Fecal Calgranulin C a Novel Noninvasive Marker in Predicting Activity and Severity of Ulcerative Colitis Compared with Colonoscopy.

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ABSTRACT

Background: In spite of being invasive and expensive, endoscopic and histologic evaluation measures remain the gold standard for diagnosis of ulcerative colitis. There is a need for widely available, reasonably priced biomarkers for testing outside of endoscopic evaluation. **Objective**: To evaluate fecal calgranulin C, Neutrophil / Lymphocyte ratio and Lymphocyte / Monocyte ratio in ulcerative colitis patients as noninvasive biomarkers of disease activity and severity compared with colonoscopy.

Patients and Methods: A cross - sectional study was conducted on 50 patients with ulcerative colitis and were classified into two groups: Group I: (50) patients in active state and Group II: the same (50) patients in remission state. Patients were subjected to thorough clinical examination, laboratory investigations including fecal calgranulin C and colonoscopic assessment.

Results: Fecal calgranulin C, neutrophils, monocytes and N/LR were reliable indicators of activity and severity of active UC compared to inactive UC ($p < 0.001$). The mean fecal calgranulin C level for UC in exacerbation and remission was (709.30 ± 172.31 and 84.86 ± 19.42) pg/ml respectively. The optimal cutoff was estimated at 185pg/ml with sensitivity and a specificity of 94% and 92%, respectively. Significant elevation of NLR was observed in active UC group compared to inactive UC (2.44 ± 0.56 and 1.56 ± 0.36) respectively.

Conclusion Fecal calgranulin C and NLR could be used as noninvasive markers to predict activity and severity of UC and to reduce the need for invasive endoscopies.

Keywords: Ulcerative colitis, Calgranulin C, Neutrophils, NLR, LMR, Colonoscopy.

INTRODUCTION

The chronic relapsing type of inflammatory bowel disease (IBD) known as ulcerative colitis (UC) is characterized by ongoing mucosal inflammation in the superficial layers of the colon and rectum. Evaluation of intestinal inflammation and recovery with a long-term prognosis is a major issue for UC [1].

It is a significant topic of interest and a challenging issue. Despite their effectiveness in practice, endoscopic and histological examinations are intrusive, expensive, and fraught with issues [2].

With sensitivities and specificities ranging between 50 and 60%, UC activity has been measured in a variety of investigations employing laboratory indicators such erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [3].

Several investigations have been conducted to determine the importance of various fecal, serum, or mucosal indicators, including S100 protein family members S1OOA8/9 and S1OOA12 [4].

The S100 protein family, which includes calcium-binding proteins, includes the S100 A12, often referred to as calgranulin C. Similar to S100 A8/A9 (calprotectin), S100 A12 is thought to be phagocyte-specific, demonstrates proinflammatory features, and has already been connected to a number of inflammatory disorders, including IBD [5]. Fecal (f-) calprotectin has been demonstrated to correlate strongly with endoscopic disease activity, in contrast to clinical activity indices and inflammatory markers such C-reactive protein, erythrocyte sedimentation rate, and leukocytes [6, 7].

S100A12 is only released by active neutrophils and functions independently of calprotectin [8], whereas calprotectin is secreted by activated and injured cells such as granulocytes, monocytes, and epithelial cells. We believe that S100A12 may be more selective for IBD-associated inflammation than calprotectin since neutrophil infiltration into the intestinal mucosa is one of the most notable histological characteristics in IBD [9].

Certainly, macrophages and neutrophils play an intriguing role in the pathogenesis of IBD [10]. Moreover, during regular clinical visits, alterations in the quantity of leukocytes, particularly monocytes, can be seen as an early indicators of inflammation in IBD [11]. A high absolute monocytic count and a low lymphocyte to monocyte ratio (LMR) were found to be predictive of disease activity in UC patients in 2015 as disclosed by Cherfane *et al.* [12].

PATIENTS AND METHODS

This study was conducted on 50 patients with ulcerative colitis from Hepatology and Gastroenterology department inpatient and outpatient

clinic at El-Mahalla Hepatology teaching Hospital and Benha University Hospital within the period from January 2021 to October 2022.

Patients who refused to be entitled in the study, and patients with: gastritis, gastric cancer, gastroenteritis, necrotizing enterocolitis, irritable bowel syndrome and digestive tract cancers, were excluded.

Patients have ulcerative colitis (UC) (diagnosis was dependent on clinical, laboratory investigations, colonoscopic and histologic examination) in whom fecal calgranulin C , fecal calprotectin , Neutrophil / lymphocyte ratio (N/LR) , Lymphocyte / Monocyte ratio (L/MR) and other laboratory investigations were done during active and remission states (remission state diagnosis was dependent on clinical based scoring system called Simple Clinical Colitis Activity Index) for the same patients.

Patients were classified into two groups:
Group I: including (50) patients have active ulcerative colitis (UC) and group II: including the same (50) patients have ulcerative colitis (UC) in remission.

All patients were subjected to full history taking, thorough clinical examination, including: age, gender, disease duration, family history, DM, smoking, blood transfusion and symptoms such as: abdominal pain, bleeding per rectum, diarrhea and dysentery.

Laboratory investigations included**:** Complete blood count (CBC) with differential count, serum creatinine, serum albumin, C - reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin by ELISA kits, fecal calgranulin C measured using assay of human S100A12 ELISA kits.

Colonoscopy and histological examination: were done in patients who have ulcerative colitis (UC) in active state after patient consent and proper preparation to assess the extent and severity according to endoscopic Mayo Scoring Index and Montreal classification in the active state of UC.

Ethical consent:
The study received approval from the Benha University Academic and Ethical Council (giving it clearance number MD.12.7.2020). Each patient consented to participate in the trial by signing a written informed consent form. The conduct of this study was governed by the Declaration of Helsinki, the International Medical Association's code of ethics for human subjects research.

Statistical Analysis
The SPSS, version 24.0, was used to analyze the data. For communicating quantitative data, the mean and standard deviation were utilized (SD). We used frequency and percentage to communicate qualitative data. Mann-Whitney test: used to compare two groups under study for aberrant quantitative variables. Tests for analysis of variance (f) based on the SPSS for Windows computer software. The ANOVA test was employed to compare more than two means. Receiver Operating Characteristics Curve Analysis Test (ROC-curve). P value less than 0.05 was regarded as significant. Pearson's correlation coefficient (r) test was used for correlating data.

$$r = \frac{\Sigma(X - \overline{X})(y - \overline{y})}{\sqrt{\{\Sigma(X - \overline{x})2\ \}\{\Sigma(y - \overline{y})2\}}}$$

RESULTS
Fifty (50) patients with ulcerative colitis were involved in this study, and were classified into two groups: Group I: (50) patients in active state and Group II: The same (50) patients in remission state.

Table 1 displays the sociodemographic features and clinical presentation of the individuals under investigation. Age and gender distribution among the research groups were similar, and no noteworthy findings were found.

Patients disease duration range was (1-9) with mean (4.37 ± 1.86) and the mean age was (35.36 ± 10.43) years with 14 (28 %) were men while 36 (72 %) were women.

Highly statistical significant difference between both groups as regards (bleeding per rectum, diarrhea and dysentery) and significant difference as regards (abdominal pain and bleeding with colonoscopy).

Table (1): Socio-Demographic characteristics and clinical picture of studied patients

Socio-Demographic characteristics		Range	Mean ± S. D
Disease duration (in years)		1 – 9	4.37 ± 1.86
		N	**%**
Age	Range	20 – 70	
	Mean ± S. D	35.36 ± 10.43	
Sex	Male	14	28
	Female	36	72
Family history	No	49	98
	Yes	1	2
HTN	No	50	100
	Yes	0	0
DM	No	47	94
	Yes	3	6
Smoking	No	48	96
	Yes	2	4
History of blood Transfusion	No	45	90
	Yes	5	10
Bleeding during colonoscopy	No	36	72
	Yes	14	28

Clinical picture		Active No. = 50		Remission No. = 50		Test value	P-value
		N	%	N	%		
Abdominal Pain	No	18	30	30	60	5.769	0.016*
	Yes	32	64	20	40		
Bleeding per rectum	No	10	20	50	100	66.667	0.001**
	Mild	21	42	0	0		
	Moderate	14	28	0	0		
	Severe	5	10	0	0		
Diarrhea	No	0	0	2	4	43.086	0.001**
	Mild	5	10	33	66		
	Moderate	29	58	15	30		
	Severe	16	32	0	0		
Dysentery	No	39	78	50	100	12.360	0.001**
	Yes	11	22	0	0		
Bleeding with colonoscopy	No	45	90	50	100	5.263	0.022*
	Yes	5	10	0	0		

*SD; standard deviation, *Significant difference, **Highly significant difference.

In table 2 there were highly statistical significant difference as regards (Hb) and (WBC) and mild increases in PLT count in remission state in comparison with active state. There were highly statistical significant difference as regards (Neutrophil and N / L R) and statistical significant difference as regards (Monocyte) in both studied groups.

There were highly statistical significant difference as regards ESR and CRP (P-value <0.05) and statistical significant difference as regards S. albumin. There was highly significant elevation of f. calprotectin and f. calgranulin c levels in active group in comparison with remission group.

Table (2): Laboratory findings between both studied groups.

		Active UC	UC in Remission	t. test	p. value
Hb (gm/dl)	Mean ± S. D	18.81±1.31	11.75±1.20	3.699	**0.0**81**
WBC(thousand /cm)	Mean ± S. D	11866.68±697.79	8176.16±167.81	6.796	**0.001**
PLT(thousand /cm)	Mean ± S. D	693.66±66.99	313.24±76.41	1.638	8.666
Neutrophil(thousand/cm)	Mean ± S. D	6730.50±517.55	4373.00±186.63	6.670	0.001**
Lymphocyte(thousand/cm)	Mean ± S. D	3201.8±776.12	3036.14±752.96	0.826	0.411
Monocyte(thousand/cm)	Mean ± S. D	890.66±76.07	807.20±104.25	3.573	0.012*
N / L R	Mean ± S. D	2.44±0.5	1.56±0.36	3.910	0.001**
L / M R	Mean ± S. D	3.58±0.87	3.85±0.89	1.114	0.268
ESR 1 (mm)	Mean ± S. D	55 ± 12.8	15.5 ± 3.7	Z: 7.352	0.001**
ESR 2(mm)	Mean ± S. D	90 ± 20.7	30 ± 7.3	Z: 7.666	0.001**
CRP (mg/l)	Mean ± S. D	18 ± 4.2	5 ± 1.2	Z: 7.635	0.001**
S. Creatinine (mg/dl)	Mean ± S. D	1.26±0.31	1.15±0.28	T: 1.719	0.089
S. albumin (g/dl)	Mean ± S. D	3.74±0.30	3.91±0.37	T: 2.524	0.013*
F. Calprotectin (pg/ml)	Mean ± S. D	671.24±166.34	74.50±16.81	T: 11.402	0.001**
F. Calgranulin C (pg/ml)	Mean ± S. D	709.30±172.31	84.86±19.42	T: 11.687	0.001**

*Significant difference. **Highly significant difference. Hb, hemoglobin; WBC, white blood cells; PLT, platelets; N / L R, Neutrophil / lymphocyte ratio; L / M R, lymphocyte / Monocyte ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

In table 3 there were significant correlation between both F. calprotectin and F. calgranulin c levels with (Pulse) and some laboratory parameters (PLT, N / L R, S. albumin, ESR and CRP).

Table (3): Correlation between F. Calprotectin levels and Calgranulin C with different studied parameters

	F. Calprotectin		F. Calgranulin C	
	R	**P value**	**R**	**P value**
Age (years)	0.035	0.811	0.015	0.920
Disease Duration (years)	-0.030	0.836	-0.010	0.946
S –BP (mmhg)	-0.114	0.432	-0.092	0.524
D – BP (mmhg)	-0.109	0.453	-0.093	0.520
Pulse (b/m)	0.629	0.001*	0.622	0.001*
Temperature (c)	0.261	0.067	0.270	0.058
Hb (gm/dl)	-0.119	0.412	-0.102	0.481
WBC(thousand /cm)	0.157	0.276	0.149	0.301
Platelets (thousand /cm)	0.280	0.049*	0.305	0.042*
Neutrophil(thousand /cm)	0.258	0.071	0.259	0.070
Lymphocyte(thousand /cm)	-0.072	0.618	-0.087	0.549
Monocyte(thousand /cm)	0.101	0.486	0.085	0.559
N / L R	0.291	0.048*	0.299	0.043*
L / M R	-0.083	0.569	-0.095	0.514
S. Creatinine (mg/dl)	-0.049	0.737	-0.043	0.767
S. albumin (g/dl)	-0.324	0.022*	-0.312	0.027*
ESR 1 (mm)	0.646	0.001*	0.610	0.001*
ESR 2 (mm)	0.544	0.001*	0.507	0.001*
CRP (mg/l)	0.398	0.004*	0.386	0.006*

*Significant difference. **Highly significant difference. S –BP, systolic blood pressure; D – BP, diastolic blood pressure.

Table (4) demonstrates comparison between studied active UC patients regarding: I-Colonoscopic severity of UC: in which a) Mild cases were (26%) b) Moderate cases were (40%) c) Severe cases were (34%). II-Colonoscopic extension: in which a) Proctitis /segmoiditis (E1) cases were (14%) b) Lt sided colitis (E2) cases were (36%) c) pan colitis (E3) cases were (50%) III-Histopathology (Activity): in which a) Mild activity cases were (16%) b) Moderate activity cases were (32%) c) Marked activity cases were (52%).

Table (4): Colonoscopic finding and activity index of the studied patients with active UC.

Colonoscopy (Severity)	N	%
Mild	13	26
Moderate	20	40
Severe	17	34
Total	50	100
Endoscopic extension		
Ulcerative proctitis / segmoiditis (E1)	**:**	**47**
Lt sided colitis (E2)	**4;**	**69**
Pan colitis (E3)	**58**	**85**
Total	**85**	**455**
Histopathology (Activity)		
Mild	8	16
Moderate	16	32
Marked	26	52
Total	50	100

Table (5): Diagnostic performance of F. Calprotectin and F. Calgranulin C in predicting activity of UC.

	Cut off	AUC	Sensitivity	Specificity	Accuracy
F. Calprotectin (pg/ml)	160	0.916	92 %	90 %	91
F. Calgranulin C (pg/ml)	185	0.949	94 %	92 %	93

Table (9) demonstrates comparison between studied active UC patients regarding: I- F. Calprotectin: in which a) Cut off level was 160 pg/ml b) AUC was 0.916 c) Sensitivity was 92% d) Specificity was 90% e) Accuracy was 91. II- F. Calgranulin C: in which a) Cut off level was 185 pg/ml b) AUC was 0.949c) Sensitivity was 94% d) Specificity was 92% e) Accuracy was 93.
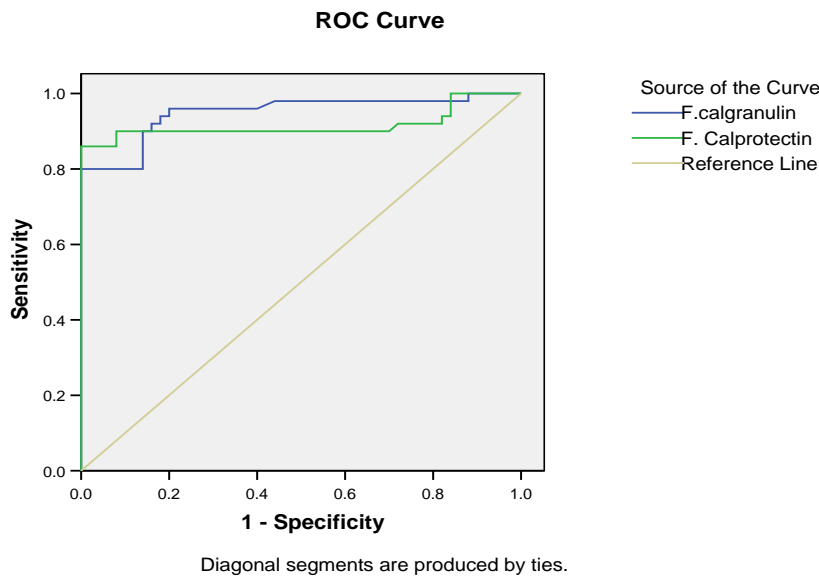
Fig. (1): Receiver Operator Curve (ROC) Analysis, demonstrates the diagnostic value of F. Calprotectin and F. Calgranulin C levels in predicting activity of UC .

DISCUSSION

The diagnosis of IBD, which presents a variety of variable symptoms and indications, continues to be difficult for clinicians. Distinguishing CD or UC from other gastrointestinal disorders, particularly from IBS, might be difficult in certain patients because of a mild or unusual appearance [13]. Many researches have looked at the importance of various fecal, serum, or mucosal indicators, including S100A8/9 and S100A12 protein family members [5-7].

In the present study, the age ranged from 20 to 70 years with a mean value (35.36 ± 10.43) years. This was close to **Hanauer** [14] **and Sandler et al.** [15]. Despite the fact that illness can happen at any age, they observed that the peak age of onset for IBD is between the ages of 15 and 30 years. Nevertheless, disagreeing with **Kiudelis et al.** [16] who claimed that the majority of UC patients had their diagnosis between the ages of 40 and 50 years.

In this study it was found that the majority of the patients were (72%) females while (28%) were males. This was in disagreement with **Bernstein et al.** [17] who reported that in UC population-based studies have shown no significant differences between sexes.

In the current study, as regards mean haemoglobin (Hb) levels, there was a statistical significant difference between UC (in exacerbation) 10.81±1.34 g/dl, and UC (in remission) 11.75 ± 1.20g/dl (P< 0.05).

This was close to **Gasche et al.** [18] who reported similar data that one third of IBD patients have hemoglobin level below 12 g/dl. **Ozlen et al.** [19] reported that the frequency of anemia in patients with UC was (55.7%). But these results are in disagreement with **Vermeire et al.** [20] who stated that Hb found to have no value in assessment of UC activity and could be replaced by an equally simple test as the hematocrit.

Regarding WBCs, in our study there was statistical significant difference between the mean white blood count for UC (in exacerbation) 11866.68±6897.79 x10^9 /L and for UC (in remission) was 8476.12 ± 1627.84 x10^9/L, which is within the normal reference range for age and sex (4.5-11.0 x10^9 /L). Our results are in agreement with **Mpufo and Ireland** [21], to a modestly raised leukocyte count is a sign of disease activity, whereas a marked elevation suggests the presence of an infection, or in CD of an abscess or other suppurative complication. But our results are in disagreement with **Desai et al.** [22] leucocytosis is not a helpful indicator of disease activity in clinical practice, since it is influenced by a number of other variables, such as the existence of an abscess, systemic glucocorticoids, and immunosuppressants.

In our study, the mean platelets (PLT) count for UC (in exacerbation) was 293.22± 62.99x10^9/L, whereas for UC (in remission) 313.24 ± 76.41 x10^9/L, which is within the normal reference range for age and sex (150-350 x109/L). Although **Desai et al.** [22] noted that platelets count correlates with disease activity in inflammatory bowel disease (IBD), they also noted that other factors, such as hemorrhage from other sites and iron deficiency anemia, can cause platelets count to rise. As a result, platelet count is not used in clinical practice in IBD.

Regarding neutrophils and N / L R, in our study, there was highly statistical significant difference between both studied groups (P-value<0.01). The mean neutrophils count for UC (in exacerbation) 6730.50 ±1517.55x10^9/L and for UC (in remission) was 4373.00 ± 1086.63 x10^9 /L, which is within the normal reference range for age and sex (2.5-7.0 x10^9/L) with slight elevation in UC (in exacerbation) than UC (in remission). According to the current findings, earlier research has shown that people with active UC had considerably higher NLR [25-26]. Moreover, our findings concur with those of **Torun et al.** [24], who found elevated NLR levels in active UC patients as compared to inactive UC patients and controls. Our findings conflict with those of **Cherfane et al.** [12], who claimed that NLR levels between individuals with active colonoscopy and those with quiescent colonoscopy were not substantially different.

In the current study, the mean monocyte count for UC (in exacerbation) was 890.66 ± 76.07 and for UC (in remission) was 807.20 ± 104.25, which is within the normal reference range for age and sex (200-800) with slight elevation in UC (in exacerbation) than UC (in remission) and this was statisticaly significant between both studied groups (P-value <0.01). These results are in agreement with according to **Cherfane et al.** [12], monocytosis and a low LMR can be used to identify individuals with active UC. Despite this, NLR levels in their research did not substantially differ between the two groups.

Our findings demonstrated that individuals with active UC had considerably higher blood levels of CRP and ESR than those with inactive UC (p 0.0001).

We discovered that the ESR sensitivity and specificity were 88% and 85%, respectively, by applying ROC curve analysis. This was in agreement with those of **Solem et al.** [25], increased CRP in UC patients was not connected with histologic inflammation but was substantially associated with severe clinical activity, an elevated ESR, and active illness.

As regards CRP in our study, we found highly significant difference between levels of CRP in UC (in exacerbation) compared with UC (in remission) (p value <0.001), with Mean 18±4.2 and 5±1.2 respectively and by using ROC curve analysis, we found that the CRP sensitivity and specificity was 86% and 91% respectively.

The same data reported by **Solem et al.** [25] **and Poullis et al.** [26] who disclosed that, for UC, CRP

broadly correlates with clinical activity. **Onal et al.** [27], patients with active UC had greater levels of CRP, ESR, and leukocyte count than patients with inactive UC, however the only difference that was statistically significant was seen in CRP. Similar findings were made by **Xiang et al.** [28], who discovered that patients with active UC had higher CRP and ESR levels than those with inactive UC and the control group.

In our study, we found significant difference between levels of serum albumin in UC (in exacerbation) compared with UC (in remission) (P-value <0.05), our results are in concordant with **Khan et al.** [29], through a variety of processes, including malnutrition, malabsorption, a quicker fractional albumin catabolic rate, and an increase in albumin transfer out of the vascular system, UC inflammation, can reduce albumin levels (3.5 gm/dL).

The present study revealed that there was a high significant level of F. calprotectin level in UC (in exacerbation) compared to UC (in remission) as the mean F. calprotectin level for UC (in exacerbation) was 671.24±166.34 pg/ml, UC patients in remission 74.50± 16.81 pg/ml. The diagnostic performance analysis revealed that at cut-off 160 pg/ml, the sensitivity and specificity were (92% and 90%) respectively with AUC was 0.916.

This was consistent with **Shimoyama et al.** [30] findings, which showed that in UC patients, the median FC level was lower in patients who obtained clinical remission compared to those who did not.

In the our study, there was a high significant level of F. calgranulin C level in UC (in exacerbation) compared to UC (in remission) as the mean F. calgranulin C level for UC (in exacerbation) was 709.30 ± 172.31 pg/ml and UC patients in remission was 84.86 ± 19.42 pg/ml. The diagnostic performance analysis revealed that at cut-off 185 pg/ml, the sensitivity and specificity were (94% and 92%) respectively with AUC was 0.949.

The current investigation found a significant relationship between certain intestinal inflammation (Platelets (P value 0.042), N/L R (P value 0.043), S. albumin (P value 0.027), ESR 1 (P value 0.001), ESR 2 (P value 0.001), and CRP (P value 0.006)) and fecal biomarkers (calprotectin and calgranulin C). Contrarily, a number of studies have revealed that clinical and endoscopic ratings have limited use in assessing the progression of illness.

Fecal calgranulin C was shown to distinguish between active and inactive UC with great diagnostic accuracy in this investigation. Moreover, the fecal calgranulin C test functions well regardless of where the illness is located. These results are comparable to calprotectin, a more reliable indicator of ulcerative colitis [31]. Similar findings were also reported by **De Jong et al.** [32].

The gold standard for diagnosis in the current study was histopathology. N/L R (P value 0.043),

ESR 1 (P value 0.001), ESR 2 (P value 0.001), and CRP (P value 0.006) indicate that the invading neutrophils are the predominant source of fecal calgranulin C, which is correlated with intestinal tissue inflammation. Infiltrating neutrophils are the primary source of fecal S100A12, according to **Kaiser et al.** [33] research, which demonstrated that immunohistochemistry labelling of tissue sections verified S100A12 (calgranulin C) expression in the gut of patients with active IBD more than inactive illness. Similar to **Foell et al.** [34], who found higher S100A12 levels in a sample of 74 adult patients with IBD, 40 of whom had CD and 34 had UC. Active CD (470–125ng/mL) and active UC (401–20ng/mL) had higher levels of S100A12 than healthy people (75–15ng/mL).

In our study we found positive correlations between S100A12 and well known marker of inflammation CRP. Our results are in agreement with those conducted by **Manolakis et al.** [35].

In the current study there is a statistical positive correlation was found between Calgranulin C levels in UC patients and ESR. This can be explained by a research by **Desai et al.** [24] who found that ESR is an indirect indicator of plasma acute phase protein content and is impacted by both the shape of erythrocytes and certain plasma components, such as immunoglobulins.

Also there is a significant positive correlation between calgranulin C and the endoscopic picture regarding degree of severity in UC patients as mean value of calgranulin C in patients with mild disease activity in colonoscopy was 396.92± 151.79 pg / ml, in patients with moderate disease activity in colonoscopy was 570.25± 234.16 and in patients with high disease activity in colonoscopy was 1111.76 ± 273.59 pg / ml. Similarly **Foell et al.** [34] reported that S100A12 (calgranulin C), was more prevalent in endoscopically active UC than inactive illness. Few neutrophils are still present in intestinal tissue even in dormant illness, which may be the cause of these individuals' increased numbers. Hence, S100A12 can be a particularly sensitive marker of lingering disease activity. S100A12 may potentially be a helpful marker in identifying IBD recurrence since neutrophil influx occurs very early in the inflammatory phase of IBD.

CONCLUSION

Fecal calgranulin C could be used to forecast the activity and severity of UC, making it possible to monitor the disease's progression in such individuals without the need for frequent endoscopic evaluation. When fecal calgranulin C is combined with blood laboratory inflammatory indices (CRP), NLR and LMR are more helpful. They may also be used to predict the endoscopic activity of the UC to avoid invasive endoscopies.

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