotic heart diseases, renal diseases were excluded from the study group. The patients who were receiving antihyperlipidemic treatment, particularly statins were excluded from the study. Control group was selected among the subjects who were in similar age and gender.

Biochemical Measurements

Blood count parameters of the patients were measured using Pentra Dx Nexus 120 (England) device following 15 min of mixing in room temperature. The NLR was calculated as a simple ratio between the absolute neutrophil and the absolute lymphocyte counts. The PLR was defined as the platelet counts to lymphocyte ratio. Venous blood obtained in the morning following 8-10 hour of fasting period was used for biochemical measurements. All biochemical measurements were done using commercial kits in Cobas C 501 Roche, (Tokyo, Japan) biochemistry analyser.

Statistical Analysis

PASW® Statistics 18 for Windows statistical package program was used for data transfer to computer environment and statistical analysis. Distribution of variables was tested with Kolmogorov Smirnov test. For normally distributed variables, variance analysis (ANOVA) was used when comparing three groups, Tukey test was used for subgroup comparisons. For variables not normally distributed, Kruskall-Wallis test was used for comparison for three groups and Mann Whitney U test was used for subgroup comparisons. p value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 337 patients were included in the study. Age range of the subjects was 17 to 85 years with median age of 55. Of the participants, 186 were male and 151 were female. Of 100 patients in Group A who had colorectal neoplastic polyp, 64 had tubular adenoma, 28 had tubulovillous adenoma and 8 had villous adenoma. The CRC patients in Group B, 9, 29, 52 and 23 were in stage 1, 2, 3, 4, respectively.

Median WBC, neutrophil, lymphocyte, platelet values of the groups are presented in Table I. While there was not a statistically significant difference between groups with regard to WBC count, a statistically significant difference was detected between Group B and C with regard to neutrophil count ($p < 0.005$), there was a statistically significant difference between Group A and B, between Group B and C with regard to lymphocyte and platelet counts ($p < 0.001$).

Median values of NLR were 1.90 (0.26-6.45), 2.88 (0.42-23.55), 1.78 (0.54-5.29) in Group A, B and C, respectively. A statistically significant difference was detected between Group A and B, Group B and C ($p < 0.001$).

Median values of PLR were 115.19 (0.26-977.66), 193.06 (19.86-885.71), 112.43 (26.50-453-64) in Group A, B and C, respectively. A statistically significant difference was detected between Group A and B, Group B and C ($p < 0.001$).

A statistically significant difference was not detected between Group A and C with regard to NLR and PLR.

Table I. Stastical analysis of groups.

Variable	Group A (n: 100)	Group B (n: 118)	Group C (n: 124)	Comparison	p
White cell count ($\times 10^9$)	6.90 (1.68-15.22)	7.00 (2.28-20.81)	6.97 (4.02-13.32)	A vs. B A vs. C B vs. C	NS NS NS
Neutrophil count ($\times 10^9$)	4.01 (1.04-64.90)	4.39 (1.38-17.90)	3.83 (1.58-10.06)	A vs. B A vs. C B vs. C	NS NS < 0.005
Lymphocyte count ($\times 10^9$)	2.13 (0.93-34.90)	1.59 (0.31-21.10)	2.17 (1.10-7.32)	A vs. B A vs. C B vs. C	< 0.001 NS < 0.001
Platelet count ($\times 10^9$)	252.10 (8.20-608.00)	312.50 (52.00-748.00)	236.00 (101.30-449.00)	A vs. B A vs. C B vs. C	< 0.001 NS < 0.001
NLR	1.0 (0.26-6.45)	2.88 (0.42-23.55)	1.78 (0.54-5.29)	A vs. B A vs. C B vs. C	< 0.001 NS < 0.001
PLR	115. 9 (0.26-977.66)	193.06 (19.86-885.71)	112.43 (26.50-453-64)	A vs. B A vs. C B vs. C	< 0.001 NS < 0.001

Group A: Patients with colorectal polyp, Group B: Patients with colorectal cancer, Group C: Control group, NS: not significant.

NLR and PLR were found statistically significantly high in Group B (CRC), Group A (colorectal polyp) and Group C (healthy individuals) ($p < 0.001$ and $p < 0.001$).

ROC curve analysis suggested that the optimum NLR cut-off point for colorectal cancer was 2.39 (sensitivity: 72%, specificity 59.8%) (Table II).

Our study showed that the optimum NLR cut-off point for neoplastic polyps was 2.28 (sensitivity: 68.7%, specificity: 42.3%). When the sensitivity and specificity levels of the PLR were assessed, they were 68.7% and 46.5% for neoplastic polyps, 80% and 68.9% for colorectal cancer (Table III).

Discussion

Adenomas and carcinomas have a similar distribution in the colo-rectum, and adenomas usually precede cancer by about 15 years. Endoscopic removal of polyps decreases the occurrence of subsequent colorectal cancer in treated subjects[2,15]. Colon cancer is a disease which has low mortality and morbidity when diagnosed early and it may frequently be treated curatively through surgical intervention[16]. However some part of the cases are in advanced stages at the time of diagnosis and 5-year survival does not exceed 8%. Five-year survival is 93% in stage I tumors, 78% in stage II tumors, 64% in stage III tumors[17].

Leukocytes were first discovered in malignant tissue specimens by the pathologist Rudolf Virchow about 150 years ago[18]. Neutrophilia has been associated with malignancy, although the cause is not completely understood. The malignant process also produces myeloid growth factors as part of a paraneoplastic syndrome and this

Table II. Stastical analysis of patients with colorectal cancer grouped by NLR and PLR.

	NLR (cut-off = 2.39)	PLR (cut-off = 143.74)
Sensitivity	72%	80%
Specificity	59.8%	68.9%
Mean	3.86	225.69
SD	2.42	134.79

Table III. Stastical analysis of patients with neoplastic polyps grouped by NLR and PLR.

	NLR (cut-off = 2.28)	PLR (cut-off = 141.21)
Sensitivity	68.7%	68.7%
Specificity	42.3%	46.5%
Mean	2.07	123.63
SD	1.08	62.60

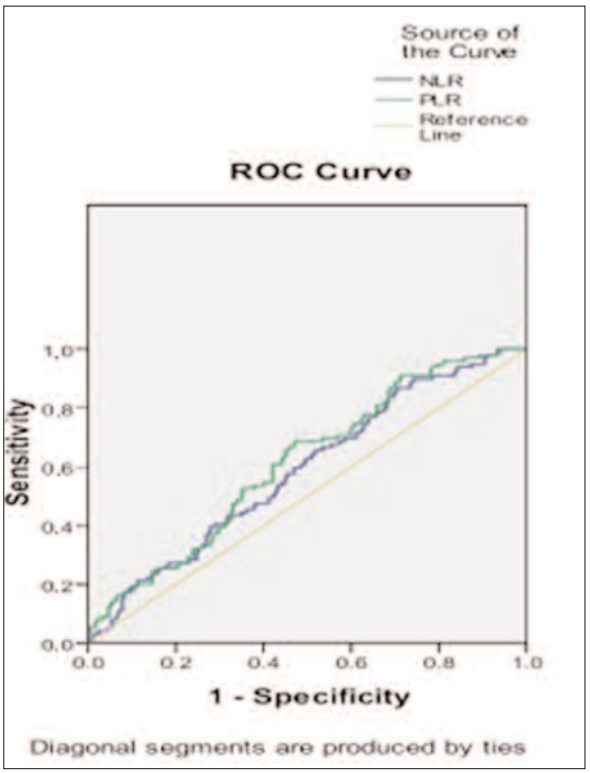

Figure 1. Group 1 (neoplastic polyps).

may be one of the causes of neutrophilia. In addition, another factor granulocyte colony stimulating factor produced by the malignant cells has also been attributed to be the cause of neutrophilia because of its action on bone marrow granulocytic cells[19-22]. Neutrophils can promote tumor growth and metastasis by remodeling the extracellular matrix and releasing reactive oxygen species (ROS), nitric oxide (NO), and arginase which suppress the T-cell response and increase the rate of mutagenesis[23-25]. Granulocytes have also been found to proportionally inhibit the function of cytotoxic lymphocytes[26]. In this study, median neutrophil count of CRC group was found statistically significantly higher than that of control group.

Blood platelets are a key element linking the processes of hemostasis, inflammation, and tissue repair[27]. The presence of both neutrophilia and thrombocytosis tends to represent a nonspecific response to cancer-related inflammation[28]. Cancer has been shown to produce myeloid growth factors, such as granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin-1, and interleukin-6, which may influence tumor-related leukocytosis and neutrophilia[29,30]. Lymphocytes play a large role in cancer immunesurveillance, which suppresses tumor maturation[31]. Tumor infiltrating lymphocytes were detected to be associated with a better overall survival in early stage CRC patients[32]. In this study, median lymphocyte values were found statistically significantly low in CRC group compared to colorectal polyp group and control group.

Some biomarkers representing the degree of systemic inflammation[33], such as the Glasgow prognostic score, NLR and PLR, have been shown to have prognostic value in many kinds of cancer patients[4]. NLR could be an important measure of systemic inflammation as it is cost effective, readily available[34]. The NLR can be considered as the balance between pro-tumor inflammatory status and antitumor immune status. Patient swith elevated NLR have a relative lymphocyt openia and neutrophilic leukocytosis which denote that the balance is tipped in favor of protumor inflammatory and is associated with poor oncologic outcome[11,14,35]. He et al[36] investigated the prognostic and predictive value of the NLR and PLR in 243 patients with initially metastatic CRC patients and identified the NLR and PLR as statistically significant poor prognostic factors

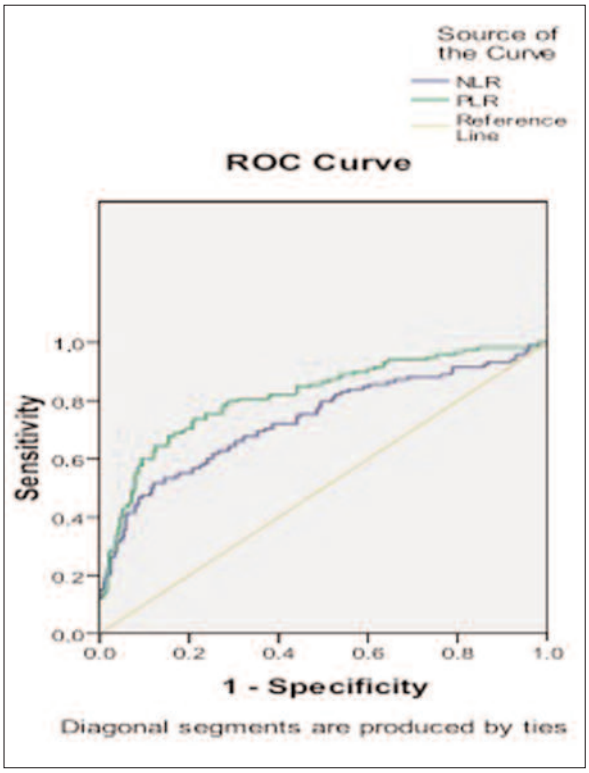

Figure 2. Group 2 (colorectal cancer).

for overall survival, while only the NLR was validated as independent predictor. And also, they suggested, NLR will bean alternative indicator as current genetic or immunohistochemistric indicators. Karaman et al[37] detected NLR high in neoplastic polyps and reported that it could be used in differential diagnosis of neoplastic and non-neoplastic colon polyps in their study which compared neoplastic polyps and non-neoplastic polyps. In this study, NLR was found highest in CRC group compared to colorectal polyp and control group.

In an attempt to better estimate the patients' clinical outcome, preoperative PLR has been investigated in various cancer entities[38-40]. In CRC, Kwon et al[41] demonstrated that an elevated PLR is independently associated with decreased overall survivalan, analyzing 200 patients who underwent curative resection. More recently, another work[42] including 140 patients with resectable CRC found a statistically significant association between an elevated PLR and decreased overall 5-year survival in uni and multivariate analysis. Both studies, however, included only a small number of patients and analyzed overall survival but not time to recurrence which might be influenced by numerous other factors including cancer-related deaths. In this study, PLR was found high in CRC group compared to other two groups.

Conclusions

NLR and PLR could be an important measure of systemic inflammation as it is cost effective, readily available. As the result of this study, although we concluded that NLR and PLR may be used for follow up conversion of colonic and rectal neoplastic polyps to invasive tumor, we consider that studies conducted with larger series are required.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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