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Original Research Paper

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NEUTROPHIL-TO-LYMPHOCYTE RATIO IN INFLAMMATORY BOWEL DISEASE – A MARKER OF DISEASE ACTIVITY

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ABSTRACT

Introduction: The neutrophil-to-lymphocyte ratio (NLR) is a marker of subclinical inflammation already used to determine outcomes in coronary artery disease and some malignancies. However, it is not clear whether the NLR is a useful and simple indicator of clinical activity in inflammatory bowel disease.

Aim: The purpose of this study is to investigate the utility of neutrophil-to-lymphocyte ratio (NLR) as a simple and readily available predictor for clinical disease activity in inflammatory bowel disease (IBD).

Methodology: 104 (36 with Crohn's Disease and 68 with Ulcerative colitis) and 48 healthy controls were included in the study. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels and complete blood count (CBC) were measured. The neutrophil and lymphocyte counts were recorded and NLR was calculated. The patients with active or inactive Ulcerative Colitis (UC) and Crohn's Disease (CD) were classified according to the severity of the disease.

Results: The mean NLR values of active CD patients were significantly higher than those of inactive CD patients (5.68±1.62 vs 1.56±0.62, p 0.000). Mean NLR values of active UC patients were significantly higher than those of inactive UC patients (4.38±1.12 vs 1.4±0.12 0.45, p = 0.000). The optimum NLR cut-off point for active CD was 2.9 with a sensitivity, specificity, PPV and NPV of 83%, 68%, 90%, and 78%, respectively (AUC – 0.780). NLR cut-off point for active UC was 2.72 with a sensitivity, specificity, PPV and NPV of 79%, 67%, 86%, and 62%, respectively (AUC – 0.730).

Conclusion: The NLR might be effective, readily available, and low-cost markers for assessing activity in inflammatory bowel disease patients.

KEYWORDS : Neutrophil-to-lymphocyte ratio, NLR, C-reactive protein, CRP, Erythrocyte sedimentation rate, ESR, Inflammatory bowel disease, IBD

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease are inflammatory bowel disease (IBD), which are chronic, idiopathic, relapsing inflammatory condition of the gastrointestinal tract. Histopathological examinations play a major role in the diagnosis and management, 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 IBD. It is crucial to monitor the disease via clinical, endoscopic, and laboratory indices of inflammatory activity. Among the indices of clinical activity, the CDAI (Crohn's Disease Activity Index) and Harvey-Bradshaw index (HBI) are the most widely used [1-6]. CDAI is considered the gold standard for assessing the activity of the disease because this validated index has been widely used for more than 25 years in clinical protocols and in studies seeking drug approval [7]. It is important to determine disease activity of UC early as this will significantly reduce the surgery rate, and therefore reduce mortality in patients with serious UC [8]. UC activity have been assessed in different studies using laboratory markers as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), with sensitivities and specificities ranging between 50 and 60% [9]. Other markers as fecal calprotectin and lactoferrin are more specific and sensitive. However, both of them are costly and not commonly utilized in clinical practice [9, 10]. This indicates a need for simply reachable, efficacious and cost-effective biomarkers for proper management of IBD. 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 [11]. A growing body of evidence suggests that the neutrophil-to-lymphocyte ratio (NLR) is a useful biomarker of systemic inflammation responses [12-15]. Evidence also suggests that it is a predictor of mortality in patients with cancer, including colorectal [16,17], biliary tract [18], bladder [19,20], and breast cancer [21]. 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 [22-25]. However, the data on NLR and its association with other inflammatory serum markers are not convincing. Blood neutrophil-to-lymphocyte (NLR) ratio is a simple marker of subclinical inflammation that can be easily obtained from the differential WBC count. In recent years, neutrophilia and relative lymphocytopenia were shown to be independent predictors of mortality in patients with acute heart failure [26-28]. In addition, recent studies introduce NLR as a potential marker to determine inflammation in both cardiac and non-cardiac disorders [29–32]. The aims of this study were to investigate the utility of NLR as a simple and readily available predictor for clinical disease activity in IBD.

AIM

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 IBD.

METHODOLOGY

This study included 104 IBD patients, who attended Gastroenterology Departments from January 2018 to January 2020. The control group consisted of 48 healthy subjects matched as to their age and gender. Patients were excluded from the study if they had hypertension, any acute inflammation, infection, acute or chronic renal failure, chronic liver or heart diseases, coronary artery disease.

The diagnosis of IBD was based on standard clinical, radiological, endoscopic and histological criteria. Complete blood count (CBC), ESR, and CRP were also recorded for each IBD patient. NLR was calculated. The disease activity in UC

patients was assessed by Mayo Endoscopic Score. The endoscopic assessment of ulcerative colitis was categorized according to the endoscopic pictures as the following: inactive disease (normal mucosa), mild (erythema, decreased vascular pattern, mild friability), moderate (marked erythema, erosions, marked friability) and severe (spontaneous bleeding, ulcerations, pseudo polyps). The disease activity of UC was evaluated using Mayo UC score and the disease was considered active if the score was > 2 and in remission if the score was = 0 – 1. The activity of Crohn's disease was evaluated with Harvey-Bradshaw index - HBI (1980) which is strongly correlated with Crohn's Disease Activity Index (CDAI) and is easier to use. It evaluates five clinical parameters including well-being, abdominal pain, number of liquid stools each day, abdominal mass, and complications. A score inferior to 5 indicates an inactive disease while that above 5 indicates that the disease is active. The Same patients included in the present study within the activation period were reassessed two months after clinical remission. NLR values of IBD patients in whom clinical remission was achieved were noted.

Statistical Analysis:

The Statistical Package for Social Sciences (SPSS) 18.0 for Windows was used to analyze the data. Continuous Values were presented as mean ± standard deviation or in case of non-normally distributed data, as median and range. Comparisons of percentages between different groups of patients were carried out using the Chi-Square test. All normally distributed data were analyzed using unpaired or paired student t test. Data found to be non-normally distributed were analyzed using Mann–Whitney U test for independent subgroups, and Wilcoxon test for dependent subgroups. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of NLR with maximum sensitivity and specificity for differentiation of activation of IBD from remission. A p value of less than 0.05 was deemed statistically significant.

METHODOLOGY

The study included 104 patients. 36 patients had Crohn's Disease and 68 with Ulcerative Colitis. 48 normal subjects were used as controls.

Table 1: Demographic and laboratory features of CD (active) patients and controls:

Variable	Crohn's Disease (Active)	Control	P
Gender - M/F	27/9	30/18	0.086
Age (years)	32 ± 14.2	41 ± 9.23	0.948
CRP (mg/dl)	6.21 ± 6.9	0.36 ± 0.34	0.001
ESR (mm/h)	46.72 ± 26.31	11.29 ± 2.11	<0.001
WBC (mm^3 x 103)	13.57 ± 3.22	4.85 ± 1.44	<0.001
Neutrophil	10.33 ± 3.32	3.32 ± 1.36	<0.001
Lymphocytes	2.71 ± 0.43	2.31 ± 0.472	0.003
NLR	5.68 ± 1.62	1.43 ± 0.39	<0.001

The mean age of CD and control groups was 32.40 ± 14.2 and 41 ± 9.2 years respectively (p = 0.948). There were no statistically significant differences in age and gender between study participants. ESR, CRP, WBC count was significantly high in active CD group than controls. The mean NLR values of active CD patients and controls were 5.68 ± 1.62 and 1.43 ± 0.39, respectively (P <0.001).

Table 2: Laboratory features of CD (remission) patients and controls:

Variable	Crohn's Disease (remission)	Control	P
CRP (mg/dl)	0.5 ± 0.33	0.36 ± 0.34	NS
ESR (mm/h)	11.05 ± 3.52	11.29 ± 2.11	NS
WBC (mm^3 x 103)	6.7 ± 1.2	4.85 ± 1.44	0.005
Neutrophil	4.36 ± 0.66	3.32 ± 1.36	0.001
Lymphocytes	2.8 ± 0.45	2.31 ± 0.472	0.033
NLR	1.56 ± 0.62	1.43 ± 0.39	NS

Mann-Whitney U Test was used. CD – Crohn disease, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, WBC – white blood cells, NLR – neutrophil-to-lymphocyte ratio, NS – non-significant.

The mean NLR values of inactive CD patients and controls were 1.56 ± 0.62 and 1.43 ± 0.39 respectively. The other demographic and laboratory features of inactive CD and control group are given in table 2.

Table 3: Demographic and laboratory features UC patients(active) and controls.

Variable	Ulcerative Colitis (Active)	Control	P
Gender - M/F	42/26	30/18	0.003
Age (years)	36 ± 10.15	41 ± 9.23	0.126
CRP (mg/dl)	8.99 ± 4.26	0.36 ± 0.24	<0.001
ESR (mm/h)	41.72 ± 23.31	11.29 ± 2.11	<0.001
WBC (mm^3 x 103)	12.57 ± 3.22	4.85 ± 1.44	<0.001
Neutrophil	9.13 ± 1.32	3.32 ± 1.36	<0.001
Lymphocytes	2.25 ± 0.43	2.31 ± 0.472	0.033
NLR	4.38 ± 1.12	1.43 ± 0.39	<0.001

The mean age of patients in Active UC and control groups was 36 ± 10.15 vs 41 ± 10.15 respectively. Males were higher than females in UC. CRP, ESR and WBC counts were significantly higher in active UC than controls. The mean NLR values of active UC patients and controls were 4.38 ± 1.12 and 1.43 ± 0.39, p <0.001.

Table 4: Laboratory features of UC (remission) patients and controls:

Variable	Ulcerative Colitis (remission)	Control	P
CRP (mg/dl)	0.47 ± 0.61	0.36 ± 0.24	NS
ESR (mm/h)	12.31 ± 3.69	11.29 ± 2.11	NS
WBC (mm^3 x 103)	8.41 ± 1.52	4.85 ± 1.44	0.023
Neutrophil	4.26 ± 0.98	3.32 ± 1.36	0.007
Lymphocytes	2.61 ± 0.55	2.31 ± 0.472	0.002
NLR	1.4 ± 0.12	1.43 ± 0.39	NS

Mann-Whitney U Test was used. UC – ulcerative colitis, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, WBC – white blood cells, NLR – neutrophil lymphocyte ratio, NS – non-significant.

The mean NLR values of inactive UC patients and controls were 1.4 ± 0.12 and 1.43 ± 0.39, respectively and thus Nonsignificant. Other inflammatory markers values of UC patients (inactive period) and controls are summarized in Table 4.

The mean NLR values of active CD patients were significantly higher than those of inactive CD patients (5.68 ± 1.62 vs 1.56 ± 0.62, p 0.000). Mean NLR values of active UC patients were significantly higher than those of inactive UC patients (4.38 ± 1.12 vs 1.4 ± 0.12, p = 0.000). Inflammatory markers such as WBC, CRP and ESR, were found to be significantly elevated in active CD and UC compared to those in inactive CD and UC.

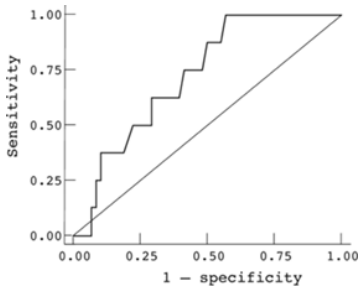

Fig. 1: Receiver operating characteristic (ROC) curve of

neutrophil to lymphocyte ratio (NLR) in active Crohn's Disease

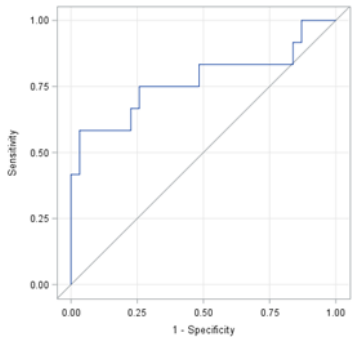

Fig. 2: Receiver operating characteristic (ROC) curve of neutrophil-to-lymphocyte ratio (NLR) in predicting active UC.

ROC curve analysis suggested that the optimum NLR cut-off point for active CD was 2.9; with a sensitivity, specificity, PPV and NPV of 83%, 68%, 90%, and 78% respectively (AUC – 0.780). NLR cut-off point for active UC was 2.72 with a sensitivity, specificity, PPV and NPV of 79%, 67%, 86%, and 62%, respectively (AUC – 0.730).

DISCUSSION

Our findings revealed that elevated NLR, which is derived from complete blood counts, were significantly different between active CD and Ulcerative colitis patients and controls. There is also a significant increase in NLR between active IBD patients and patients who are in remission. Furthermore, these ratios correlated strongly with CRP and ESR. The values of NLR, CRP and ESR were also found to be decreased after remission of CD and UC. Compared to inactive IBD and controls, high levels of N/L ratio in active IBD patients support the view that neutrophils have a role in the inflammatory cascade of IBD. A large number of invasive and non-invasive methods have also been investigated for IBD diagnosis and determination of disease activity [33,34]. Although there is no ideal single serum marker for predicting disease severity, WBC, CRP and ESR are the most commonly used inflammatory indices in routine clinical practice for determining IBD 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 [35]. Despite the better-known role of inflammatory cells in IBD pathogenesis, there are a few data in literature describing the role of NLR as a predictor of disease severity. In this context, this study was designed to evaluate the role of NLR in prediction of IBD activation in conjunction with other clinical and biochemical severity indices. NLR was described in cardiac and non-cardiac disorders [39,36]. It was found that NLR was significantly higher in patients with chronic renal failure than in the control group [37,38]. Besides, it was found to be correlated with the activation of ulcerative colitis [38].

The NLR has been generally investigated in inflammatory and neoplastic diseases, such as ST-segment elevation myocardial infarction (STEMI), ulcerative colitis, colorectal cancer, hepatocellular cancer, multiple myeloma, and type 2 diabetes, as a prognostic index [40,41–46]. One study showed that CD patients with high NLR before infliximab therapy had a lower NLR after 52 weeks of therapy compared with controls. The authors suggested that NLR may be a useful predictor of response to infliximab and could be utilized to optimize the infliximab dosing schedule [47]. Another study verified that elevated NLR could differentiate CD patients from non-CD controls [48], which was in line with our findings. The elevated NLR and PLR stem from both a reduction in the lymphocyte count and an increase in the neutrophil count and the platelet count.

The study by Catarzi et al. [31] found that the apoptosis of polymorphonuclear neutrophils. (PMN) was delayed and that the life of circulating PMN was prolonged, which can be responsible for their excessive migration to inflamed intestinal sites [49]. Excessive activation of leukocytes and aberrant innate or adaptive immunity are known to be involved in the pathogenesis of CD [50].

The Ashraf M. Okba et al study [51] demonstrated significant elevation of both absolute neutrophilic count and NLR in patients with active UC compared with inactive UC patients and controls while the absolute lymphocytic count was significantly lower.

Torun and colleagues conducted a study, including 196 UC patients not on treatment (119 are active and 77 are inactive) compared to 59 group-matched healthy individuals. They detected raised NLR values in active UC compared to inactive UC patients and controls. By the ROC analysis, the cut-off value of 2.16 with a sensitivity of 81.8% and a specificity of 80.5% indicated active UC [52]. Akpinar and colleagues investigated the sensitivity of NLR to predict endoscopic disease severity in 104 patients with active UC, 104 patients in remission, and 105 healthy individuals. The mean NLR were significantly higher in the active group compared to the other study groups ($p < 0.001$). They detected that NLR can identify activity and were associated with mucosal injury [53].

In contrast, 71 patients with UC and 140 healthy individuals (control group) were enrolled in a study by Demir et al. [54], in which the NLR values of the active UC group were elevated compared with those of the patients with inactive UC and the controls ($p = 0.005$). In their results, the ROC analysis revealed 2.39 as the optimum NLR cut-off value for active UC with a sensitivity of 48.6 and specificity of 77.5%. Hence, they concluded that only CRP was able to significantly differentiate active from inactive UC due to the low sensitivity and specificity rates of NLR in determining active UC compared to that of the CRP (63% and 57% respectively). Cherfane and colleagues who conducted a study, including 110 UC patients, 75 patients infected with C. Difficile, and 75 non-IBD individuals. The authors concluded that the NLR was effective to distinguish active UC from non-IBD controls, but not from quiescent UC [55].

Our results demonstrated that the NLR were higher in patients with active UC and CD than in patients within remission and controls. small sample size is a limitation of our study.

CONCLUSION

NLR appear to be promising inflammatory biomarkers in inflammatory bowel disease patients. NLR may guide in assessment of UC and CD activity and mucosal injury, when colonoscopy is not available. We do need prospective multi center studies with large cohort of patients with long term follow up with studying various treatment effects on NLR in these patients. These biomarkers have the advantage of being routinely available, noninvasive, and low-cost.

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