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Original Article

Neutrophil-lymphocyte ratio: a controversial marker in predicting Crohn's disease severity

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Abstract: Peripheral blood-derived inflammation-based scores such as the neutrophil-lymphocyte ratio (NLR) have recently been proposed as prognostic markers in ulcerative colitis. In some previous serological markers are commonly used to detect the severity of the Crohn's disease (CD), but their sensitivity and specificity are relatively low. So we want to use simple indicators which are easy to obtain to predict disease severity. Now, we investigated and compared the capacity of NLR and other inflammatory markers in detecting CD activity and differentiating CD patients from healthy controls. These CD patients had not received corticosteroid or immunosuppressive drugs within a defined period of time. Data from our hospital between 2010 and 2012 was used. Neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), platelet count and albumin were measured in 44 patients with active CD, 66 patients with inactive CD, and 55 healthy blood donors. Disease activity was assessed by the Crohn's Disease Activity Index. In the active CD group, NLR values were found to be elevated compared to inactive CD patients and controls (6.00±7.38, 5.53±6.18 and 1.84±0.85, respectively), but statistical difference was not found between active and inactive CD groups. The overall accuracy of NLR (cutoff: 2.13 fl), CRP (cutoff: 10.5 mg/dl), ESR (cutoff: 19.5 mm/hour) and WBC (cutoff: 9.2 × 10^9/l) in differentiating CD patients from healthy controls was 80.9%, 67.3%, 71% and 60% respectively. NLR values were found to be correlated with WBC and CRP levels. NLR increased in CD patients compared with healthy subjects. NLR had the best accuracy in determination of CD patients and healthy controls. NLR did not show a discriminative value in disease activity.

Keywords: Crohn's disease, neutrophil-lymphocyte ratio, noninvasive monitoring

Introduction

Crohn's disease (CD) is chronic relapsing and remitting diseases of the bowel, with an unknown etiology and appears to involve interaction between genetic susceptibility, environmental factors and the immune system. Previous studies suggested that early detection of disease activity could significantly reduce the mortality of CD [1]. Non-invasive tests, such as C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), acid glycoprotein, platelet count and albumin are therefore being increasingly recognized as important markers for initial diagnosis and disease activity detection [2].

A simple, inexpensive and effective marker of inflammation that has been linked with several inflammatory and neoplastic diseases is the neutrophil-lymphocyte ratio (NLR). NLR on the outcome of many kinds of malignancies, including colorectal cancer, ovarian cancer, gastric cancer, intrahepatic cholangiocarcinoma, hepatocellular carcinoma and pancreatic cancer has been well demonstrated [3-10].

Materials and methods

Patients and methods

We prospectively collected 110 CD patients and 55 healthy subjects between January 2010 and December 2011 (**Figure 1**). The control group consisted of 55 healthy, age and gender matched subjects (male/female: 32/23). The diagnosis of CD was based on standard clinical, radiological, endoscopic and histological criteria. The classification of patients with CD was based on the Vienna classification of Crohn's disease [11]. The following data were extracted from the hospital database: age, sex, body

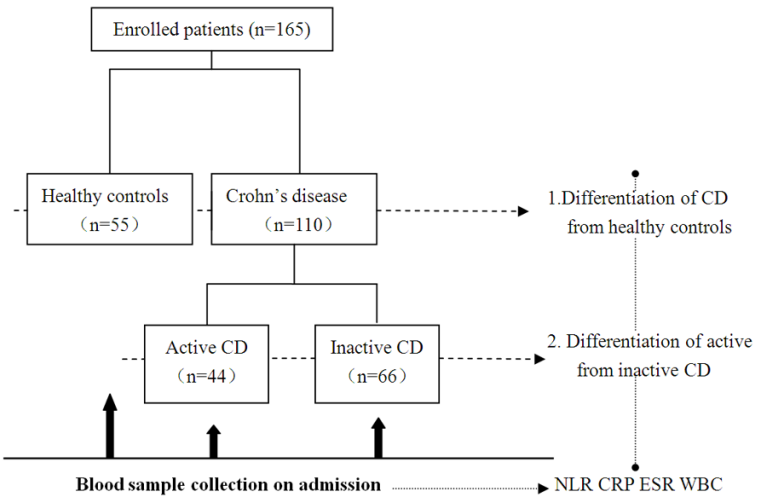

Figure 1. Study design. A total of 165 subjects were enrolled in the current study. 55 healthy controls were differentiated with 110 Crohn's disease (CD) patients using neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cells (WBC). Furthermore, the 110 CD patients were divided into active (n = 44) and inactive (n = 66) groups and distinguished using the same inflammatory biomarkers. All blood sample collections were obtained on admission (before any medication or procedure). Abbreviations: CD, Crohn's disease; NLR, neutrophil-lymphocyte ratio; CRP, C-reative protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

mass index, smoking history, behavior, Extraintestinal manifestations, activity, treatment and localization of the disease. Complete blood count (CBC) ESR, and CRP were also recorded for each CD patient. All CBC analysis was performed in hematology laboratory of our hospital. CBC analysis was performed with the same analyzer within 2 hours after collection of blood samples with the use of a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer.

Exclusion criteria for the entry into the study can be summarized as prior treatment with corticosteroids, hematological or neoplastic disorders, and clinical evidence of active infection, since NLR may be affected by those conditions.

Disease activity

For CD patients, the disease activity was defined according to the Crohn's Disease Activity Index (CDAI) [12]. Patients were further divided into an active CD group (CDAI > 150) and an inactive CD group (CDAI < 150) based on the number bloody stools per day, degree of abdominal pain, general health, complication, body temperature and hematocrit, abdominal mass.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) 19.0 for Windows was used to analyze the data. Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Values were presented as mean ± standard deviation or, in the case of non-normally distributed data, as median and range. For categorical variables, percentages were provided and the chi-squared test was used. Independent-samples *t*-test, paired *t*-test, one-way analysis of variance parametric tests, and Mann-Whitney U, Wilcoxon-*t*, and Kruskal-Wallis H nonparametric tests were used for the comparison of continuous variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of NLR and other inflammatory markers. The overall accuracy was also calculated by additional true-positive and true negative test results divided by all tests: (a + d)/(a + b +c + d).

Results

The demographic features of CD patients and healthy controls are shown in **Table 1**. The distributions of age, gender, smoking habit and body mass index were not statistically significant between groups.

The mean NLR values of CD patients and controls were 5.72±6.66 and 1.84±0.85, respectively ($P < 0.001$). Mean NLR values of active CD patients and inactive CD patients were significantly higher than those of control CD patients (6.00±7.38 and 5.53±6.18 vs. 1.84±0.85) ($P < 0.001$) (**Figure 2**).

Table 2 demonstrates that there is a significant decline in NLR of CD patients compared with healthy controls (5.72±6.66 vs. 1.84±0.85, $P < 0.001$). Meanwhile, CRP (36.05±45.2 mg/dl vs. 8.48±6.44 mg/dl, $P < 0.001$), ESR (27.41±19.24 mm/h vs. 11.79±5.81 mm/h, $P < 0.001$) and WBC (11.57±7.81 × 10^9/l vs. 7.35±3.57 × 10^9/l, $P < 0.001$) were statistically higher in the

Table 1. Demographics of patients and controls

	Crohn's disease (n = 110)	Control group (n = 55)	*P*
Age (years)	33.5±14.1	47.3±9.43	NS
Male (%)	58.2	64.5	NS
Smoking	35 (31.8%)	15 (27.3%)	NS
Boby mass index (kg/m^2)	19.7±2.73	19.1±2.13	NS
Active disease	44 (66.7%)	-	-
Disease location (%)			
A1 (ileal)	42 (38.2%)	-	-
A2 (colonic)	45 (40.9%)	-	-
A3 (ileocolonic)	23 (20.9%)	-	-
+A4 (upper gastrointestinal tract)	0 (0%)	-	-
Disease behavior (%)			
B1 (inflammatory)	68 (61.8%)	-	-
B2 (penetrating)	15 (13.6%)	-	-
B3 (stricturing)	27 (24.5%)	-	-
Treatment			
	51 (46.4%)	-	-
	16 (14.5%)	-	-
	43 (39.1%)	-	-
Intestinal manifestations	25 (22.7%)	-	-

Data are presented as median (range) or mean ± SD. NS: non-significant.

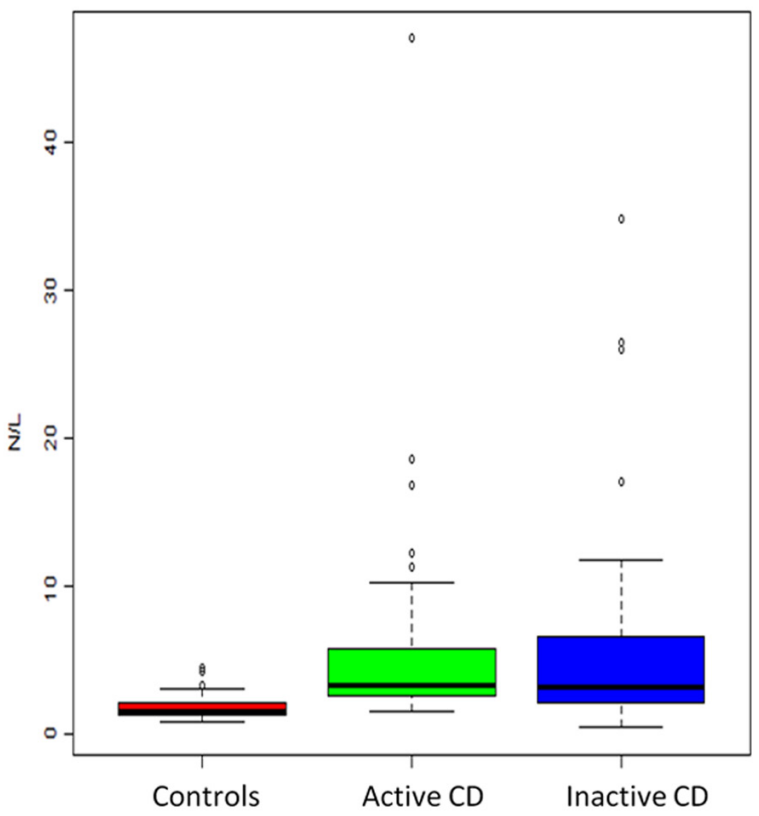

Figure 2. Box-plot representation of neutrophil to lymphocyte ratio (NLR) in patients with CD (active and inactive) and healthy controls.

CD group than those in the control group. Mean NLR values of active CD patients were significantly higher than those of control group (6.00±7.38 vs. 1.84±0.85) (P < 0.001) (**Figure 1**). **Table 3** shows mean NLR values and the other inflammatory markers of study participants at the onset of the study. No significant differences were observed with respect to NLR, WBC and ESR levels between study participants.

Although Spearman correlation analysis indicated a significant correlation of NLR with WBC (r = 0.493, P < 0.001) and CRP (*r* = 0.327, P < 0.001), no correlation was found with ESR (*r* = 0.137, P = 0.082).

ROC curve analysis suggested that the optimum NLR cut-off point for active UC was 2.13, with a sensitivity and specificity of 82.7%, 76.9% respectively (AUC: 0.85) (**Figure 3**). The overall accuracy of NLR in determination of active UC was 80.9%. The same analysis for other inflammation markers is summarized in **Table 4**.

Discussion

Crohn's disease (CD) is a chronic inflammatory bowel disease with a complex etiology involving genetic factors, priming by enteric microflora, environmental factors and an alteration in the immune-mediated response [13]. Previous studies have demonstrated that appropriate and effective therapy could significantly control symptoms, maintain remission, prevent relapse, improve quality of life

Table 2. Comparison of NLR and other inflammatory markers between Crohn's disease and control groups

	Crohn's disease (n = 110)	Control group (n = 55)	*P* value
NLR	5.72±6.66	1.84±0.85	< 0.001
CRP (mg/dl)	36.05±45.2	8.48±6.44	< 0.001
ESR (mm/h)	27.41±19.24	11.79±5.81	< 0.001
WBC (× 10^9/l)	11.57±7.81	7.35±3.57	< 0.001

NLR, neutrophil-lymphocyte ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.

Table 3. Comparison of NLR and other inflammation markers between active and inactive CD patients

	Active CD (*n* = 44)	Inactive CD (*n* = 66)	*P*
NLR	6.00±7.38	5.53±6.18	NS
CRP (mg/dl)	48.53±52.10	27.74±38.23	< 0.001
ESR (mm/h)	37.09±19.14	20.95±16.50	NS
WBC (× 10^9/l)	10.84±6.79	8.01±3.61	NS

CD: Crohn's disease; WBC: white blood cells; NLR: neutrophil-lymphocyte ratio; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NS: non-significant.

and reduce mortality [14]. The early determination of diagnosis and detection of disease activity are therefore essential for tailoring therapy [15].

As invasive techniques, including endoscopic, radiological and histopathologic methods, are routinely used for diagnostic decision and disease activity supervision, an ideal non-invasive test is increasingly expected for initial diagnosis and identification of disease activity [16].

In CD, the intestinal inflammation is confined to the colon mucosa. In active disease, this results in specific symptomatology with frequent diarrhea and blood loss. The Truelove and Witts score was the first index used to quantify disease activity in UC. Disadvantages of this index are that the difficulty of classifying some patients in the appropriate disease category, and changes in disease activity over time are difficult to quantify [17]. Other activity indices have been proposed by various authors. Endoscopic assessment of disease activity is important because the complaints of the patients do not always correspond to the severity and extent of the disease. Rachmilewitz developed an endoscopic index, scoring for granularity, vascular pattern, vulnerability, and mucosal damage [18]. The Rachmilewitz score is numerical and has been used in clinical trials. To combine the advantages of the clinical Truelove and Witts index and the endoscopic Rachmilewitz score, the DAI score from the Mayo clinic was elaborated [19]. Currently, the Mayo score is the most used in clinical studies.

To monitor accurately intestinal inflammation, symptoms and clinical examination, combined with endoscopy and histology, are required. Because of the invasiveness of endoscopy, several laboratory markers have been evaluated.

Although there is no ideal single serum marker for predicting disease severity, white blood cell count, CRP and ESR are the most commonly used inflammatory indices in routine clinical practice for determining CD activity. These parameters can change according to the degree of the inflammatory state, but they do not adequately reflect disease activity because of their low sensitivity and specificity for intestinal inflammation [20].

C-reactive protein (CRP) is a marker of inflammation, and serum CRP concentration reflects disease activity in patients with CD [21]. CRP is a pentameric protein produced almost exclusively by hepatocytes in response to stimulation by Interleukin 6, Interleukin 1α, and tumor necrosis factor β [22]. CRP is the most important acute-phase protein. The baseline concentration of CRP is 1 mg/l and levels are partially genetically regulated. Levels of CRP increase dramatically in the presence of an acute-phase inflammation or infection. CRP concentrations also quickly decrease when the inflammation process is treated [23].

Recently, a series of stool tests, such as fecal lactoferrin, calprotectin and elastase, were investigated as novel inflammatory markers. Even though they may be superior to CRP or ESR with higher sensitivity and specificity in detecting gastrointestinal inflammation, they are not specific markers for IBD; and they are inconvenient and unpleasant for stool sampling [15, 24, 25]. NLR is a simple and inexpensive

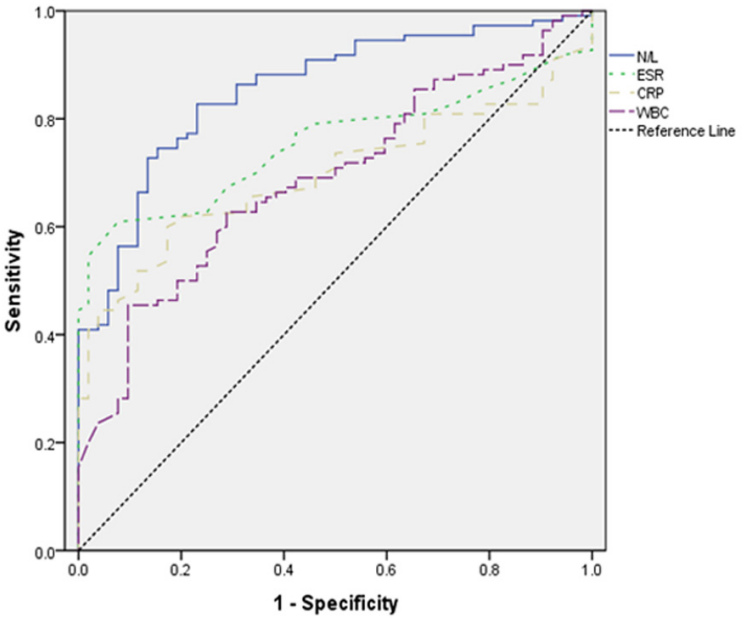

Figure 3. Receiver operating characteristic (ROC) curve of neutrophil to lymphocyte ratio (NLR) vs. other inflammation markers in predicting active disease for CD.

Table 4. Accuracy and ROC analyses of NLR and other inflammatory markers in differentiate patients and controls

	AUC	Sensitivity (%)	Specificity (%)	Overall Accuracy (%)
NLR (cutoff: 2.13)	0.8545	82.7	76.9	80.9
ESR (cutoff: 19.5)	0.7540	60.9	92.3	71
CRP (cutoff: 10.5)	0.6961	60	82.6	67.3
WBC (cutoff: 9.2)	0.6892	45.4	90.3	60

AUC, area under the curve; NLR, neutrophil-lymphocyte ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ROC, receiver operating characteristic; WBC, white blood cells.

index of systemic inflammatory burden that correlates with prognosis in distinct disease states. It has been generally investigated in inflammatory and neoplastic diseases, such as acute pancreatitis, ulcerative colitis, colorectal cancer, hepatocellular, ovarian, nasopharyngeal, and metastatic renal cell carcinoma, recurrent optic neuritis, critical limb ischemia, esophageal squamous cell carcinoma, as a prognostic index [3-10, 26-32]. The NLR is correlated with disease severity in patients with nonalcoholic fatty liver disease [33]. Elevated levels of NLR were also found to be associated with poor survival in patients after percutaneous coronary intervention and in those undergoing coronary artery bypass graft [34, 35].

Neutrophils, one of the most abundant and important mediators of innate immunity, are professional phagocytes which mount the acute inflammatory response and act as the first line of defense against invading pathogens [36]. The role of neutrophils in CD pathology remains obscure. Impaired neutrophils function may result in limited bacterial clearance and fuel an ongoing, chronic inflammatory response. Neutrophils accumulation within epithelial crypts and in the intestinal lumen directly correlates with clinical disease activity and epithelial injury. On the other hand, previous studies in patients with inflammatory bowel disease have strongly revealed that their lymphocyte function is abnormal at both the peripheral and mucosal level [37].

In conclusion, our study demonstrated increase of MPV in CD patients compared with healthy controls. We also compared NLR with other inflammatory markers including CRP, ESR and WBC. NLR had the best accuracy in determination of CD patients and healthy controls. NLR did not show a discriminative value in disease activity. Finally, we suggested that it should be cautious to use MPV as a marker in determination of CD activity. Large multicenter studies are expected to resolve the controversy.

Disclosure of conflict of interest

None.

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