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A STUDY TO ASSESS PLATELET-TO-LYMPHOCYTE RATIO AND NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR PREDICTING SEVERITY OF MUCOSAL DISEASE IN ULCERATIVE COLITIS.

Pathology

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ABSTRACT

Background: Ulcerative colitis (UC), a chronic inflammatory bowel disease of uncertain etiology, is characterized by recurring episodes of inflammation limited to mucosal layer of colon and rectum. As systemic inflammatory response is associated with alteration in circulating leukocytes, specifically the presence of neutrophilia with relative lymphocytopenia; and thrombocytosis; these inflammatory changes were studied to predict the level of inflammation in UC by using derived markers. **Methods:** This hospital-based analytical observational study was conducted using 3 groups (active UC disease; UC patients in remission; and healthy controls) with sample size of 30 each. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were derived from neutrophil count, lymphocyte count and platelet count. **Results:** Mean values of NLR, ESR and CRP were highest in active group and lowest in controls while PLR was highest in remission group and lowest in controls. This difference was statistically significant ($p<0.05$). Between mild disease subgroup and moderate-to-severe disease subgroup, no statistically significant difference was found for all the studied CBC parameters, NLR, PLR, ESR and CRP. There was no statistically significant correlation of ulcerative colitis endoscopic index of severity (UCEIS) with different variables in active and remission groups. **Conclusion:** NLR and PLR were significantly elevated in UC patients.

KEYWORDS

Ulcerative Colitis, Neutrophil-to-lymphocyte Ratio, Platelet-to-lymphocyte Ratio, Ulcerative Colitis Endoscopic Index of Severity.

INTRODUCTION

Ulcerative colitis (UC), a chronic inflammatory bowel disease (IBD) of uncertain etiology, is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon and rectum. The main complaints of the patients are rectal bleeding, frequent stools, mucus discharge from the rectum, tenesmus, and lower abdominal pain. Clinical features, laboratory parameters, imaging tests, endoscopic examination, and histopathology are used to determine disease extent and severity [1]-[3].

Systemic inflammatory response is associated with alteration in circulating leukocytes, specifically the presence of neutrophilia with relative lymphocytopenia; and an increase in platelet count [4]. UC being a systemic inflammatory condition, these inexpensive, accessible, non-invasive, quick and easily reproducible markers of inflammation can be studied to predict level of inflammation in UC.

MATERIAL AND METHODS

A hospital-based analytical observational study was conducted at SMS Medical College & Hospitals, Jaipur, Rajasthan, India. 30 UC patients having Ulcerative Colitis Endoscopic Index of Severity (UCEIS) >1 were enrolled in active disease group; 30 UC patients having UCEIS 0 to 1 were enrolled in remission group; and 30 healthy individuals with no history of inflammatory bowel disease and with normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBC) count and platelet count were taken as controls.

A proforma sheet was prepared to get information on age, sex, address. A complete history was taken. Blood sample of cases of each study groups were taken in ethylenediaminetetraacetic acid (EDTA) vials at lab. Neutrophil, lymphocyte and platelet count measured by automated haematology analyser (Sysmex XN-1000); neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were derived from these values; ESR was measured by automated TEST-1 THL device; CRP was measured by AQT90 FLEX analyzer; Colonoscopy was done using Olympus CF-Q150L colonoscope (Olympus Medical Systems Corp., Tokyo, Japan). Ulcerative colitis endoscopic index of severity (UCEIS) was evaluated for quantification of mucosal severity of UC, using vascular pattern, bleeding, erosions and ulcers.

Data management and analysis were performed using IBM Statistical Package of Social Sciences (SPSS) trial version 25, USA. Qualitative data were expressed in proportions and analysed using Chi-square test. Quantitative data were expressed in mean & standard deviation and analysed using Student's t test and Anova test. Post hoc analysis was done after Anova. Values of $p < 0.05$ were considered statistically significant.

RESULTS

For the mean age, no significant difference was found among 3 groups. Male to female ratio in all the groups was 3:2. Both active and remission groups were comparable in view of duration of disease and distribution of UC type (p value>0.05).

Mean value of haemoglobin, total lymphocyte count and lymphocyte percentage in DLC was highest in participants of control group while total leukocyte count, platelet count, total neutrophil count and neutrophil percentage in differential leukocyte count (DLC) was highest in active disease group participants and lowest in controls. Differences in all complete blood count (CBC) parameters except platelet count were found to be statistically significant (p value<0.05) among participants of all 3 study groups (Table 1).

Table 1: Comparison Of CBC Parameters Among The Groups

Variables	Active UC disease group (n=30)	UC patients in remission group (n=30)	Healthy control group (n=30)	p value
Hb (gm/dL)	10.49±2.18	11.07±2.86	13.93±1.42	<0.001 S
Total Leukocyte Count (×109/L)	9.44±4.36	8.08±3.82	7.17±1.43	0.042S
Neutrophil percentage in DLC	70.73±12.37	69.3±9.99	60.52±5.41	<0.001 S
Total Neutrophil Count (×109/L)	6.82±3.83	5.81±3.31	4.36±1.03	0.008S
Lymphocyte percentage in DLC	22.59±11.47	22.57±9.17	32.41±4.95	<0.001 S
Total Lymphocyte Count (×109/L)	1.95±0.86	1.63±0.65	2.31±0.51	0.001S
Platelet count (×109/L)	282.2±108.23	266.1±99.23	271.23±61.21	0.787NS

The difference in mean value of ESR, CRP, NLR and PLR among each study group participants was statistically significant (p value<0.05). ESR, CRP & NLR values were significantly higher in active disease group as compared to controls. No significant difference in PLR was found between active disease group and controls. ESR and CRP values were significantly higher in active disease group as compared to remission group. No significant difference in NLR and PLR values were found between active disease group and remission group. ESR, NLR & PLR values were significantly higher in remission group than controls. No significant difference in CRP value was found between remission group and controls (Table 2).

Table 2: Comparison Of ESR, CRP, NLR And PLR Among The Groups

Variables	Active UC disease group (n=30)	UC patients in re-mission group (n=30)	Healthy con-trol group (n=30)	p value (ANOVA)	POST HOC TEST		
					Active vs Control	Active vs Re-mission	Remission vs Control
ESR (mm/1st hour)	39.3 ±26.97	25.23 ±25.47	4.43 ±2.01	<0.001 S	S	S	S
CRP (mg/L)	31.29 ±52.56	7.96 ±18.68	1.43 ±0.96	<0.001 S	S	S	NS
NLR	4.34 ±2.98	3.94 ±2.56	1.94 ±0.5	<0.001 S	S	NS	S
PLR	183.96 ±139.95	192.09 ±116.96	121.21 ±32.56	0.023S	NS	NS	S

Active disease group was divided into two subgroups on the basis of UCEIS. Mild disease subgroup was having UCEIS value 2-4 and moderate to severe disease subgroup was having UCEIS value 5-8. There was no statistically significant difference found in mean duration of disease, CBC parameters, ESR, CRP, NLR and PLR in participants of both subgroups of active cases (p value>0.05) (Table 3).

Table 3: Subgroup Analysis Of Active Disease Group Cases

Variables	UCEIS 2-4 (Mild disease) (n=12)	UCEIS 5-8 (Moderate to Severe disease) (n=18)	P value
Mean age (in years)	40.00±19.22	37.72±15.00	0.718NS
Mean Duration of Disease (months)	51.54±41.85	27.67±29.88	0.079NS
Hb (gm/dL)	10.15±2.3	10.72±2.14	0.493NS
TLC (×109/L)	8.8±3.44	9.86±4.93	0.524NS
Neutrophil percentage in DLC	68.15±12.06	72.45±12.61	0.468NS
Total Neutrophil Count (×109/L)	6.18±3.48	7.24±4.09	0.468NS
Lymphocyte percentage in DLC	24.93±10.66	21.04±12.01	0.372NS
Total Lymphocyte Count (×109/L)	2.03±0.85	1.9±0.89	0.693NS
Platelet count (×109/L)	287.33±72.11	278.78±128.78	0.836NS
ESR (mm/1st hour)	37.17±23.73	40.72±29.52	0.731NS
CRP (mg/L)	24.09±56.1	36.1±51.14	0.549NS
NLR	3.66±2.78	4.79±3.1	0.317NS
PLR	154.27±46.35	203.76±176.02	0.352NS

There was no statistically significant correlation of UCEIS was found with different variables in active disease group and remission group (p value>0.05) (Table 4).

Table 4: Correlation Of UCEIS With Different Variables In Active Disease Group And Remission Group

Variables	Pearson's coefficient	p value
Hb (gm/dl)	0.036	0.85
TLC (×109/L)	0.267	0.154
Neutrophil percentage in DLC	0.255	0.174
Total Neutrophil Count (×109/L)	0.287	0.124
Lymphocyte percentage in DLC	-0.273	0.145
Total Lymphocyte Count (×109/L)	-0.104	0.584
Platelet count (×109/L)	-0.037	0.844
ESR (mm/1st hour)	0.096	0.614
CRP (mg/L)	0.012	0.948
NLR	0.321	0.084
PLR	0.153	0.419

Receiver operating characteristic (ROC) curve of NLR and PLR was plotted to differentiate between active and remission cases. Area under curve for NLR was 0.529 (0.381-0.678) which was higher than area under curve for PLR 0.454 (0.307-0.602), indicating higher diagnostic accuracy of NLR comparable to PLR. Cut off value of NLR was 2.2, at this value sensitivity was 80% and specificity was 33.3% and cut off value of PLR was 174.06, sensitivity was 46.7% and specificity was 63.3% (Figure 1).

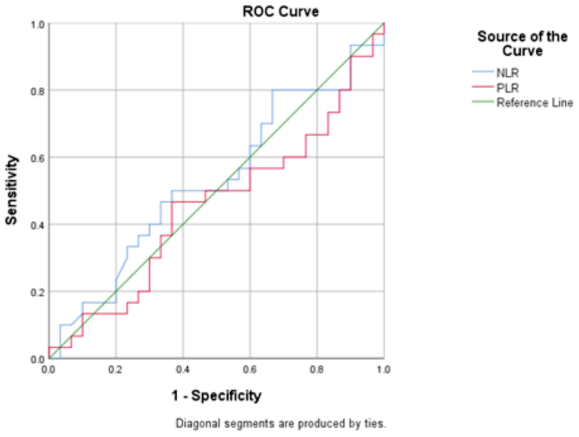

Figure 1: ROC Curves Of NLR and PLR

DISCUSSION

In our study we noted that the mean value for TLC (×10^9/L), neutrophil percentage in DLC and total neutrophil count (×10^9/L) was found lowest in control group and was highest in active group, similar to the study done by Serkan Torun et al. (2012) [5] who found mean TLC (×10^9/L) for active, remission and controls group as 9.6, 7.6, 7.1 respectively and study conducted by Muhammet Yener Akpinar et al. (2018) [6] who showed the mean TLC (×10^9/L) as 9.376, 7.87, 6.5 in 3 groups and total neutrophil count (×10^9/L) as 5.792, 4.891, 3.925 in 3 groups.

Neutrophil infiltration in the mucosa helps to remove cellular debris and clear bacteria that may contaminate intestinal wounds. Besides, these recruited neutrophils release defensins and cathelicidin to stimulate the migration and proliferation of epithelial cells, and enhance the production of protective mucins [7]. Surprisingly neutrophils also can facilitate intestinal repair by inducing proteins and lipid mediators [8]. This explains the increased absolute neutrophilic count in active UC.

In this study, there was a significant difference found among the 3 groups for mean ESR (mm/1st hour). Active group is having the highest mean ESR (39.3) followed by remission group (25.23) and control group is having the lowest value (4.43). Similar significant difference was found in a study conducted by Serkan Torun et al. (2012) [5] (p<0.001).

Our study shows significantly higher CRP (mg/L) in active group (31.29) than remission group (7.96) and control group (1.43) but there was no significant difference found between remission group and control group, this was different from the studies done by Serkan Torun et al. (2012) [5], Ayse Kevser Demir et al. (2015) [9] and Ashraf M. Okba et al. (2019) [10] in which there was significant difference found between remission group and control group also (p value 0.008, <0.001 and 0.000 respectively). During routine follow up, the most

commonly utilized serum markers to assess active disease are ESR and CRP. In terms of differentiating disease activity, our results emphasized that serum levels of CRP and ESR were significantly higher in patients with active UC.

There was a significantly low NLR value in control group (1.94) in comparison to active group (4.34) and remission group (3.94) but there was no significant difference found between active group and remission group. This was in accordance with studies done by Ahmad et al. (2018) [11] ($p<0.05$), which noted higher NLR values in UC compared to controls. These findings were different from the study done by Xu et al. (2019) [12] in which they noted no differences in NLR between active and remission groups ($p = 0.273$).

In active group, around three fourth (23/30) of participants had left sided UC, 13.3% (4/30) had proctitis and 10% (3/30) had pan-ulcerative colitis. There was almost similar distribution of type of ulcerative colitis among participants of remission group.

Active disease group was divided into two subgroups on the basis of UCEIS. Mild disease subgroup was having UCEIS value 2-4 and moderate to severe disease subgroup was having UCEIS value 5-8. There was no statistically significant difference found in mean duration of disease, CBC parameters, ESR, CRP, NLR and PLR in participants of both subgroups of active cases (p value>0.05). Similar findings were seen in a study carried out by Mehmet Celikbilek et al. (2013) [13], in which there was no significant difference between mild disease group and moderate to severe disease group.

Area under curve for NLR was 0.529 (0.381-0.678) which was higher than area under curve for PLR 0.454 (0.307-0.602), indicating higher diagnostic accuracy of NLR comparable to PLR. Cut off value of NLR was 2.2, at this value sensitivity was 80% and specificity was 33.3% and cut off value of PLR was 174.06, sensitivity was 46.7% and specificity was 63.3%. These results were in accordance with the studies done by Serkan Torun et al. (2012) [5], where the cut-off value for NLR was determined as 2.16 (sensitivity 81.8%, specificity 80.5%). Akpinar M et al. (2018) [6] concluded that either high NLR or PLR levels can predict active endoscopic disease and the use of these parameters in combination is more accurate in evaluating mucosal disease and inflammation in UC.

CONCLUSION

We found that NLR and PLR were significantly elevated in UC patients. As the sensitivity and specificity of NLR and PLR are not very high, these markers cannot be used as a screening tool for mucosal disease severity but can aid to the endoscopic examination in assessment of the mucosal disease severity and are more useful when utilized together with serum laboratory inflammatory indices (ESR, CRP). Awareness of the levels of these parameters before colonoscopy may guide the clinician to a more careful examination during colonoscopy.

Limitations And Future Scope

As the study was done in tertiary care centre where the patients generally reach after multiple hospital visits and admissions, or referred after complications, patients without prior treatment were considerably lesser in number. Also, after receiving treatment, inflammatory process begins to diminish, hampering the values of inflammatory markers. Small sample size and single-centre study were other limitations of this study. One of the limitations of the UCEIS score is the unclear differentiation between erosion and superficial ulceration. In future, multiple-centre studies with large sample size will be more informative.

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