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Significant difference of neutrophil-lymphocyte ratio between colorectal cancer, adenomatous polyp and healthy people

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Abstract. – OBJECTIVE: Tumor was reported to correlate with inflammation and the host's inflammatory response to tumor has been shown to independently predict the outcome. Many measures of the systemic inflammatory response have been studied in recent years. In the present study the full blood count (leukocyte, neutrophil, lymphocyte) of colorectal cancers (CRCs) adenomatous polyps, and healthy people were collected, and the difference of ratios was studied.

PATIENTS AND METHODS: A total of 752 individuals (242 colorectal cancers, 248 adenomatous polyps, and 262 healthy people) were randomized enrolled in the present study. The full blood counts (leukocyte, neutrophil, and lymphocyte) of each individual were collected and the NLRs were calculated.

RESULTS: The leukocyte count, neutrophil ratio and neutrophil-lymphocyte ratio were the highest in colorectal cancer group, the second in adenomatous polyp group, and the lowest in healthy control ($p < 0.001$). The lymphocyte ratio was in the reverse order ($p < 0.001$). The ROC curve analysis showed that sensitivity and specificity levels of NLR were 66.9% and 77.6% for CRCs, 36.7% and 80.9% for adenomatous polyp. The leukocyte count was higher in the advanced adenomatous polyp compared with low-risk group ($p = 0.042$). Further analyses of the diagnostic value of NLR are warranted in the future.

CONCLUSIONS: Difference of leukocyte count, neutrophil ratio and NLR may provide available information in the differential diagnosis of CRC, adenomatous polyp and healthy people.

Key Words:
Neutrophil-lymphocyte ratio, Colorectal cancer, Adenomatous polyp.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females' worldwide[1]. An estimated 376,300 new cases and 191,000 deaths occur in China in 2015[2]. Adenomas, the most common form of colorectal polyps, are associated with an increased risk for CRC[3] and about 50-70% of CRCs arise from the benign lesion[4]. The detection and removal of adenomatous polyp is important for reducing the incidence and mortality of CRC[5].

The incidence of adenomatous polyp increases with age and the symptoms are not usually obvious. Colonoscopy is an effective method for screening[3]. Adenomatous polyps are histopathologically classified into three types: tubular, villous, and tubulovillous. Advanced adenomas are defined as polyps (≥ 10 mm) or with histologically high-grade dysplasia or significant villous components[3].

It has been reported that cancers are linked with inflammation[6]. Inflammation in the tumor microenvironment plays an important role in the proliferation and survival of malignant cell[7]. Recently, the host's inflammatory response to tumor has been shown to independently predict outcome[7]. Various biomarkers representative of the inflammatory response have been examined over the past decade in attempt to stratify cancer patients and to predict survival. One routinely available and cost-effective marker is neutrophil-lymphocyte ratio (NLR), which is derived from the absolute neutrophil and absolute lymphocyte counts of a full blood count. NLR has been used to evaluate the prognosis in many types of cancers, including breast cancer[8], CRC[9], gastric cancer[10], renal cell carcinoma[11], non-small cell lung cancer[12], hepatocellular carcinoma[13], and cervical cancer[14]. The relationship between colonic polyp type and the NLR was reported by Karaman et al[15]. They showed that the NLR was significantly higher in patients with neoplastic polyp as compared with non-neoplastic polyp

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group. However, little was reported about the NLR and its association with CRC, adenomatous polyp and healthy people.

In the present study, the NLR was analyzed between CRC, adenomaous polyp, and healthy people to investigate the difference of NLR between the three groups.

Patients and Methods

Patients

All the patients with CRC or adenomatous polyp in this study were histologically confirmed. Healthy people were randomly selected without symptoms and cancer history. The blood samples were collected and kept in EDTA tubes. Exclusive criteria were acute infective disease and hematological disorders. Written informed consent was obtained from the family of each patient. This study was retrospectively performed and approved by the institutional Ethics Committees of Beijing Chao-Yang Hospital, Capital Medical University.

Methods

Medical records were reviewed to find data on medical history, age, sex, pathologic results and full-blood count (leukocyte, neutrophil, lymphocyte), when diagnosed for each of the individuals, were obtained. Neutrophil ratio was defined as neutrophil count divided by the count of white blood cell (WBC). Lymphocyte ratio was defined as lymphocyte count divided by the count WBC. NLR was defined as neutrophil count divided by lymphocyte count. In the present study, adenomatous polyps were classified into low-risk and advanced groups. The presence of multiple (3-10) adenomatous polyps, adenomas $\geq$ 10 mm with > 25% villous histology or having high-grade dysplasia were classified as advanced group. Informed consent was obtained from all the patients before enrollment in the study.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to evaluate the normality of the data. Kruskal-Wallis H test was used to compare the differences between three groups. Mann-Whitney U test was used to compare the differences between two groups. A level of $p < 0.05$ was considered to indicate a statistically significant difference. The level of significance is corrected to $\alpha' = 0.05/3$ when comparison between any two groups. Receiver operating characteristic (ROC) curves were constructed by plotting sensitivity *vs.* (1-specificity), and the areas under the ROC curves (AUCs) were calculated.

Results

Patient Characteristics

A total of 752 individuals (242 colorectal cancers, 248 adenomatous polyps, and 262 healthy people) were randomly enrolled between 2011 and 2013 from Beijing Chao-Yang Hospital, affiliated to Capital Medical University of China. The median age was 71.5 ± 11.3 years (range 28-87) for CRC cancer group, 61 ± 10.4 years (range 29-83) for adenomatous polyp group, and 57 ± 11.6 years (range 22-91) for healthy people. Although the difference of age between the three groups was significant, the statistical analysis showed that there was no correlation between age and NLR (data not shown).

Comparisons Between Colorectal Cancer, Adenomatous Polyp and Healthy People

The medians and interquartile ranges of leukocyte count, neutrophil ratio, lymphocyte ratio and NLR, were presented in Table I. The results showed that the differences of the leukocyte

Table I. Comparisons of WBC, neutrophil ratio, lymphocyte ratio and NLR between three groups.

Group	n	Median (interquartile range)			
		WBC (*10^9/L)	Neutrophil/WBC (%)	Lymphocyte/WBC (%)	NLR (%)
CRC	242	6.62 (5.52, 7.78)	66.50 (60.90, 73.23)	23.95 (18.15, 29.20)	2.76 (2.11, 4.06)
Adenomatous polyp	248	6.22 (5.24, 7.12)	58.15 (52.00, 64.88)	31.50 (25.43, 36.85)	1.875 (1.44, 2.53)
Healthy people	262	6.15 (5.30, 7.03)	56.75 (50.20, 61.68)	35.15 (29.68, 40.25)	1.60 (1.25, 2.00)
Comparison F, *p*		16.587, < 0.001	160.877, < 0.001	191.274, < 0.001	186.741, < 0.001

Table II. Multiple comparisons of WBC, neutrophil ratio, lymphocyte ratio and NLR between three groups.

Group	Multiple comparison (*F*, *p*)			
	WBC	Neutrophil/WBC	Lymphocyte/WBC	NLR
CRC *vs* Adenomatous polyp	13.626, < 0.001	87.062, < 0.001	84.603, < 0.001	89.255, <0.001
CRC *vs* Healthy people	11.360, < 0.001	147.370, < 0.001	176.305, < 0.001	172.393, < 0.001
Adenomatous polyp *vs* Healthy people	0.123, 0.725	7.775, < 0.005	26.794, < 0.001	19.261, < 0.001

count, neutrophil ratio, lymphocyte ratio and NLR between the three groups were statistically significant ($p < 0.001$, respectively). The leukocyte count, neutrophil ratio and NLR were highest in CRCs group and the lowest in healthy people ($p < 0.001$, respectively). The lymphocyte ratio is highest in healthy people and the lowest in CRCs group ($p < 0.001$). With multiple comparisons, no statistical significance was seen in the difference of leukocyte count between adenomatous polyp and healthy people ($p = 0.725$, Table II). The differences of neutrophil ratio, lymphocyte ratio and NLR between any two groups were statistically significant ($p < 0.05$, respectively).

ROC Curves of NLR of Colorectal Cancer and Adenomatous Polyp

ROC curve analysis showed that the cut-off point of NLR for colorectal cancer at 2.33 was associated with optimal sensitivity and specificity of 66.9% and 77.6%, respectively (Figure 1). The cut-off point of NLR for adenomatous polyp was 2.14 (sensitivity: 36.7%, specificity: 80.9%) (Figure 2).

Comparisons Between Low-Risk and Advanced Adenomatous Polyps

Two hundreds and forty-eight adenomatous polyps were classified into low-risk and advanced groups. The low-risk group contained 132 samples (53.2%) and the advanced group contained 116 samples (46.8%). The medians and interquartile ranges of leukocyte count, neutrophil ratio, lymphocyte ratio and NLR were presented in Table III. The leukocyte counts, neutrophil ratios and NLR were higher in advanced group than that in low-risk group. The lymphocyte ratios were lower in advanced group. The results of

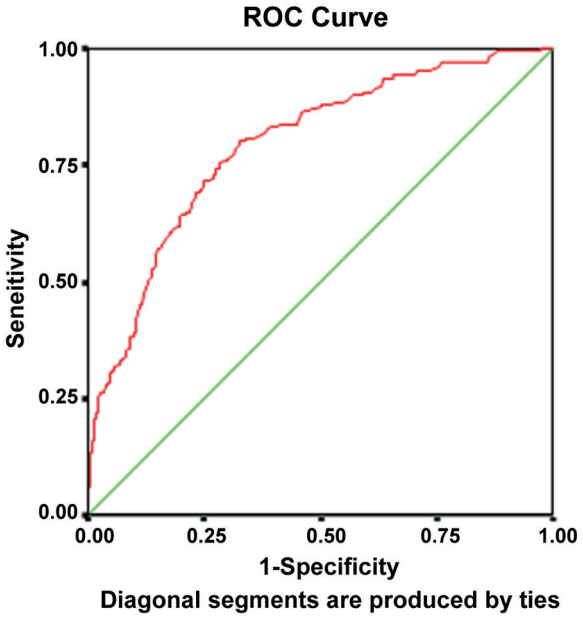

Figure 1. ROC curve of NLR of colorectal cancer (AUC = 0.794, $p < 0.001$).

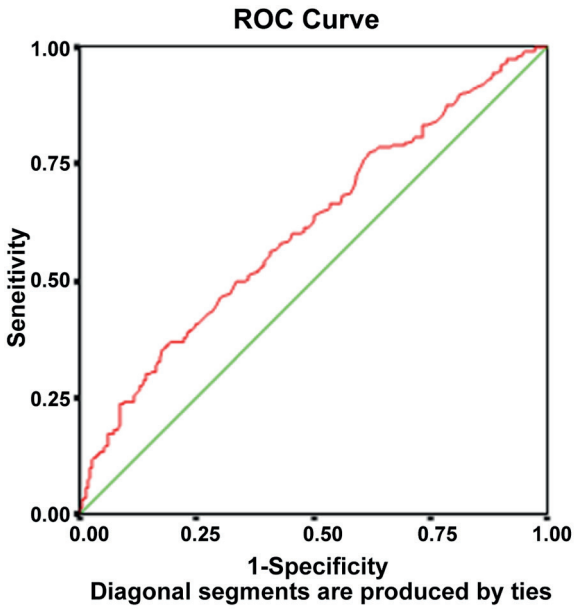

Figure 2. ROC curve of NLR of adenomatous polyp (AUC = 0.612, $p < 0.001$).

Table III. Comparisons between low-risk and advanced adenomatous polyps.

	Median (interquartile range)		
	Low-risk	Advanced	*p*
WBC (*10^9/L)	6.00 (4.98, 6.91)	6.38 (5.41, 7.27)	0.042
Neutrophil/WBC (%)	58.00 (52.00, 62.10)	58.80 (52.15, 66.58)	0.183
Lymphocyte/WBC (%)	31.70 (27.33, 37.70)	30.55 (24.80, 36.58)	0.122
NLR (%)	1.83 (1.43, 2.26)	1.93 (1.45, 2.70)	0.138

statistical analysis showed that difference of the leukocyte count between low-risk and advanced groups was significant ($p = 0.042$). There was no statistical significance of neutrophil ratios, lymphocyte ratios and NLR between the two groups.

Discussion

The relationship between inflammation and cancer has been investigated from Virchow's hypothesis that the origin of cancer is at sites of chronic inflammation in 1683. However, the complexity of tumor inflammatory microenvironment and the host's response to tumor has begun to be understood in the last decade. It is now widely recognized that cancer-associated inflammation is a key determinant of disease progression and survival in most cancers[16,17]. The systemic inflammatory responses may reflect the promotion of angiogenesis, DNA damage and tumor invasion through upregulation of cytokines[18-20].

Many measures of the systemic inflammatory response have been studied in recent years. CRP (C-reactive protein), a marker of acute phase response, was first reported with independent prognostic value in operable colorectal cancer[21]. Glasgow Prognostic Score (GPS) based on combination of CRP and albumin was reported to predict survival in both operable and inoperable cancer patients[22].

The systemic inflammatory response is associated with changes of hematological components except acute-phase proteins elevating[23]. Recently, the combination of hematological components such as NLR, was investigated by many research groups in some chronic diseases and cancers. A high density of neutrophils was observed to promote tumor growth and metastasis[20]. Experiments have revealed that some cytokines or other molecules produced by neutrophils contribute to tumor angiogenesis and microenvironment for cancer cells growth[24,25]. On the other hand, tumor-infiltrating lymphocytes have been reported to indicate tumor related immune response[26], and increased lymphocytic infiltration may predict a better survival[27]. Neutrophils have also been indicated to inhibit lymphocyte activity[28]. The theory may partly explain the neutrophilia and a relative lymphocytopenia in peripheral blood of cancer patients.

The NLR has been examined in multiple cancers and was indicated with prognostic value in over 60 studies[7]. In operable colorectal cancer, NLR was reported as a biomarker to predict poor prognosis. Pre-operative NLR greater than 5 was correlated with overall and cancer-specific survival[29]. Chua et al[9] also indicated that NLR > 5 was associated with increased risk of progression in patients with advanced colorectal cancer and normalization of the NLR after one cycle of chemotherapy in a subset of patients resulted in improved progression-free survival.

Some studies have investigated NLR in colonic polyp. Karaman et al[30] found that statistically significant differences in NLR were seen in patients with neoplastic polyp compared to nonneoplastic polyp group. However, Emir et al[31] showed that there was no significance of NLR between neoplastic colorectal polyp and healthy individuals. In the present study, we found that NLRs of CRC patients were the highest in the three groups. We also found that the difference of neutrophil or lymphocyte ratio was statistically significant between the three groups. The ROC curve analysis also showed that the cut-off point of NLR for adenomatous polyp was 2.14 and specificity level was 80.9%. Moreover, the adenomatous polyp, a benign tumor, was found to have a higher neutrophil ratios and NLR and a lower lymphocyte ratio than normal control. The results suggested that we should pay more attention to adenomatous polyp, which is considered as the intermediate stage in the process of CRC development. The NLR, as a biomarker, showed a high specificity in distinguishing adenomatous polyp from healthy people.

Compared with low-risk adenomatous polyp, the leukocyte count was higher in advanced group ($p = 0.042$). A trend was also seen that neutrophil ratio and NLR were higher and lymphocyte ratio was lower in advanced group. There were no significant differences between the two groups.

Conclusions

The NLR, as well as leukocyte count, neutrophil, and lymphocyte ratio, can be calculated easily and available from routine laboratory tests. They may be used as a cost-effective ways to evaluate the systemic inflammatory response.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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