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Does neutrophil-to-lymphocyte ratio predict active ulcerative colitis?

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Summary
Background Inflammatory markers have been studied in ulcerative colitis (UC) for diagnosis, disease activity, and prediction of relapse. Blood neutrophil-to-lymphocyte (N/L) ratio has been used to determine outcomes of some malignancies and coronary artery disease. Blood N/L ratio is a simple sign of clinical inflammation. In this study, we examined N/L ratio in recurrent patients suffering from UC.

Methods The aim of the present study was to analyze N/L ratios in serum samples of UC patients in remission and active phases. Patients' age, extend of the disease, disease duration, disease activity, drug, and other medical history were all noted for patients. C-reactive protein, erythrocyte sedimentation rate, and complete blood count were determined for patients.

Results Forty-nine UC patients were admitted into the present study. The blood N/L ratios were significantly increased in active phase compared with inactive UC patients ($p<0.05$). The cut-off value for N/L ratio for the detection of active UC patients was calculated as ≥2.3 using receiver operating characteristic analysis [sensitivity: 61.2 %, specificity: 66.7 %, AUC: 0.650 (0.540–0.760), $p=0.01$].

Conclusions Present study shows that in patients with UC, the blood N/L ratio is associated with active disease. N/L ratio may be used as an activity parameter in UC.

Keywords Neutrophil-to-lymphocyte ratio · Severity · Recurrence · Ulcerative colitis

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Sagt der Neutrophilen/Lymphozyten Quotient die Aktivität einer Colitis ulcerosa voraus?

Zusammenfassung
Grundlagen Entzündungsmarker sind hinsichtlich ihrer Brauchbarkeit für die Diagnose, die Krankheitsaktivität und die Vorhersage eines Rezidivs der Colitis ulcerosa (CU) untersucht worden. Der Neutrophilen/Lymphozyten (N/L) Quotient im Blut ist ein einfaches Zeichen einer klinischen Entzündung. Er ist zur Abschätzung der Prognose mancher maligner Erkrankungen und der koronaren Herzkrankheit zum Einsatz gekommen. In der vorliegenden Studie haben wir die N/L Quotienten bei Patienten mit CU in der Aktiven Phase und in Remission untersucht.

Methodik Es wurden 49 Patienten mit CU in die Studie aufgenommen. Das Alter der Patienten, das Ausmaß, die Dauer und die Aktivität der Erkrankung, sowie die Anamnese inklusive der Medikamentenanamnese wurden bei allen Patienten erhoben. Das C reaktive Protein, die Blutsendkung und das komplette Blutbild wurden bestimmt.

Ergebnisse Die N/L Quotienten im Blut waren bei den Patienten in der aktiven Phase im Vergleich zu den Patienten mit einer CU in Remission erhöht ($p<0{,}05$). Der Grenzwert für die Erkennung einer aktiven Phase der CU wurde mit >2,3 errechnet. Die ROC Analyse ergab

eine Sensitivität von 61,2 %, eine Spezifizität von: 66,7 %, sowie eine AUC: 0,650 (0,540–0,760), $p = 0{,}01$.

Schlussfolgerungen Die vorliegende Studie zeigt, dass der N/L Quotient bei Patienten mit einer CU mit der Aktivität der Erkrankung im Zusammenhang steht. Der N/L Quotient kann bei der CU als Aktivitätsparameter eingesetzt werden.

Schlüsselwörter Neutrophile/Lymphozyten Quotient · Schweregrad · Rezidiv · Colitis ulcerosa

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that causes continuous mucosal inflammation of the colon characterized by remission and relapse periods [1]. Classification of UC based on disease activity and severity is important in clinical practice because it dictates the patient's management. Early determining of disease activity reduces surgery rate and mortality in serious UC patients [2].

In clinical practice, combination of clinical features, laboratory studies, imaging tests, and endoscopic parameters, including histopathology is used for determining activity of disease. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), fecal calprotectin in common use in reflecting disease activity in UC [3, 4]. Because these parameters are not specific for UC disease activity, adjunctive use of additional serum markers is needed for monitoring disease activity.

Blood neutrophil-to-lymphocyte (N/L) ratio is a marker of subclinical inflammation that has been used to determine outcomes of some malignancies and coronary artery disease [5–9]. In addition it has been shown that N/L ratio is superior to WBC in the prediction of adverse outcomes in a variety of inflammatory and surgical conditions [8, 10–12]. By using N/L ratio, it is possible to have an idea about two different immune pathways; the first one is neutrophil which is accountable for continuing inflammation and the second one is lymphocytes that shows regulatory pathways [13, 14].

In this study we aimed to investigate that N/L ratio is a possible indicator of disease activity.

Materials and methods

Patients

A total of 49 patients with UC were enrolled in our study. Of those were 27 men and 22 women. The study was approved by the local Ethical Committee. The demographic particulars of patients are summarized in Table 1. The median disease duration in UC patients was 3 years.

The diagnosis of UC was based on standard clinical, radiological, endoscopic, and histological criteria. Patients' age, disease duration, location, activity, drug, and other medical history were recorded for all subjects.

Table 1 Clinical characteristics of patients with ulcerative colitis

N	49
Age	43.0 ± 14.6 (21.6–77.0)
Sex (M/F)	27 (55.1)/22 (44.9)
Distribution	
E1-proctitis	24 (49.0)
E2-left-sided	9 (18.4)
E3-extensive	16 (32.7)
Disease activity (Truelove and Witts)	
Mild	43 (87.8)
Moderate	4 (8.2)
Severe	2 (4.1)
Disease duration (years)	3.0 (1.2–7.0)
Time to relapse	34.8 (6.8–73.0)
Operation	2
Mesalazine	49
Infliximab	2
Adalimumab	4
Azathioprine	12
Corticosteroid	
None	25
1	12
≥2	12

Complete blood count, CRP, and ESR were determined for patients. The WBC, neutrophil, and lymphocyte counts were noted, and the N/L ratios were calculated from these parameters. Those were established anew after disease remission was achieved in active UC patients.

All patients underwent total colonoscopic examination at study entry. The endoscopic disease activities of UC patients were classified according to Schroder et al. [15]. Based on first colonoscopic examination, patients were divided into three groups with mild, moderate, and severe disease.

Clinical disease activity was determined using a modified Truelove–Witts severity index (MTWSI). Clinical active disease was defined as an estimated MTWSI score of 4 or higher and patients with a lower score than 4 were considered in to be remission (inactive). The extent of the disease was classified according to the Montreal classification.

Statistical analysis

A statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). All normally distributed data were analyzed using paired sample *t*-test. A comparison of the nonnormally numerical variables was performed using the Wilcoxon test. A p value < 0.05 was considered statistically significant. The sensitivity and specificity of N/L ratio for a diag-

Table 2 Laboratory value of ulcerative colitis patients with active and inactive phase

	Inactive	Active	*p*
White blood cells	7.2 ± 2.0	8.6 ± 3.0	0.004
Lymphocytes	2.08 ± 0.68	1.97 ± 0.62	0.26
Neutrophils	4.1 (3.4–5.3)	5.0 (4.0-6.3)	0.008
Neutrophil/lymphocyte ratio	2.04 (1.59–2.87)	2.63 (1.93–3.46)	0.012
Erythrocyte sedimentation rate	9 (6–20)	27 (11–61)	0.07
C-reactive protein	4.2 (2.1–9.9)	19.7 (4.3–34.8)	<0.001
Hemoglobin	13.3 ± 1.8	12.6 ± 1.6	0.014
Platelets	278.3 ± 64.1	330,8 ± 107.8	<0.001

nosis of active phase of UC patients were calculated by the receiver operating characteristic curves.

Results

The mean N/L ratios of the inactive and active UC patients were 2.04 and 2.63, respectively ($p < 0.05$). The blood N/L ratios of active patients were significantly higher than those of inactive UC. The cut-off value for N/L ratio for the discrimination of active phase in UC patients was calculated as ≥ 2.3 using receiver operating characteristic analysis [sensitivity: 61.2 %, specificity: 66.7 %, AUC: 0.650 (0.540–0.760), $p = 0.01$]. The serum neutrophil count increases in active patients, but it was in normal range. Table 2 shows the serum N/L ratio and other laboratory values in both the active and remission phase of UC patients. In all, 16 patients were classified as having extensive disease, 9 patients as left-sided and 24 patients as proctitis according to the endoscopic examination on study entry. The disease activity was mild in 43, moderate in 4, and severe in 2 patients at the initial endoscopic examination. All of the patients with UC had been taking oral mesalamine. Twenty-five patients did not use corticosteroids. Only two patients underwent elective colectomy. WBC count, platelet, and CRP levels of the active UC patients were significantly higher than those of inactive patients ($p < 0.05$). ESR was increased in active phase of UC patients, but this was not statistically significant.

Discussion

UC is a chronic inflammatory disease of the colon characterized by relapses and remission periods [1]. According to activity of disease it is generally grouped in to mild, moderate, severe, and remission [16, 17]. Classification and assessment of disease activity is important for detecting the treatment modality. Although in clinical practice, the Truelove and Witts classification that is composed of ESR, heart rate, hemoglobin level, fever, and stool frequency is one of the most widely used disease activity index, categorization of disease can be difficult in some patients [18–20]. For this reason, combination of clinical features, laboratory studies, imaging tests, and endoscopic parameters, including histopathology is more useful in determining the activity of disease.

CRP, ESR, WBC, fecal calprotectin, mean platelet volume are the laboratory parameters that are commonly used for detecting the disease activity in UC [3, 4, 21]. Karoui et al. [20] showed that there was a significant association between disease activity index and CRP, and they reported that cut-off CRP level is 10 mg/l to separate active from inactive disease. And also, Solem et al. [22] reported that CRP elevation in UC patients was associated with clinical disease activity and endoscopic inflammation. Yüksel et al. [21] reported that overall accuracy of WBC count and ESR in determining disease activity was 57 (sensitivity 58 %) and 65 % (sensitivity 70 %), respectively. Moreover, Beyazit et al. [23] reported that overall accuracy of WBC count and ESR in determining disease activity was 74.4 and 67.4 %, respectively. Onal et al. reported that fecal calprotectin was a useful marker in diagnosis of active disease and evolution of clinical and endoscopic activity in UC. Oztürk et al. [24] showed that in patients with active UC and Crohn's disease, there was a significant decrease in mean platelet volume. Although all these laboratory parameters are in common use for detecting disease activity in UC, because of their low sensitivity and specificity for intestinal inflammation, these parameters are inadequate for determining the activity of disease [25].

Blood N/L ratio is a simple and inexpensive marker of systemic inflammation that has been used to determine outcomes of some malignancies such as colorectal cancer, gastric cancer, ovarian cancer, cholangiocarcinoma, hepatocellular carcinoma, and coronary artery disease [5–9]. Neutrophil is the one of the most important leukocyte on the cause of inflammation and tissue injury in UC disease [26]. Neutrophil accumulation and abscess formation within intestinal crypts at the apical epithelial surface is seen in the pathological aspect of UC [27]. Conversely, the lymphocyte function was not normal in both the peripheral blood and mucosal level in inflammatory bowel disease patients [28]. The peripheral lymphocytes of patients with from both Crohn's disease and UC had shown a reduction in responsiveness to the nonspesific mitogen phytohemagglutinin [29]. Studies on the basis of these results, Torun et al. found that N/L ratio levels are significantly elevated in active UC patients and correlated with and laboratory indices [30]. And also Çelikbilek et al. demonstrated that in patients with UC, the N/L ratio is strongly associated with active disease [31].

Conflict of interest

The authors report no conflicts of interest. This is not an industry supported study.

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