The Clinical Value of Neutrophil to Lymphocyte Ratio in the Diagnosis and Treatment of Crohn's Disease

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Abstract **Background:** To evaluate the clinical value of neutrophil to lymphocyte ratio in the diagnosis and treatment of Crohn's disease. **Methods:** Between March 2018 and April 2020, patients diagnosed with CD at the First Affiliated Hospital of Nanjing Medical University were identified. A total of 128 patients with definite diagnosis, and 123 healthy people as the control group at the same time. The data of these patients were extracted retrospectively from their medical record. counts of white blood cells (WBC), counts of Neutrophils (NE), counts of lymphocyte (LY), hypersensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR) were recorded at the same time of colonoscopy. The IBM SPSS 20.0 software was used for the statistical analysis of data. **Results:** Levels of NLR in CD with ileocolon lesions were significantly higher than those in CD patients with ileum lesions (3.13 vs 2.72) (Z=-2.326, P=0.02). Levels of NLR in CD with colon lesions were higher than those in CD patients with ileocolon lesions (4.07 vs 3.13) (Z=-2.409, P=0.04). The levels of NLR, WBC, hs-CRP in activity stage were significantly higher than those in remission stage (P < 0.05), ESR levels in activity stage was higher than that in remission stage. the optimal cutoff point for the NLR level in order to predict the diseases was 2.18, and a highest AUC equal to 0.762 (0.700-0.823, P < 0.001). the optimal cutoff point for the WBC level in order to predict the diseases was 5.51 10^9/L, and a highest AUC equal to 0.634 (0.565-0.703, P < 0.05), the optimal cutoff point for the hs-CRP level in order to predict the diseases was 3.02 mg/L, and a highest AUC equal to 0.676 (0.606-0.746, P < 0.05), the optimal cutoff point for the ESR level in order to predict the diseases was 8.5 mm/h, and a highest AUC equal to 0.726 (0.660-0.793, P < 0.05). **Conclusions:** Neutrophil to lymphocyte ratio can be used as a sensitive and reliable noninvasive marker in the course of Crohn's disease.

Keywords: *Crohn's disease, neutrophil to lymphocyte ratio*

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1. Introduction

Crohn's disease is a chronic idiopathic intestinal inflammatory disease with unknown etiology and pathogenesis [1,2,3]. It has the characteristics of long course, difficult to control, alternating remission and activity. Therefore, diagnose and assess the disease activity accurately in patients with Crohn's disease is helpful to alleviate the disease and improve the prognosis [4,5,6]. Colonoscopy is the most accurate method to diagnose and evaluate the disease activity of Crohn's disease. However, enteroscopy is an invasive examination with poor compliance, which is not conducive to routine clinical monitoring and prognosis follow-up. The inflammatory indicators which used commonly such as white blood cells, C-reactive protein, the sensitivity and specificity of them in the diagnosis and treatment of Crohn's disease are not ideal [7,8,9]. Calprotectin is an indicator of intestinal inflammation. The detection process is complicated, there are many influencing factors, and the

results are quite different [10]. Therefore, it is necessary to find more accurate and simple inflammatory markers. Neutrophil to lymphocyte ratio (NLR) is a simple and effective index of inflammation. It is closely related to various inflammatory diseases such as acute pancreatitis and hepatitis [11,12,13]. There are few studies on the relationship between NLR and Crohn's disease now, the purpose of this article is to explore the clinical value of neutrophil to lymphocyte ratio in the diagnosis and treatment of Crohn's disease.

2. Materials and Methods

2.1. Patients

Between March 2018 and April 2020, patients diagnosed with CD at the First Affiliated Hospital of Nanjing Medical University were identified. The diagnosis of CD was based on clinical manifestations, abdominal imaging, and intestinal pathology. A total of 128 patients with definite diagnosis, and 123 healthy people were

selected as the control group at the same time. This study has been approved by our ethics committee. The data of these patients were extracted retrospectively from their medical records. The exclusion criteria include those without laboratory test results and incomplete clinical data. Other exclusion criteria: (1) patients with colorectal cancer and polyp. (2) infectious enteritis and atypical enteritis with unclear diagnosis. (3) patients with history of colectomy and recent history of taking aspirin or non steroidal anti-inflammatory drugs. (4) patients with primary immunodeficiency disease and other chronic diseases. (5) patients with pregnancy.

2.2. Description of Variables

For these patients, data including gender, age, smoking history, drinking history, weight change, symptoms, disease behavior, location, disease activity, hormone treatment. Additionally, counts of white blood cells (WBC), counts of Neutrophils (NE), counts of lymphocyte (LY), hypersensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), were recorded at the same time of colonoscopy.

To assess disease activity, we also recorded the score of simplified Crohn's Disease Activity Index (CDAI), As for disease activity, simplified CDAI < 3.3 denoted clinical remission, simplified CDAI < 11 denoted low activity, simplified CDAI < 26 denoted moderate activity, simplified CDAI ≥ 26 denoted high activity [14].

2.3. Assay of Samples

Level of WBC, NE, LY was measured by automatic hematology analyzer (Beckman Coulter, America), Level of hs-CRP was measured by IMMAGE 800 protein analysator through the velocity turbidimetry (Beckman Coulter, America), Level of ESR was measured by full-automatic rapid ESR analyzer TEST1 (ALIFAX, Italy).

2.4. Statistical Analysis

The IBM SPSS 20.0 software was used for the statistical analysis of data. The continuous variables which were non-normally distributed expressed as the median and range, using Mann-Whitney test or Kruskal-Wallis test for comparison as appropriate.

Receiver operating characteristic (ROC) analysis was conducted with GraphPad Prism 8.0 for the assessment of the validity of WBC, NLR, hs-CRP and ESR levels in distinguishing the patients with and without CD, the optimal cutoff point was identified by calculating the area under the curve (AUC). P<0.05 was considered statistically significant.

3. Result

3.1. Demographics and Clinical Characteristics

In total, 128 participants with incident CD (median age 29.0 years, 87 males, 41 females,) were identified in department of gastroenterology of the First Affiliated Hospital of Nanjing Medical University from March 2018 to April 2020, and 123 healthy individuals (median age 30.0 years, 83 males, 40 females,) were collected as control during the same period. There was no statistical difference in gender and age between the two groups. The levels of NLR, WBC, ESR, hs-CRP in patients with Crohn's disease was significantly higher than that in the healthy controls, the difference was statistically significant (P<0.05), see in Table 1.

3.2. Receiver-Operating Characteristic for NLR, WBC, CRP, ESR in Discriminating between Patients with CD and Healthy People

Using ROC analysis, the optimal cutoff point for the NLR level in order to predict the diseases was 2.18, with a sensitivity of 74.22%, a specificity of 74.19%, and a highest AUC equal to 0.762 (0.700-0.823, P < 0.001). the optimal cutoff point for the WBC level in order to predict the diseases was 5.51 10^9/L, with a sensitivity of 70.31%, a specificity of 56.45%, and a highest AUC equal to 0.634 (0.565-0.703, P < 0.05), the optimal cutoff point for the hs-CRP level in order to predict the diseases was 3.02 mg/L, with a sensitivity of 51.56%, a specificity of 87.90%, and a highest AUC equal to 0.676 (0.606-0.746, P < 0.05), the optimal cutoff point for the ESR level in order to predict the diseases was 8.5 mm/h, with a sensitivity of 50.00%, a specificity of 99.19%, and a highest AUC equal to 0.726 (0.660-0.793, P < 0.05), see in Table 2, Figure 1.

Table 1. Levels of NLR, WBC, ESR, hs-CRP in CD and healthy control

	Crohn n=128	Healthy control n=123	t	P
NLR	2.67(0.26-15.22)	1.66(0.82-8.23)	-5.848	0.000
WBC (10^9/L)	6.07(3.09-12.59)	5.39(3.31-9.50)	-2.987	0.003
ESR (mm/h)	18.50(2.00-132.00)	8.00(2.00-21.00)	-6.22	0.000
hs-CRP (mg/L)	5.65(0.56-84.4)	4.01(3.00-7.50)	-4.834	0.000

Table 2. Sen, Spe, Acc, PPV and NPV for WBC, NLR, CRP and ESR in discriminating between patients with CD and healthy people

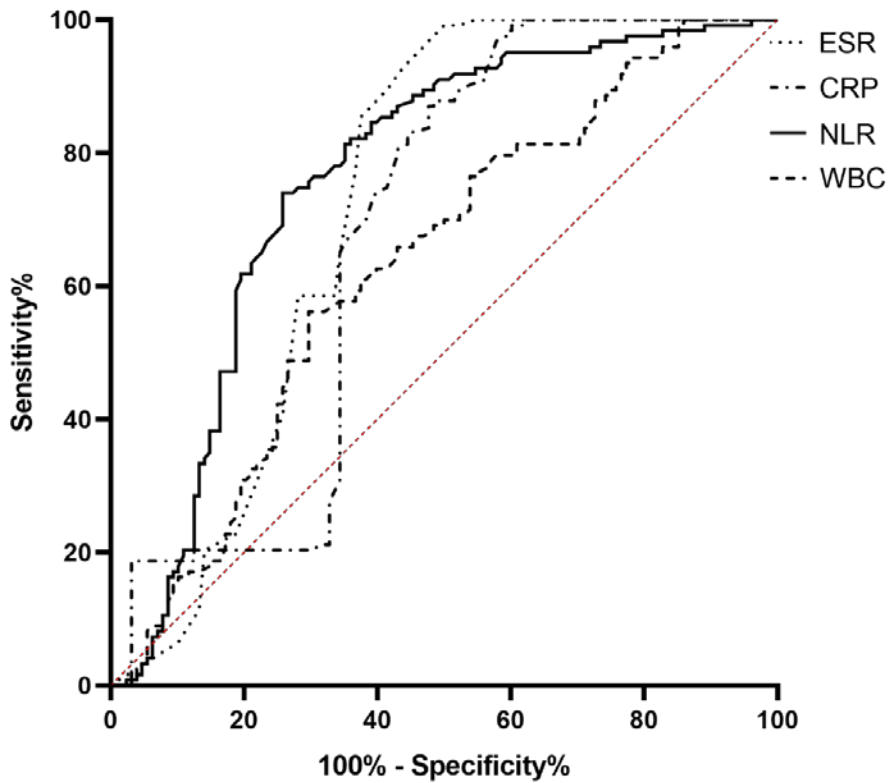|	Sen(%)	Spe(%)	Acc(%)	PPV(%)	NPV(%)
NLR (in cutoff 2.18)	74.22	74.19	74.21	74.81	73.60
WBC (in 10^9/L cutoff 5.51)	70.31	56.45	63.49	62.50	64.81
hs-CRP (in mg/L cutoff 3.02)	51.56	87.90	69.44	81.48	63.74
ESR (in mm/h cutoff 8.5)	50.00	99.19	74.21	98.46	65.78

Figure 1. Receiver operating characteristics (ROC) curves for WBC, NLR, CRP and ESR in patients with and without CD

Table 3. Levels of NLR, WBC, ESR, hs-CRP with different lesions in CD cohort

	Ileum n=68	Colon n=15	Ileocolon n=45	χ^2	P
NLR	2.72(0.26-11.49)	4.07(0.90-15.22)	3.13(0.81-9.36)	6.055	0.045
WBC (10^9/L)	6.07(3.09-15.99)	6.79(4.54-19.65)	6.57(3.23-19.00)	5.192	0.075
ESR (mm/h)	16.00(2.00-132.00)	33.00(5.00-85.00)	21.00(2.00-88.00)	5.310	0.070
hs-CRP (mg/L)	5.05(0.56-76.80)	18.30(3.02-84.4)	7.14(3.02-77.60)	10.369	0.006

Table 4. Levels of NLR, WBC, ESR, hs-CRP with difference disease activity in CD

	Remission stage n=87	Active stage n=41	t	P
NLR	2.67(0.26-8.41)	3.64(2.07-15.22)	-3.838	0.000
WBC (10^9/L)	5.88(3.09-12.59)	7.08(3.44-19.65)	-3.756	0.000
ESR (mm/h)	16.00(2.00-132.00)	25.00(2.00-120.00)	-1.814	0.070
hs-CRP (mg/L)	5.10(0.56-77.60)	8.00(2.01-84.4)	-2.425	0.015

3.3. Levels of NLR, WBC, ESR, hs-CRP with Different Lesions in CD cohort

Levels of NLR in CD with ileocolon lesions were significantly higher than those in CD patients with ileum lesions (3.13 vs 2.72) (Z=-2.326, P=0.02). Levels of NLR in CD with colon lesions were higher than those in CD patients with ileocolon lesions (4.07 vs 3.13) (Z=-2.409, P=0.04). Levels of ESR in CD with ileocolon lesions were significantly higher than those in CD patients with ileum lesions (21.00 mm/h vs 16.00 mm/h) (Z=-2.150, P=0.032). Levels of hs-CRP in CD with colon lesions were significantly higher than those in CD patients with ileum lesions (18.30 mg/L vs 5.05 mg/L) (Z=-2.615, P=0.009). Levels of hs-CRP in CD with ileocolon lesions were significantly higher than those in CD patients with ileum lesions (7.14 mg/L vs 5.05 mg/L) (Z=-2.417, P=0.016), see in Table 3.

3.4. Levels of NLR, WBC, ESR, hs-CRP with Difference Disease activity in CD

According to the simplified CDAI, Patients were divided into remission stage and active stage, 87 cases in remission stage and 41 cases in active stage, The levels of NLR, WBC, hs-CRP in activity stage were significantly higher than those in remission stage (P < 0.05), ESR levels in activity stage was higher than that in remission stage, see in Table 4.

4. Discussion

Crohn's disease is a chronic inflammatory bowel disease with unknown causes. It is caused by many factors such as heredity, environment, infection and so on. With the development of the disease, serious complications such as

lumen stenosis and perforation will occur, which will seriously affect the patient's health and reduce the quality of life [15]. Therefore, the accurate diagnosis of Crohn's disease and the judgment of disease activity are of great significance to improve the prognosis of patients. Endoscopy is a standard for clinical evaluation of inflammatory activity, The characteristics of recurrent disease increase the number of endoscopic examination. Patients' compliance is poor, which affects the judgment and prognosis of the disease. There is an urgent clinical need for non-invasive, economical, convenient and accurate molecular markers to dynamically monitor CD disease activity. To provide the basis for clinicians to make treatment plan, avoid the overuse of colonoscopy and save medical resources.

Neutrophil to lymphocyte ratio (NLR) is a simple and effective indicator of inflammation [16]. It can reflect the level of neutrophils and lymphocytes, It is a new inflammatory marker in recent years, Neutrophils are important infiltrating and regulating cells in innate immunity [17], It can respond to active nonspecific inflammatory response by secreting cytokines such as interleukin-1 (IL-1) and IL-6. Lymphocytes and their subgroups also play an important role in the pathogenesis of CD, Interferon - γ induces Th1 cell proliferation, activating dendritic cells, trigger local persistent inflammation. A large number of clinical studies have shown that NLR can be used as a predictor of inflammatory diseases such as acute pancreatitis, cerebral infarction, coronary heart disease and malignant tumor [18,19,20,21]. The results showed that NLR in patients with Crohn's disease was significantly higher than that in healthy people. Use ROC curve to analyze the relationship between NLR and CD, the optimal cutoff point for the NLR level in order to predict the diseases was 2.18, with a sensitivity of 74.22%, a specificity of 74.19%, and a highest AUC equal to 0.762, The diagnostic efficiency of NLR is better than WBC, ESR and CRP, which proves the clinical value of NLR in Crohn's disease. The NLR levels of patients with Crohn's disease at different lesion sites were different. Levels of NLR in CD with ileocolon lesions were significantly higher than those in CD patients with ileum lesions. Levels of NLR in CD with colon lesions were higher than those in CD patients with ileocolon lesions. Therefore, according to different NLR levels, the lesion location of the patient can be initially indicated, which is helpful for clinicians to carry out treatment. At the same time, the results of remission and activity were analyzed. The results show that the levels of NLR, WBC, hs-CRP in activity stage were significantly higher than those in remission stage. If NLR increases, it indicates that the patient is in the active stage of the disease, and corresponding treatment measures should be taken to alleviate the disease.

In conclusion, NLR is an important indicator in the diagnosis and treatment of Crohn's disease, which is helpful for the diagnosis and evaluation of Crohn's disease.

The innovation of this study is to use application of easy-to-obtain peripheral blood routine results to predict the location and activity of the disease. Blood routine test is widely used in clinic, which is an economic and efficient index. The disadvantage of this study is that the number of samples is small, and it is a single-center retrospective study. We look forward to the further development of large-sample, multi-center research.

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