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Can Neutrophil-Lymphocyte Ratio and Lymphocyte-Monocyte Ratio be Considered as Non-Invasive Biomarkers of Disease Activity and Severity in Ulcerative Colitis?

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Abstract **Original Research Article**

Some inflammatory biomarkers have been routinely used to evaluate activity and severity in ulcerative colitis (UC), but none of them seems to be pertinent apart from endoscopic interventions. The aim of this study is to evaluate the utility of neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) as simple and cost-effective non-invasive biomarkers for detecting disease activity in patients with UC. Also, the correlation between both NLR or LMR and the other studied inflammatory markers in patients with UC was also investigated. ***Methods***: We designed a retrospective study including 69 UC patients admitted to our hospital between January 2021 to January 2024. This patients were classified into two groups: Group 1 (active UC) and group 2 (inactive UC). The disease activity was assessed according to Mayo score. The White blood cell count (WBC), NLR, LMR, C-reactive protein (CRP) and fecal calprotectin (FC) were measured and recorded. Statistical analysis was performed using IBM Statistical Package of Social Sciences (SPSS) version 20. ***Results***: Significant elevation of NLR was observed in active UC group compared to inactive UC group (2.74 ± 1.13 and 1.61 ± 0.41 respectively; $p < 0.0001$). The LMR values in the UC active group were significantly lower compared to patients with inactive UC (3.32 ± 1.25, 4.04 ± 1.18 respectively; $p = 0.017$). The receiver operating characteristic (ROC) analysis showed that the optimal NLR and LMR cut-off values for active UC was of 2.46 [sensitivity: 48.4 %, specificity: 66.7 %, AUC: 0.46] and < 3.45 [sensitivity: 76.5 %, specificity: 62.9 %, AUC: 0.71] respectively. Moreover, NLR values were found to be significantly correlated with CF and CRP levels in active UC. Also, LMR showed a significant correlation with CF in patients with active UC. Furthermore, NLR and LMR were positively correlated with endoscopically severe disease. ***Conclusion*:** The present study has demonstrated that high NLR levels and low LMR levels are associated with active disease in UC. They may be used as an additional marker of activity parameter in UC.

Keywords: Neutrophil-Lymphocyte Ratio - Lymphocyte-Monocyte Ratio – Severity – Activity - Ulcerative Colitis.

INTRODUCTION

Ulcerative colitis is a form of inflammatory bowel disease characterised by diffuse inflammation of the colonic mucosa that affects the rectum and can extends along of the colon. Endoscopy with mucosal biopsy seems to be the gold standard for the diagnosis and for evaluating disease activity and severity in ulcerative colitis (UC) but they are costly and invasive.

In clinical practice, some laboratory tests as white blood cells (WBC), C-reactive protein (CRP) and fecal calprotectin (CF) arewidely acknowledged for initial diagnosis and for monitoring disease activity in UC [1, 2]. But these parameters have a humble precision in reflecting UC disease activity [3-5].

Therefore, finding non-invasive accessible and cost-effective biomarkers that can be used to evaluate disease activity is strongly needed for optimal management of UC.

Systemic inflammation induces an increase in circulating neutrophils and a relative decrease in the percentages of lymphocyte [6].

Previous research has suggests that the neutrophile-lymphocyte ratio (NLR) is a useful

biomarker of systemic inflammation responses [7-10]. NLR can predict mortality in some diseases as coronary artery disease and malignancy, including gastric cancer, colorectal cancer, intrahepatic cholangiocarcinoma, pancreatic cancer and hepatocellular carcinoma [11, 12].

In inflammatory bowel disease (IBD), recent research have showed the potential of NLR to assess UC endoscopic activity and severity [13-15].

Besides, absolute monocyte counts seems to be elevated during active inflammation [16], and found to be correlated with the severity of IBD [17]. Cherfane *et al*., [18], noticed that low lymphocyte to monocyte ratio (LMR) can predict disease activity in UC patients.

In the present study, we aimed to establish whether NLR and LMR levels are modified in UC patients. Also, we tried to determine their correlation with usual inflammatory serum markers in patients with UC.

MATERIALS AND METHODS

Patients and Methods

This was a retrospective study including sixty nine (n=69) patients diagnosed as ulcerative colitis. The diagnosis of UC was based on usual clinical, radiological, endoscopic and histological criteria. Participants were recruited from the gastroenterology I department Military Hospital Mohamed V of Rabat-Morocco over a period of one year (January 2021 to January 2024).

We classified the sixty nine patients into two groups: Group 1 (34 patients with inactive disease) and group 2 (35 patients with active disease).

The patients' age, sex, medical history, disease duration, smoking status, location and drug intake were recorded. Clinical data were collected (frequency of defection, abdominal pain, rectal bleeding) and physical examination were performed (body temperature, general well-being, Heart rate) in all patients.

Laboratory findings, including WBCs, neutrophil, monocytes and lymphocyte count, CRP and fecal calpotectin were noted for each UC patient. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. These measured parameters were assessed for the two groups; patients with active disease and from those in remission.

All patients underwent total colonoscopic examination at study entry. The disease was divided according to the Montreal classification [19]: ulcerative proctitis, left side colitis and pancolitis splenic flexure. The disease activity of UC was evaluated using Mayo UC score [20]. Patients were divided into four subgroups with inactive, mild, moderate and severe disease. The disease was considered active if the score was > 2 and in active if the score was = 0–1.

Exclusion criteria for entry into the study were: prior treatment with corticosteroids, hematological or neoplastic disorders, chronic renal failure, chronic liver or heart diseases, autoimmune diseases and clinical evidence of active infection.

Statistical Analysis

We used the Statistical Package for Social Sciences (SPSS) 20.0 to analyze the data. Continuous variables were tested for normality by the Kolmogorov—Smirnov test. All normally distributed data were presented as mean ± standard deviation and the nonnormally distributed data were presented as median and range. All normally distributed data were analyzed using paired sample t-test. A comparison of the nonnormally variables was performed using the Mann-Whitney test. Comparison between two groups with qualitative data was done by Independent t-test. We used Spearman's correlation to analyze the correlation between quantitative parameters. A multivariate logistic regression analysis model was applied to assess predictors of activity with its odds ratio and 95% confidence interval. Multivariate logistic regression analysis model was used to evaluate predictors of activity with its odds ratio and 95% confidence interval. The sensitivity, specificity and cut-off points were calculated by the receiver operating characteristic curves (ROC). A p value < 0.05 was considered statistically significant.

RESULTS

Subject Characteristics

A total of 69 UC patients were included for the present study. Demographic particulars and disease characteristics of UC patients are summarized in **Table 1**. In the group 1 (inactive UC), the mean age was 39.26 ± 13.12 years and 21 (61.8%) were male. In the group 2 (active UC), the mean age was 41.83 ± 15.36 years and 19 (54.3%) were male. There were no statistically significant differences between the ages and genders between the two groups (p= 0.536 and p=0.529 respectively).

Laboratory Values of the Study Groups

We compared the mean values of the biomarkers between patients with active UC and those with inactive disease. The results are summarized in **Table 2** and showed a significantly high WBC, absolute monocytic count, absolute neutrophilic count, CRP, Faecal calprotectin and LNR in active UC group compared to inactive UC one. While, it indicated significant decrease LMR in active UC compared to inactive UC patients.

The mean NLR values of the inactive and active patients were 1.61 ±0.41 and 2.74 ± 1.130, respectively (p<0.0001). The NLR levels of active patients were

significantly higher than those of inactive UC. Besides, the mean LMR values of the inactive and active patients were 4.04 ±1.18 and 3.32± 1.25, respectively (p =0.017). Patients with active UC had significantly lower LMR compared to those with inactive UC.

Correlation between Both NLR and LMR and the other inflammatory Biomarkers in UC Patients

Spearman's correlation analysis indicated a significant positive correlations between NLR and WBC (r = 0.289, p = 0.016), faecal calprotectin (r = 0.578, p = 0.00) and CRP (r = 0.257, p = 0.033) in the among all UC patients. In UC active patients, NLR showed a significant positive correlation with faecal calprotectin (r = 0.337, p = 0.048) and CRP (r = 0.333, p = 0.05). However, no correlation was found between the NLR and CRP, Faecal calprotectin or WBC count in patients with inactive UC. Moreover, in sum of all UC patients, LMR showed a significant negative correlation between LMR with faecal calprotectin (r = − 0.506, p = 0.00) **(Table 3)**. In UC active patients, Spearman correlation analysis indicated a negative significant correlation between LMR with faecal calprotectin (r = − 0.678, p = 0.00). However, no significant correlation was found between the LMR and CRP, FC or WBC count in patients with inactive disease.

Predictors Factors of Disease Activity in UC Patients

A linear regression model was performed to elucidate the associations between UC activity and studied inflammatory biomarkers. In a multivariate regression analysis, significant associations were shown between NLR, LMR, CRP, WBC and FC in active UC **(Table 4)**. After adjusting for the confounding variables, only NLR remained an independent predictor of disease activity (OR: 2.8, 95%CI: 0.98–3.43, p = 0.05). This result can conclude that NLR could discriminate active from inactive UC.

Receiver Operating Characteristic Curve (ROC) For Predictors of Active Disease

ROC curve analysis suggested that the optimum cut-off NLR value for active UC was 2.46, with sensitivity and specificity of 79.4 % and 66.7 % respectively (AUC: 0.46). The LMR cut-off value for active UC was ≤ 3.45 with sensitivity and specificity of 76.5% and 62.9% respectively (AUC: 0.71). The inflammatory biomarkers accuracy that assessed by the AUC, sensitivity, specificity for discriminating active from inactive UC are summarized in **Table 5.**

Relation between Disease Extension, Endoscopic Activity with NLR and LMR

Our data found that there was no significant difference between NLR and LMR and disease extension on endoscopic examination (p=0.061 and p = 0.274 respectively) **(Table 6).** Moreover, we found a significant difference of NLR and LMR values according to the endoscopic activity. NLR was significantly higher and LMR was significantly lower in patients with severe ulcerative colitis **(Table 7)**.

DISCUSSION

UC is a chronic inflammatory disease of the colon characterized by a continuous inflammation of the colonic mucosa that affects the rectum and colon to a variable extent [21]. In clinical practice, we commonly used clinical symptoms, endoscopic appearance, histopathology findings, radiological imaging and inflammatory biomarkers to evaluate the disease activity and severity in UC [22]. Endoscopic examination with histological study is an efficient and practical tool to estimate the disease severity and assesse mucosal healing [23]. However, endoscopy may not always be applicable to monitor UC in routine practice due to its unavailability, possible complications and it high cost. Although, noninvasive and easily accessible biomarkers are required to avoid the complications of this invasive procedure.

Several studies have evaluated the efficiency of circulating leukocyte subtypes as biomarkers during non-infectious inflammatory disorders [15-28].

Therefore, the aim behind the current study was to assess the role of NLR and LMR as accessible and available predictive markers of disease activity in patients with UC. Also, we evaluate their possible association with the disease extension and endoscopic severity.

During routine clinical practice, the most commonly used inflammatory indices to assess active disease are the WBC count, CRP, ESR and faecal calprotectin [29]. Though, they do not properly reflect disease activity because of their low sensitivity and specificity, for reflecting the bowel inflammation [30, 31].

Our results emphasized that WBC levels, neutrophils count and fecal calprotectin were significantly higher in patients with active UC compared with non-active disease. ROC curve analysis indicated that the cut off value for WBC and fecal calprotectin was 7.7 and 22.5 respectively, with sensitivity and specificity of 69% and 57.4% and 88.2% and 57.5% respectively.

Our results are consistent with those of Yüksel *et al*., [32], who stated that overall accuracy of WBC count in determining disease activity was 57% (sensitivity 58 %). Moreover, Schoepfer AM *et al*., [33], reported that fecal calprotectin was a useful marker in diagnosis of active disease. They found that FC levels allowed discriminating between active and inactive UC.

Although in our study CRP levels in active UC patients were higher than inactive UC patients, but this was not statistically significant (p= 0.091). The cut off value for CRP was 3.35 with sensitivity and specificity

of 79.4% and 43.4% respectively. This results are consistent with those of Serkan. T and Al who reported that the optimal cut-off CRP value for indicating active UC was 3.23 mg/l, with a sensitivity and specificity of 65.3 and 58.4%) respectively [34].

In sum, we found that diagnostic accuracy of the inflammatory biomarkers in UC patients were disappointing, as none of them had an AUC >0.7. These parameters are inadequate for determining the UC activity in clinical practice because of their heterogeneous sensitivity and specificity for intestinal inflammation [35].

In the present study, we use to evaluate NLR as an efficient marker of disease activity in UC. Our findings revealed that patients with active UC have significantly elevated NLR in comparison with inactive UC. These results are in accordance with previous studies results that demonstrate significantly elevated NLR in patients with active UC [2-15].

In previous studies, the sensitivity and specificity values were different and the optimum NLR cutoff value indicating the presence of active disease active UC was in the range of 2.16-3.1 [15-38].

Our results showed that the optimum cut-off value for active UC was 2.46, with sensitivity and specificity of 79.4 % and 66.7 % respectively. This finding seems to be close to those reported by Celikbilek *et al*., [36], who found that the cut-off point indicated the presence of active disease was 2.47, with sensitivity and a specificity of 53.9% and 63.2% respectively. But according to our data, NLR had an AUC under 0.07, thus we judge that NLR was not effective for determining active UC.

NLR is a simple and cost-effective marker of systemic inflammation that can be easily obtained from the differential WBC count. NLR can determine outcomes of some diseases as coronary artery disease and malignancy [11, 12].

Neutrophil is the one of the most important leukocyte causing inflammation and tissue injury in UC disease [39]. Neutrophil accumulation and abscess formation within the intestinal crypts at the apical epithelial surface are typically seen in the pathological aspect of UC [40].

Prior studies have detected abnormal lymphocyte function in the peripheral blood and mucosal level in inflammatory bowel disease patients. The peripheral lymphocytes had a decreasing responsiveness to the mitogen phytohemagglutinin [40, 41]. In the present study, the mean peripheral lymphocyte count was not statistically significant from patients with inactive UC. Hence, these mechanistic pathways can clarify increased NLR in active UC patients and confirms the key role of neutrophils in the inflammation process.

In our data, Spearman's correlation analysis demonstrated that there was a significant correlation between the NLR with CRP ($r = 0.333$, $p = 0.05$) and faecal calprotectin ($r = 0.337$, $p = 0.048$). Ashraf M *et al*., revealed a significant positive correlations between NLR and CRP ($r = 0.490$, $p = 0.082$) in patients with active UC [42]. Moreover, after adjusting for the other inflammatory markers in the multivariate regression analysis, NLR was found to be an independent marker that could discriminate active from inactive UC (OR: 2.8, 95%CI: 0.98–3.43, $p = 0.05$).

Akpinar and al showed that the mean NLR values were significantly higher in the active group compared to those in the remission (2.9 ± 0.8 vs. 2.2 ± 0.9 vs. 1.8 ± 0.6; $p<0.001$). They conclude that NLR may identify endoscopic active disease [28]. This goes in line with our study, NLR was significantly higher in patients with severe ulcerative colitis compared to those with moderate and mild disease on the endoscopic examination (2.71 ± 0.92 vs. 2.62 ± 1.24 vs. 2.11 ± 0.92; $P=0.005$).

In the otherwise, we found that NLR was not able to predict the extension of the disease. In two previous studies, NLR did not differ between patients with extensive and non-extensive disease [28-36].

Monocytes are recruited to the inflamed tissues during infectious and non-infectious inflammatory disorders [16]. Activation of monocytes is expected to be involved in the development of inflammatory bowel disease [18]. Thus, Monocyte counts are expected to be elevated during active inflammation and infections. Mee AS and al reported a significant monocytosis that was closely correlated with the total white cell count and with the activity of the disease in ulcerative colitis [43].

Through our study we evaluated LMR as a representative marker of disease activity. Our data revealed that patients with active UC have significantly decreased LMR in comparison with inactive UC. Also, we observed a significant elevation of absolute monocytes count in active UC patients compared with inactive UC patients.

Furthermore, we found that a LMR value of 3.45 can predict active disease with sensitivity and specificity of 76.5% and 62.9% (AUD = 0.71). This joins Cherfane CE and Al results that found a significantly elevated monocyte counts and decreased LMR between patients with active UC and inactive UC. The LMR optimum cut-off value of 3.1 indicated the presence of active disease with a sensitivity and a specificity of 61% % and 61% respectively [18].

Our data showed a negative significant correlation between LMR with faecal calprotectin (r = − 0.678, p = 0.00) in UC active patients. However, no significant correlation was found between the LMR and CRP, FC or WBC count in patients with inactive disease. In another study [42], they found a negative significant correlation between LMR and CRP (r = − 0.475, p = 0.034) in patients with active UC and no correlation was found between the LMR and other usual inflammatory markers in patients with inactive disease.

Our study found that LMR was significantly lower in patients with severe ulcerative colitis compared to those with moderate and mild disease on the colonoscopic examination (2.36 ± 0.25 vs. 3.23 ± 0.90 vs. 3.91 ± 1.27; p=0.008). Also, we found that LMR was not able to predict the extension of the disease.

This goes in line with a previous study that found that decreased LMR values can significantly distinguish active UC from inactive UC (p = 0.0002) [18].

This study has some limitations. First, our study was conducted among in patients at our hospital department. Hence, the findings cannot be representative of the general population of patients with UC in Morocco and may not be generalized worldwide. Second, we did not join healthy controlled groups. Third, we included patients using immunosuppressive agents, which can affect the level of inflammatory markers. Finally, it was a retrospective single center study and consisted of a relatively small sample size. A multicentric cohort, including a larger sample size, will help to better assess the place of these biomarkers.

CONCLUSION

In conclusion, the present study has demonstrated that high NLR levels and low LMR levels are associated with active disease in UC. Thus, NLR and LM can estimate disease activity in conjunction with other inflammatory markers.

Moreover, NLR showed a significant positive correlation with the other laboratory markers (faecal calprotectin and CRP) in patients with active UC.

Therefore, although the NLR is a simple and cost-effective inflammatory marker, it was not effective for determining active UC (AUC under 0.07).

Conversely, LMR had a highest discriminatory capacity for active UC, with an optimal cutoff value of 3.45.

NLR and LMR can judge the degree of endoscopic involvement but were not able to predict the extension of the disease. Therefore, NLR and LMR may be used to evaluate endoscopic activity in UC and reduce the need for invasive endoscopies. Future studies are needed to validate our findings in a large cohort of UC patients.

Table 1: Clinical characteristics of patients with ulcerative colitis

Variables	n = 69(%)
Age(years)	40.6 ± 14.2
Gender	
Males	40 (58)
Females	29 (42)
Disease duration (years)	6.9 ± 2.6
Smoking	12 (17.4)
Localization of disease (Montreal)	
Proctitis (E1)	10 (14.5)
Left-sided (E2)	46 (66.7)
Extensive (E3)	13 18.8)
Extraintestinal manifestation	5 (7.2)
Surgery for ulcerative colitis	2 (2.9)
Mayo UC score	
Normal/inactive	13 (18.8)
Mild	30 (43.5)
Moderate	20 (31.9)
Severe	4 (5.8)
Drug intake	
Mesalazine	55 (79.7)
Azathioprine	13 (18.8)
Biotherapy	8 (11.6)
Infliximab	2
Adalimumab	5

UC ulcerative colitis

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

Table 2: Comparison of inflammatory markers between active and inactive UC patients

Variables	Inactive UC (n = 34)	Active UC (n = 35)	*p-value*
Hb (g/dL)	12.91 ± 0.64	13.01±1.31	0.689
CRP (mg/L)	9 (3.4–10)	10.2 (3–23)	0.091
Faecal calprotectin (µg/g of faeces)	47 (34–50)	500 (257–1234)	0.000
WBC (/mm3)	5545 ± 1477	7857 ± 2307	0.000
Absolute neutrophile count (/mm3)	3043.3 ± 942.4	5144.9 ± 1630.2	0.000
Absolute lymphocyte count (/mm3)	1875.6 ± 556.4	1933.2 ± 734.9	0.715
Absolute monocyte count (/mm3)	491 ± 223	643.6 ± 241.3	0.008
NLR	1.61 ± 0.41	2.74 ± 1.13	0.000
LMR	4.04 ± 1.18	3.32 ± 1.25	0.017

UC: ulcerative colitis; WBC: white blood cells; CRP: C-reactive protein; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio
Values are expressed as mean ± standard deviation or median (25th and 75th percentiles).

Table 3: Spearman correlation coefficients between both NLR or LMR and the other inflammatory markers in patients with UC

	WBC (/mm³)		FC (µg/g)		CRP (mg/L)	
	r	p-value	r	p-value	r	p-value
	NLR		NLR		NLR	
All UC patients	0.289	0.016*	0.578	0.000**	0.257	0.033*
Active UC	-0.034	0.845	0.337	0.048*	0.333	0.050
Inactive UC	0.159	0.369	0.119	0.502	-0.239	0.173
	LMR		LMR		LMR	
All UC patients	-0.095	0.437	-0.506	0.000**	-0.026	0.830
Active UC	0.198	0.255	-0.678	0.000**	-0.207	0.232
Inactive UC	-0.160	0.366	-0.037	0.836	0.288	0.099

WBC: white blood cells; FC: faecal calprotectin; CRP: C-reactive protein; UC: ulcerative colitis
* Significant, ** Highly significant

Table 4: Multivariate Regression Analysis of association between NLR/LMR and disease activity of UC

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p-value*	OR	95% CI for OR	*p-value*
WBC	1.001	1.000 – 1.002	0.000			
CRP	1.093	1.020 – 1.172	0.011			
FC	1.033	1.005 – 1.062	0.022			
NLR	11.26	3.36 – 37.72	0.000	2.8	0.98–3.43	0.05
LMR	0.606	0.394 – 0.933	0.023			

OR: Odds ratio; CI: confidence interval ; UC: ulcerative colitis; WBC: white blood cells; CRP: C-reactive protein; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio

Table 5: Diagnostic performance of WBC, CRP, faecal calprotectin, NLR and LMR in the detection of active ulcerative colitis

	Cut-off values	AUC	Sensitivity (%)	Specificity (%)
WBC	7700	0.21	69	57.4
CRP	3.35	0.38	79.4	43.4
FC	22.5	0.06	88.2	57.5
NLR	2.46	0.46	48.4	66.7
LMR	3.45	0.71	76.5	62.9

WBC: white blood cells; CRP: C-reactive protein; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; AUC: area under curve

Table 6: Relationship between NLR and LMR and disease extension LMR in active ulcerative colitis

Variables	Disease Extension			*p-value*
	Proctitis	Left sided	Pancolitis	
NLR	1.49 ± 0.25	2.27 ± 1.08	2.39 ± 0.98	0.061
LMR	4.08 ± 1.21	3.50 ± 1.16	3.98 ± 1.58	0.274

NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio
Values are expressed as mean ± SD

Table 7: Relationship between NLR and LMR and endoscopic disease activity

Variables	Endoscopic disease activity				*p-value*
	Normal	Mild	Moderate	Severe	
NLR	1.44 ± 0.27	2.11 ± 0.92	2.62 ± 1.24	2.71 ± 0.46	0.005
LMR	4.29 ± 1.48	3.91 ± 1.27	3.23 ± 0.90	2.36 ± 0.25	0.008

NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio
Values are expressed as mean ± SD

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