The relationship between the neutrophil–lymphocyte ratio and disease activity in patients with ulcerative colitis

Ayse Kevser Demir, Ahmet Demirtas, Suheyla Uzun Kaya, Ibrahim Tastan, Ilknur Butun, Mustafa Sagcan, Safak Sahin, Turker Tasliyurt, Abdulkerim Yilmaz

Department of Internal Medicine, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey
Department of Biochemistry, Gaziosmanpasa University Faculty of Medicine, Tokat, Turkey
Department of Gastroenterology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey

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Abstract Preliminary evidence suggests that a higher neutrophil–lymphocyte ratio (NLR) may be an indicator of active ulcerative colitis (UC). However, it is not clear whether the NLR is a useful and simple indicator of clinical activity in UC after adjusting for the other inflammatory markers. We designed a retrospective study to evaluate the role of the NLR in estimating disease severity in UC patients. The study consisted of 71 patients with UC and 140 age- and sex-matched healthy individuals (control group). The NLR, erythrocyte sedimentation rate, C-reactive protein, and white blood cell count were measured. The NLR values of the active UC group were elevated compared with those of the patients with inactive UC and the controls (2.59 ± 1.47, 2.03 ± 1.07, and 1.98 ± 0.85, respectively; p = 0.005). The receiver operating characteristic revealed that the optimum NLR cut-off point for active UC was 2.39. A multivariable logistic analysis showed that of the parameters studied, C-reactive protein was the only parameter able to significantly discriminate active from inactive UC (B: 0.222; p = 0.017; odds ratio: 1.248; 95% confidence interval: 1.041–1.497).

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* Corresponding author. Kaleardi Mahallesi, Muhittin Fisunoğlu Caddesi, Ali Şevki eker Yerleşkesi Merkez, Tokat 60600, Türkiye.
E-mail address: dsafaksahin@gmail.com (S. Sahin).
Introduction

Ulcerative colitis (UC), a type of inflammatory bowel disease, is a chronic, idiopathic, relapsing inflammatory condition of the gastrointestinal tract. Histopathological examinations play a major role in the diagnosis and management of UC, but they are invasive and costly. In addition to histological examinations, clinical, laboratory, endoscopic, and radiological tests may be needed to confirm a diagnosis of UC [1].

Systemic inflammatory conditions, such as UC, cause changes in the levels of circulating white blood cells (WBCs). It is well known that systemic inflammation induces an increase in circulating neutrophils that is accompanied by a relative decrease in the percentages of lymphocyte [2]. A growing body of evidence suggests that the neutrophil–lymphocyte ratio (NLR) is a useful biomarker of systemic inflammation responses [3–6]. Evidence also suggests that it is a predictor of mortality in patients with cancer, including colorectal [7,8], biliary tract [9], bladder [10,11], and breast cancer [12]. The NLR is a cost-effective, common, and simple biomarker. According to recent studies, the NLR may be a new promising marker of the disease severity in UC [13–16]. However, the data on NLR and its association with other inflammatory serum markers are not convincing. Therefore, in the present study, we aimed to determine the relationship between the NLR and disease activity after adjusting for other inflammatory serum markers, including C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), and WBCs, in patients with UC.

Methods

This was a retrospective chart review study. The medical records of 71 patients with UC who were admitted to the Gaziosmanpaşa University Hospital, Tokat, Turkey between December 2010 and January 2013 were included. One hundred and forty healthy patients without any illness who were admitted for routine checkups were selected as a control group. The diagnosis of UC was based on standard clinical, radiological, laboratory, endoscopic, and histological findings. The patients’ age, sex, disease duration, medical history, diabetes mellitus, smoking status, and laboratory findings, including the neutrophil and lymphocyte count, WBCs, CRP, and ESR, were recorded. The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. All these measured parameters were obtained from patients with active disease and from those in remission.

Patients who had used corticosteroids within the previous week or who had hematological or neoplastic disorders, chronic renal failure, chronic liver or heart diseases, coronary artery disease, connective tissue diseases, or clinical evidence of active infection were not included in the study. After obtaining Institutional Review Board approval of the Gaziosmanpaşa University Hospital, Tokat, Turkey (#15-KA10–16), the study was carried out in accordance with international Ethical Guidelines and the Declaration of Helsinki.

The clinical disease activity of UC was evaluated using the modified Truelove and Witts severity index [17], which is a composite score incorporating eight variables: stool frequency, nocturnal diarrhea, visible blood in a stool, fecal incontinence, abdominal pain, general well-being, abdominal tenderness, and drugs used to control diarrhea. Clinical remission was determined as a score ≤ 3 [18].

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 statistical package (SPSS, Inc., Chicago, IL, USA). The data were expressed as means ± standard deviation. The Mann–Whitney U test was used to assess differences in the demographic parameters, and the Kruskal–Wallis test was used to compare the laboratory parameters between the groups. Spearman’s correlation was used to analyze the correlation between the parameters. All the p values were two tailed, and p < 0.05 was considered statistically significant. The sensitivity, specificity, and cut-off points were assessed using a receiver operating characteristic curve analysis [19]. A multivariate logistic regression model was used to determine the association of the NLR, CRP, ESR, and WBC count with active UC.

Results

Seventy-one patients with UC and 140 control individuals were enrolled in this study. There were 47 men and 24 women in the UC group and 84 men and 56 women in the control group (p = 0.453). The demographic information on the patients and control individuals is summarized in Table 1.

The NLR was increased in the active UC patients compared with the controls and inactive UC patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 140)</th>
<th>Ulcerative colitis (n = 71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men/women)</td>
<td>84/56</td>
<td>47/24</td>
<td>0.453</td>
</tr>
<tr>
<td>Age (y)</td>
<td>44.7 ± 12.3</td>
<td>46.0 ± 14.7</td>
<td>0.496</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (21)</td>
<td>13 (18)</td>
<td>0.719</td>
</tr>
<tr>
<td>Smoking</td>
<td>36 (26)</td>
<td>26 (37)</td>
<td>0.111</td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>57.0 ± 24.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation.

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Table 1: Demographic characteristics of patients with ulcerative colitis and control participants.
Neutrophil-lymphocyte ratio and ulcerative colitis

Figure 1. Box-plot representation of neutrophil–lymphocyte ratio in patients with ulcerative colitis and controls. N/L ratio = neutrophil–lymphocyte ratio.

(Table 1). The NLRs of the control, inactive, and active UC patients were 1.98 ± 0.85, 2.03 ± 1.07, and 2.59 ± 1.47, respectively, (p = 0.005). The other inflammatory markers (WBCs, CRP, and ESR) were significantly elevated in patients with active UC compared to those with inactive UC and the controls (Table 2). A multivariate logistic regression analysis was used to explore the associations of the NLR, WBC count, CRP, and ESR with active UC. After adjusting for these inflammatory markers (WBCs, CRP, and ESR), the odds ratio of the NLR was 1.283 (95% confidence interval, 0.853–1.931). In the multivariable analysis, CRP was the only parameter capable of discriminating active from inactive UC (Table 3).

Spearman’s correlation analysis indicated that there were significant correlations of NLR with WBC (r = 0.282, p = 0.001) and ESR (r = 0.170, p = 0.043) in sum of all UC patients. There was a correlation between the NLR and WBC in patients with active UC (r = 0.360, p = 0.002); however, no correlation was found between the NLR and CRP, ESR, and WBC count in patients with remission. Details on the correlation between the NLR and the other inflammatory parameters in the patients with active disease and inactive disease and the sum of all UC patients are presented in Table 4.

The receiver operating characteristic curve analysis revealed that the cut-off point of the NLR for active UC was 2.39. The overall accuracy of the NLR in the diagnosis of active UC was 60.9%. The cut-off values of the other UC activity markers and their sensitivity, specificity, and overall accuracy are presented in Table 5.

Discussion

This study aimed to determine whether the NLR, a novel inflammatory marker, was an independent, noninvasive marker of disease activity in UC. Our results demonstrated that the NLR was higher in patients with active UC compared with controls and inactive UC patients and that a cut-off value of 2.39 indicated the presence of active disease, with a sensitivity of 48.6% and a specificity of 77.5%. However, after adjusting for the other inflammatory markers (WBCs, ESR, and CRP), the NLR was not an independent marker of the disease severity in UC. Moreover, there was no significant correlation between the NLR and the other inflammatory markers, except the WBC count, with active UC.

UC is a chronic inflammatory disease, which causes continuous inflammation of the colonic mucosa and affects the rectum and colon to a variable extent [20]. The clinical course is marked by exacerbation and remission, which

Table 3 Results of multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>0.002</td>
<td>0.981</td>
<td>1.002</td>
<td>0.860–1.168</td>
</tr>
<tr>
<td>CRP</td>
<td>0.222</td>
<td>0.017</td>
<td>1.248</td>
<td>1.041–1.497</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>-0.007</td>
<td>0.774</td>
<td>0.993</td>
<td>0.944–1.044</td>
</tr>
<tr>
<td>N/L ratio</td>
<td>0.250</td>
<td>0.231</td>
<td>1.283</td>
<td>0.853–1.931</td>
</tr>
</tbody>
</table>

CI = confidence interval; CRP = C-reactive protein; N/L ratio = neutrophil–lymphocyte ratio; WBC = white blood cells.

Table 4 Spearman correlation coefficients between neutrophil–lymphocyte ratio and other inflammatory markers in patients with ulcerative colitis.

<table>
<thead>
<tr>
<th>Patients</th>
<th>CRP rs</th>
<th>p</th>
<th>ESR rs</th>
<th>p</th>
<th>WBC rs</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active UC</td>
<td>0.141</td>
<td>0.246</td>
<td>0.121</td>
<td>0.319</td>
<td>0.360</td>
<td>0.002</td>
</tr>
<tr>
<td>Inactive UC</td>
<td>0.020</td>
<td>0.911</td>
<td>0.088</td>
<td>0.468</td>
<td>0.097</td>
<td>0.420</td>
</tr>
<tr>
<td>Active and Inactive UC</td>
<td>0.185</td>
<td>0.059</td>
<td>0.170</td>
<td>0.043</td>
<td>0.282</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; N/L = neutrophil–lymphocyte ratio; UC = ulcerative colitis; WBC = white blood cells.

Table 2 Comparison of neutrophil–lymphocyte ratio and other inflammation markers between active and inactive ulcerative colitis patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 140)</th>
<th>Inactive UC (n = 71)</th>
<th>Active UC (n = 71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (mm$^3$)</td>
<td>7638.5 ± 1785.3</td>
<td>7314.6 ± 2299.6</td>
<td>8903.7 ± 3757.6</td>
<td>0.021</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.85 ± 1.56</td>
<td>4.34 ± 1.82</td>
<td>17.21 ± 15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedimentation (mm/h)</td>
<td>10.14 ± 8.62</td>
<td>11.72 ± 10.43</td>
<td>20.94 ± 20.8</td>
<td>0.002</td>
</tr>
<tr>
<td>N/L ratio</td>
<td>1.98 ± 0.85</td>
<td>2.03 ± 1.07</td>
<td>2.59 ± 1.47</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. Different subscripts in a row indicate statistically significant difference.

CRP = C-reactive protein; N/L = neutrophil–lymphocyte ratio; UC = ulcerative colitis; WBC = white blood cells.
may occur spontaneously or in response to treatment changes or other illnesses [21,22]. In clinical practice, clinical symptoms, the endoscopic appearance, histopathology, biomarkers, and quality of life are used to assess the disease activity in UC [23]. Endoscopic techniques to identify the histological persistence of inflammation and predict relapses are valuable, simple, and practical tools that can potentially improve the management of patients with UC [24]. However, endoscopy is not able to predict relapses in patients with inactive UC. Compared with endoscopy, some noninvasive biomarkers may be more useful in predicting relapses in UC patients in remission [25,26].

The WBC count, CRP, and ESR are the most commonly used inflammatory indices in routine clinical practice for determining active UC [27]. However, they do not adequately reflect disease activity due to their low sensitivity and specificity for intestinal inflammation [28,29]. Therefore, none of these simple serum markers alone is sufficient as an activity indicator for UC. Previous studies demonstrated that CRP and ESRs are more meaningful parameters than WBC counts for determining the disease activity [14,27,29]. Osada et al [27] reported that CRP, ESRs, and WBC counts were correlated with the sum of endoscopic and histological scores. They also found that CRP and the ESR were well correlated with the activity of proximal colonic lesions but not with that of distal lesions. The use of CRP and other laboratory markers should be viewed as an addition to clinical observations and a physical examination rather than a replacement [29]. The combined use of these markers with a colonoscopy will enhance their importance in determining UC activity.

Recent studies demonstrated that the NLR was higher in patients with active UC [13,14]. The retrospective study [13], which included UC patients with active disease or patients in remission, found that an optimum cut-off value of 2.16 indicated the presence of active disease, with a sensitivity of 81.8% and a specificity of 80.5%. The other study [14], which included 40 patients with UC with active disease or in remission, reported that the cut-off point for active UC was 2.47, with a sensitivity of 53.9% and a specificity of 63.2%. In these two studies, the sensitivity and specificity values were different. Interestingly, the sensitivity and specificity values in one of the studies [14] were low, despite the high optimal cut-off value. The present study consisted of 71 UC patients with active and inactive disease and 140 control patients. We found that the optimum cut-off value for active UC was 2.39, with a sensitivity of 48.6% and a specificity of 77.5%. The optimum NLR cut-off point for active UC was in the range of 2.16–3.1 in different studies [13–16]. Our results were close to those reported by Celikbilek et al [14]. In the present study, we also evaluated the statistically significant parameters in a multivariable analysis. The results of that analysis showed that CRP was the only statistically significant parameter capable of discriminating active UC from inactive disease in those in remission. Therefore, the NLR, with its low sensitivity and specificity rates, was not as effective as CRP for determining active UC. Spearman’s correlation analysis demonstrated that there was no significant correlation between the NLR and the other laboratory markers, except the WBC count, in active UC.

Table 5: Results of diagnosing measures of white blood cells, C-reactive protein, erythrocyte sedimentation rate, and neutrophil–lymphocyte ratio variables for the determined values in the detection of active ulcerative colitis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut-off values</th>
<th>AUC</th>
<th>SEN</th>
<th>SPE</th>
<th>PPR</th>
<th>NPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (mm³)</td>
<td>6490.00</td>
<td>0.63</td>
<td>(0.54–0.71)</td>
<td>72.2</td>
<td>(61.4–83.1)</td>
<td>0.0076</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.70</td>
<td>0.70</td>
<td>(0.61–0.79)</td>
<td>63.4</td>
<td>(51.1–74.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>20.0</td>
<td>0.64</td>
<td>(0.55–0.72)</td>
<td>49.3</td>
<td>(37.2–61.4)</td>
<td>0.0037</td>
</tr>
<tr>
<td>NLR</td>
<td>2.39</td>
<td>0.64</td>
<td>(0.55–0.72)</td>
<td>49.3</td>
<td>(37.2–61.4)</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

AUC = area under the curve; CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NLR = neutrophil–lymphocyte ratio; PPR = paired-pulse ratio; SEN = sensitivity; SPE = specificity; WBC = white blood cells.
This study has several limitations. Firstly, it was conducted among inpatients at our hospital in northern Turkey. Therefore, the results may not be representative of the general characteristics of patients with UC in Turkey, and the findings cannot be generalized countrywide. Secondly, the study consisted of a relatively small sample size, and it had a cross-sectional design. Prospective studies, including a larger sample size, are needed to provide more useful information on this subject. Thirdly, our study was not designed to explain the observed increases in the NLR in patients with active UC. Finally, other factors, such as corticosteroid dosages and use of immunosuppressive agents, which may affect the level of inflammatory laboratory markers which were not evaluated in the present study.

Our study demonstrated that the NLR was elevated in patients with active UC. However, after adjusting for other statistically significant laboratory markers, including CRP, ESRs, and WBC counts, the NLR was not a useful predictor of active disease. Moreover, the NLR showed no correlation with other laboratory markers, including CRP and the ESR, in patients with active UC. Therefore, although the NLR is an inexpensive and accessible inflammatory laboratory marker, it is not an independent risk factor for indicating the disease activity in UC.

References

