ORIGINAL ARTICLE

Neutrophil–lymphocyte Ratio: Predictor of High-grade Dysplasia in Colorectal Polyp

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ABSTRACT

Objective: *To determine the value of neutrophil–lymphocyte ratio for predicting high-grade dysplasia among patients with neoplastic colorectal polyp.*

Method: *We evaluated 30 patients with non-neoplastic polyp, 61 patients with neoplastic polyp (32 with high-grade dysplasia/29 without high-grade dysplasia), and 30 patients with normal colonoscopy as control group. Mean platelet volume, red cell distribution width, neutrophil and lymphocyte levels were recorded and neutrophil–lymphocyte ratio was calculated.*

Results: *Mean neutrophil–lymphocyte ratio of patients with neoplastic polyp were higher than patients with non-neoplastic polyp and control group (2.56 ± 1.47, 1.77 ± 0.44, 1.76 ± 0.62, retrospectively) (*p *= 0.001). Mean platelet volume of patients with neoplastic polyp (8.76 ± 1.06) was lower than patients with non- neoplastic polyp (9.50 ± 1.27) and control group (10.96 ± 0.83) (*p *< 0.001). Mean neutrophil–lymphocyte ratio of patients with high-grade dysplasia (3.03 ± 1.88) was significantly higher than patients without high-grade dysplasia (2.14 ± 0.77) (*p *= 0.022). The cut-off value of neutrophil–lymphocyte ratio to predict the presence of high-grade dysplasia was 2.044 (sensitivity: 69%, specificity: 68%).*

Conclusion: *Neutrophil–lymphocyte ratio, which is a simple non-invasive index can predict high-grade dysplasia and neoplastic polyp. Although mean platelet volume and red cell distribution width are not useful for identifying high-grade dysplasia in patients with colorectal polyp, mean platelet volume may be associated with neoplastic polyp.*

Keywords: Colorectal polyp, high-grade dysplasia, neoplastic polyp, neutrophil–lymphocyte ratio.

INTRODUCTION

Colorectal polyps are histologically classified as neoplastic and non-neoplastic. Most colorectal cancers (CRCs) develop from neoplastic polyps (NPs) named as adenomatous polyps (adenomas) (1). It takes 10 years for a NP smaller than 1 cm to transform the CRC and NPs are usually asymptomatic (2). It is recognized that more than 95% of all CRCs develop from NPs (1). The risk of an adenoma becoming malignant is the greatest for advanced adenoma, defined as adenoma with size ≥ 1 cm, villous elements, or high-grade dysplasia (HGD) (3). CRC screening guidelines recommend follow-up surveillance examinations to detect additional new adenomas, missed synchronous adenomas and advanced neoplasia after polypectomy (3). It is suggested that patients with advanced adenomas should have their next follow-up colonoscopy in 3 years and patients with low risk adenomas should be screened 5-yearly until one negative colonoscopy examination, then cease surveillance (3).

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All NPs have variable degrees of dysplasia ranging from low-grade to high-grade. HGD contains the histological changes previously called 'carcinoma in situ' or 'intramucosal carcinoma'. Of all patients with adenomas, 5%–7% have HGD (1). An adenoma with HGD has a higher risk for CRC than an adenoma without it (1–3). Recently, it has been shown that chronic inflammation was a risk factor for CRC (4) and Glasgow prognostic score, an inflammation-based prognostic score including the serum C-reactive protein and albumin level, was a good, independent prognostic factor in patients with CRC (5). Neutrophil–lymphocyte ratio (NLR) was an inflammation index and recently gained a prognostic value for patients with CRC (6). Neutrophil–lymphocyte ratio could be used in patients with CRC for stratification of the patients, adjusting the treatment strategy and tumour staging (6, 7). Mean platelet volume (MPV) was an inflammatory marker in chronic illness and found to be lower in patients with ankylosing spondylitis and rheumatoid arthritis than controls (8). Conversely, in patients with CRC, it has been found that MPV was higher in patients with colon cancer than controls and elevated MPV was associated with colon cancer (9). Red blood cell distribution width (RDW) is part of an automated complete blood count and the most commonly reported index to determine the anisocytosis in red cell volume (10). Recent studies have showed the relationship between high RDW levels and increased mortality in the general population (11) and in patients with hepatitis B (12). It was reported that RDW is associated with inflammatory marker in lung cancer (13). Another study reported that RDW was found to be 84% sensitive and 88% specific for right-sided colon cancer (14). It was reported that colorectal adenomas had an increased inflammation (15). Recently, a study reported that NLR may be a biomarker for determining neoplastic colorectal polyp (16). To date, the relationship between HGD and NLR in patients with neoplastic colorectal polyps has not been evaluated.

The aim of this study was to determine the value of NLR which is a simple index calculated by using routine laboratory data for predicting HGD among patients with neoplastic colorectal polyp.

SUBJECTS AND METHODS

Laboratory data and colonoscopy results of patients who underwent total colonoscopy between January 2007 and December 2011 in the endoscopy unit of Ankara Ataturk Training and Research Hospital in Turkey were examined retrospectively. Patients with a personal history of CRC, inflammatory bowel diseases, hereditary non-polyposis CRC, familial adenomatous polyposis, active infectious disease, anaemia, haematological disorders, steroid use, having immunosuppressive therapy or incomplete colonoscopies were excluded. Patients who had only neoplastic colorectal polyp(s) (patients with or without HGD) and had only non-neoplastic colorectal polyp(s) and over 18 years old were included. Subjects were randomly selected from the files. The control groups consisted of patients who had normal colonoscopy matched for age and sex. We recorded the patients' age, sex, histological characteristics of polyps and complete blood count (MPV, neutrophil, lymphocyte, RDW, thrombocyte). Neoplastic polyp was defined as tubular, villous or tubulovillous adenoma. Non-neoplastic polyp included hyperplastic or mucosal polyp. Neoplastic polyps were divided into two groups according to the presence of HGD. An automatic blood count device was used for the complete blood count.

Standard procedures in the Statistical Package for the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) with MedCalc version 14.12.0 statistical software were used for statistical analysis. Shapiro Wilk test was used to see whether or not distribution of discrete numeric variables was close to normal. Levene test was used to assess the homogeneity of variances. Descriptive statistics were expressed as mean ± standard deviation for discrete numeric variables and as number or percentage of cases for categorical variables. Significance of differences of average values between groups was assessed by Student's *t* test when there were two independent groups and by one-way ANOVA when there were more than two independent groups. Receiver operating characteristic (ROC) curve analysis with 95% confidence intervals (CI) was used to establish optimal cut-off values of NLR for the detection of HGD and NPs in all polyps. The sensitivity and specificity were calculated to determine the diagnostic accuracy of the model. A p-value of 0.05 was considered to indicate statistical significance.

RESULTS

We evaluated 91 patients with colorectal polyp and 30 patients with normal colonoscopy as control group (15 males and 15 females). Among a total of 91 patients with polyp, 51.6% were males and 48.4% were females (n = 47/44). The mean age of the patients was 62.21 ± 14.39 years and the mean age of the control was 57.67 ± 8.80 years. The patients' descriptive characteristics were demonstrated in Table 1.

Table 1: Characteristics of patients with colorectal polyp and control group

Characters	Control	Patients with colorectal polyp	*p*-value
Age	57.67 ± 8.802	62.21 ± 14.395	0.106
Gender (M/F)	15/15	(49/42)	0.876
Leukocyte	7001.33 ± 1781.688	7337.36 ± 1650.971	0.366
Platelet	273833.33 ± 74607.69	267505.49 ± 80886.254	0.695
NLR	1.76 ± 0.62	2.30 ± 1.28	0.03
MPV	10.96 ± 0.83	9.00 ± 1.18	< 0.001
RDW	13.92 ± 1.20	15.60 ± 2.43	< 0.001

NLR = neutrophil–lymphocyte ratio; MPV = mean platelet volume; RDW = red cell distribution width; M = male; F = female.

There was not a significant difference between patients and control groups in terms of gender or age. Mean NLR (2.30 ± 1.28) and mean RDW (15.60 ± 2.43) of patients with colorectal polyp was higher than control group (1.76 ± 0.62, 13.92 ± 1.20, respectively) ($p = 0.03$, $p < 0.001$, respectively) (Fig. 1). Conversely, mean MPV of patients with polyp (9.00 ± 1.18) were lower than control group (10.96 ± 0.83) ($p < 0.001$). The patients with polyp were subdivided into two groups according to those having NP or non-NP. There were 30 patients with non-NP (16 males (53%) and 14 females (47%); mean age of 57.80 ± 14.028 years) and 61 patients with NP (33 males (54%) and 28 females (46%);

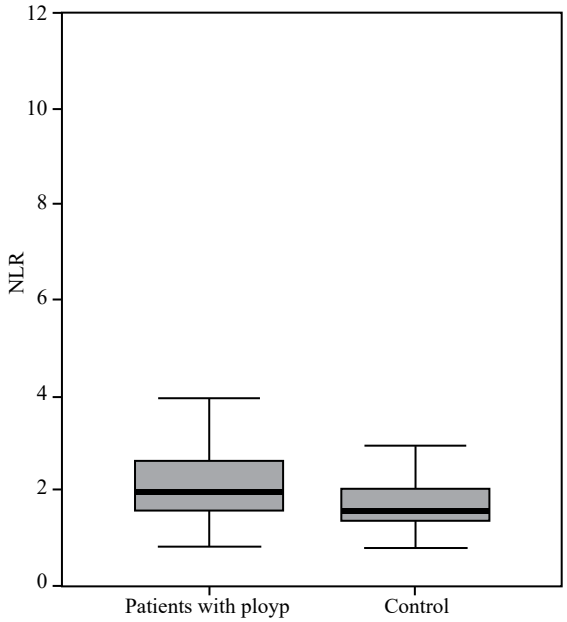

Fig. 1: Mean NLR of patients with polyp and control. NLR = neutrophil–lymphocyte ratio.

mean age of 64.38 ± 14.18 years). Control group was composed of 30 patients with normal colonoscopy. The three groups were similar in terms of gender ($p > 0.05$). Patients with NP were older than others ($p = 0.021$). No statistical difference was observed between patients with non-NP and control group according to age ($p > 0.05$). Mean NLR of patients with NP (2.56 ± 1.47) was higher than patients with non-NP (1.77 ± 0.44) and control group (1.76 ± 0.62) ($p < 0.001$) (see Fig. 2).

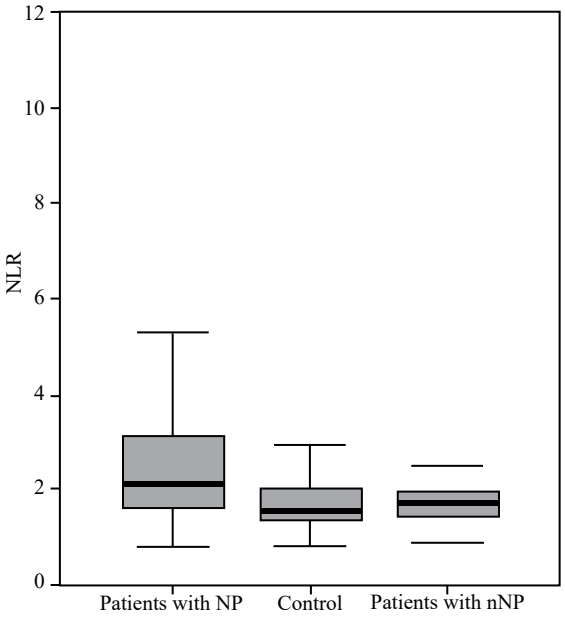

Fig. 2: Mean NLR of patients with neoplastic polyp, control and patients with non-neoplastic polyp. NLR = neutrophil–lymphocyte ratio; NP = neoplastic polyp; nNP = non-neoplastic polyp.

Table 2: Characteristics of the two patient subgroups and control group

Characters	Control	Patients with nNP	Patients with NP	*p*-value
Age	57.67 ± 8.802	57.80 ± 14.028	64.38 ± 14.185	0.021[a] 0.054[b,c]
Gender (M/F)	15/15	(16/14)	(33/28)	> 0.05[d]
Leukocyte	7001.33 ± 1781.688	6987.33 ± 1738.021	7509.51 ± 1592.845	> 0.05[d]
Platelet	273833.33 ± 74607.69	260200.00 ± 81328 ± 37	271098.36 ± 81099.67	> 0.05[d]
NLR	1.76 ± 0.62	1.77 ± 0.44	2.56 ± 1.47	0.001[a] 0.001[b] 1.000[c]
MPV	10.96 ± 0.83	9.50 ± 1.27	8.76 ± 1.06	< 0.001[d]
RDW	13.92 ± 1.20	15.21 ± 1.53	15.80 ± 2.76	< 0.001[a] 0.020[c] 0.471[b]

[a]Patients with neoplastic polyp *vs* Control, [b]Patients with neoplastic polyp *vs* Patients with a non-neoplastic polyp, [c]Patients with non-neoplastic polyp *vs* Control, [d]All group together.
NLR = neutrophil–lymphocyte ratio; MPV = mean platelet volume; RDW = red cell distribution width; M = male; F = female; NP = neoplastic polyp; nNP = non-neoplastic polyp.

There was no significant difference between patients with non-NP and the control group ($p > 0.05$). Characteristics of the two patient subgroups and control group are shown in Table 2. Mean MPV of patients with NP (8.76 ± 1.06) was lower than patients with non-NP (9.50 ± 1.27) and control group (10.96 ± 0.83) ($p < 0.001$). Mean RDW of patients with NP (15.80 ± 2.76) was higher than patients with non-NP (15.21 ± 1.53) and control group (13.92 ± 1.20) ($p = 0.471$, $p < 0.001$, respectively). But the difference between patients with NP and nNP was not statistically significant for RDW. When the ROC curve was drawn to investigate the diagnostic ability of NLR and MPV to distinguish the presence of neoplasia from the non-NP and control group, the most suitable cut-off value for NLR was 2.029 (sensitivity: 56%, specificity: 77%) and for MPV was 9.48 (sensitivity: 80%, specificity: 47%). The area under the curve (AUC) was 0.67 (95% CI 0.56, 0.78) for NLR and 0.66 (95% CI 0.54, 0.78) for MPV.

We subdivided the patients with NP into two groups according to the dysplastic grade of the polyp including HGD or not (Table 3). A total of 32 patients (17 males (53%), 15 females (47%)) with a mean age of 64.31 ± 14.50 years had NP with HGD and 29 patients (16 males (55%), 13 females (45%)) with a mean age of 64.44 ± 14.14 years had NP with low-grade dysplasia. When we compared the two patient subgroups, the mean NLR of patients with high-grade NP (3.03 ± 1.88) was significantly higher than patients with low-grade NP (2.14 ± 0.77) ($p = 0.022$) (see Fig. 3). No statistically significant differences were observed between the groups according to MPV ($p = 0.715$) and RDW ($p = 0.692$). The cut-off value of NLR to distinguish the presence of HGD was 2.044 (sensitivity: 69%, specificity: 68%) and the AUC was 0.63 (95% CI 0.49, 0.78) for NLR.

Table 3: Characteristics of patients with neoplastic polyp having high-grade dysplasia or not

Characters	Dysplasia		*p*-value
	No	Yes	
Age	64.44 ± 14.14	64.31 ± 14.50	0.972
Gender (M/F)	16/13	17/15	0.950
Leukocyte	7708.12 ± 1652.39	7290.34 ± 1522.83	0.308
Platelet	286531.25 ± 88859.80	254068.97 ± 69132.34	0.115
NLR	2.14 ± 0.77	3.03 ± 1.88	0.022
MPV	8.80 ± 1.23	8.71 ± 0.86	0.715
RDW	15.67 ± 2.85	15.95 ± 2.70	0.692

NLR = neutrophil–lymphocyte ratio; MPV = mean platelet volume; RDW = red cell distribution width; M = male; F = female.

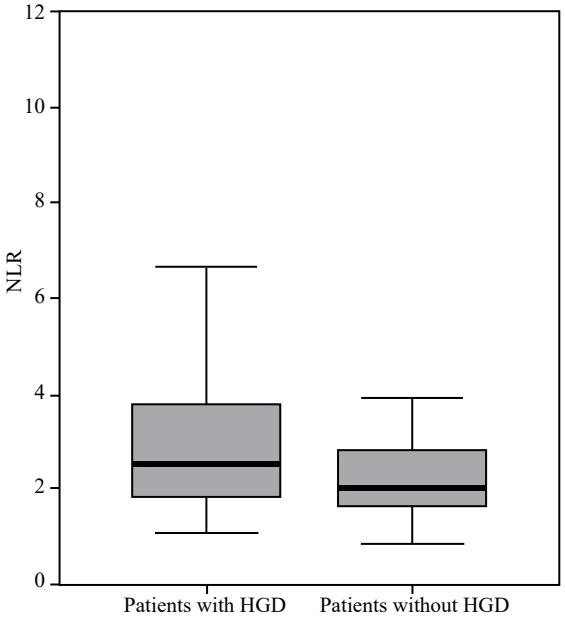

Fig. 3: Mean NLR of patients with HGD and without HGD. NLR = neutrophil–lymphocyte ratio; HGD = high-grade dysplasia.

DISCUSSION

Adenoma is the most common lesion detected in CRC screening and the most CRCs develop from normal mucosa to adenoma and then to carcinoma (17). The data of the National Polyp Study, a large longitudinal study on the surveillance of adenoma patients, showed that there was a reduction by 76%–90% in the development of CRC, following colonoscopic polypectomy (18). Adenomas with advanced characteristics (> 1 cm in diameter, with HGD, with villous histology) were the highest risk factor for malignancy (3) and HGD also was a predictor of adenoma recurrence (19). A meta-analysis reported by Saini *et al* (20) demonstrated that adenomas with HGD have an increased risk for recurrence of advanced adenomas. To the best of our knowledge, there was not a good predictor marker for determining HGD in a patient with polyp.

Recently, several studies were done on the NLR considered as a practical marker in chronic diseases. Zahorec (21) reported the NLR as a simple parameter reflecting the systemic inflammation. Recent studies have reported a relationship between NLR and coronary artery disease (22), inflammatory bowel disease (23) and cancer (24). Chronic inflammation had been demonstrated as an underlying condition for CRC (4). Recently, Walsh *et al* (25) showed that pre-operative NLR may represent a simple method of identifying CRC patients with a poor prognosis. Also, Li Mx *et al* (6) reported a systematic review and meta-analysis showing the relationship

between NLR and survival in patients with CRC and suggested that NLR could be monitored in patients with CRC for stratification of the patients and identifying the treatment strategy. Neutrophil–lymphocyte ratio has not only been studied in patients with CRC but also in patients with gastric cancer. A recent study has shown the NLR as a prognostic marker in patients with gastric cancer (26). Again, to the best of our knowledge, there has been no study about the relationship between NLR and HGD in neoplastic colorectal polyp in English literature. Karaman *et al* (16) showed that NLR may be used for identifying the NP from others. In this study, HGD was not evaluated and there was no control group. Our study demonstrated that mean NLR of patients with NP was higher than patients with nNP and control group and can be a useful, non-invasive index to predict NP and HGD in a patient with neoplastic colorectal polyp.

The present study was the first study showing NLR as a marker for determining HGD in patients with neoplastic colorectal polyp. Recently, researchers investigated some parameters of complete blood count to find an inexpensive and simple biomarker for determining the disease activity, cancer or response to the treatment in solid tumours. MPV and RDW were evaluated for these reasons. The relationship between MPV and colon cancer was reported and MPV was higher in patients with colon cancer than control group (9). Otherwise, recent studies were found that MPV was decreased in the acute stage of the rheumatic fever (27) in patients with arthritis of SLE activation (28) and acute pancreatitis (29). RDW, the other parameter of the complete blood count, was evaluated in most studies.

Spell *et al* (14) reported that RDW may be useful for detecting right-sided CRC. Recent study supported that opinion and suggested that RDW can be used as an early warning biomarker for colon cancer (30). Cengiz *et al* (31) evaluated RDW in patients with non-alcoholic steatohepatitis and demonstrated that RDW can identify the presence of non-alcoholic steatohepatitis and advanced fibrotic score. Also it was shown that RDW can predict survival in patients with hepatocellular carcinoma (32). The relationship between MPV, RDW and inflammation was demonstrated and recent study suggested that colorectal adenomas had an increased inflammation (15).

We identified the hypothesis that MPV and RDW could determine HGD in patients with colorectal polyp. We found that MPV may predict the NP but it was not useful for determining HGD. We also showed that RDW was impractical for identifying NP and HGD. There was not a good biomarker for determining NP; because of this, further studies are needed to confirm the predictive effect of MPV on determining NP.

CONCLUSION

To date, there has been no effective biomarker in distinguishing colorectal polyp for determining HGD. To the best of our knowledge, the present study was the first one evaluating the role of NLR for determining HGD in patients with colorectal polyp. Neutrophil–lymphocyte ratio which is a simple, non-invasive index, easily calculated from completed blood count can identify HGD and NP. Although, MPV and RDW are not useful for identifying high-grade dysplasia in patients with colorectal polyp, MPV may determine the neoplastic polyp.

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