



Fecal Calprotectin in Assessment of Ulcerative Colitis Activity

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Authors' contributions

This work was carried out in collaboration between the two authors. Author BAAA planned and designed the study, wrote the protocol, collected the samples, participated in the interpretation of the results and analysis, drafted and critically revised the manuscript. Author ESK participated in planning and designing the study, sample collection performed the practical laboratory activities, participated in the interpretation of the results. Both authors read and approved the final manuscript.

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ABSTRACT

Background: It is important to evaluate the activity of inflammatory bowel disease (IBD) for the treatment. Fecal Calprotectin has been shown to be excellent marker of intestinal inflammation because it is simple, rapid, sensitive, specific, inexpensive and noninvasive to detect and monitor intestinal inflammation.

Aim: The aim of this prospective study was to evaluate the role of fecal calprotectin in diagnosis and assessment of activity of ulcerative colitis.

Methods: Prospective cross sectional study was conducted to involve thirty patients with UC and five as control. The included patients attended the gastrointestinal endoscopy clinic of the departments of internal medicine in AL-Quwayyah General Hospital, Riyadh, KSA. The study was carried out for six months from August – 2015 to January – 2016. All patients underwent lower GI fiberoptic endoscopy (proctosigmoidoscopy, ES450WE5- Fujinon and colonoscopy, EC 530

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WL-Fujinon) with multiple biopsies from each patient and sent to histopathology laboratory. The patients' disease activities were assessed according to Montreal classification and Mayo subscore. Calprotectin was measured by enzyme linked immuno-sorbent assay (ELISA) method (Calprotectin ELISA Kit, Immundiagnostik AG, Bensheim, Germany). CRP and ESR were measured in the clinical laboratory, AL-Quwayyah General Hospital, Riyadh, KSA, based on the instructions provided by the reagent manufacturer.

Results: Of the patients 25 presented by active UC ranging from mild to severe picture and 5 patients were in remission. According to endoscopic Mayo score: 5(16.67) showed Mayo score 0 (remittent patients); 8(26.67%) showed Mayo score 1; 13(43.33%) showed Mayo score 2; 4(13.33%) showed Mayo score 3. The extent of UC according to Montreal classification was total (extensive) colitis 6(24%); left-sided colitis, 12(48%); and proctitis, 7(28%). There was a high significant difference in the fecal calprotectin concentration between the patients with active UC and the patients with inactive UC ($P < 0.001$). The FC concentration was significantly greater in the patients with inactive UC than in the controls ($P < 0.001$). As regard CRP and ESR; the patients with active UC had higher levels of CRP and ESR than the patients with inactive UC and the controls ($P < 0.001$), but there was no significant difference between the patients with inactive UC and the controls. Calprotectin had a good correlation with the disease activity that the concentration was greater in severe cases than in moderate and mild cases and this difference was highly statistically significant ($P < 0.001$).

Also CRP concentration in severe cases was greater than in moderate and mild cases and in comparison the difference was statistically significant ($P < 0.002$). ESR concentration was higher in severe cases than moderate and mild cases but there was only statistical significant difference as regard severe and mild cases not between moderate and mild cases.

Conclusion: Fecal calprotectin is a biomarker that could differentiate active from inactive UC and our results suggest that FC can be used as a valuable, simple, noninvasive diagnostic tool for UC compared with other markers such as CRP and ESR. Keywords: ulcerative colitis, fecal calprotectin and enzyme linked immunosorbent assay (ELISA).

Keywords: Ulcerative colitis; fecal calprotectin; enzyme linked immunosorbent assay (ELISA), disease activity and endoscopy.

1. INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease characterized by remission and exacerbation of disease activity [1].

It is important to evaluate the activity of the disease for the treatment of IBD. The evaluations of the activity of IBD have been mainly achieved by clinical, laboratory and endoscopic disease activity indices. C-reactive protein (CRP), erythrocyte sedimentation rate and white blood cells are widely used as noninvasive parameters for IBD [2,3]. But none of them are specific for gut inflammation [4]. Colonoscopy and biopsy are useful in the assessment of intestinal mucosa inflammation of patients with UC, but these examinations can be a heavy burden to the patient [5,6]. A number of neutrophil-derived proteins in stools have been studied, including fecal calprotectin [3]. Fecal biomarkers are valuable tools because of simple, rapid, sensitive, specific, inexpensive and noninvasive to detect and monitor intestinal inflammation in

IBD [7]. Fecal Calprotectin has been shown to be excellent marker of intestinal inflammation, as it reflects the migration of neutrophils through the inflamed bowel wall to the mucosa [8].

Fecal calprotectin (FC), a 36-kDa calcium and zinc binding protein, represents 60% of the cytosolic protein in the granulocytes [3]. The amount of calprotectin in feces is therefore proportional to the amount of neutrophil migration from the inflamed bowel wall to the mucosa [9]. Additionally, the FC concentration is stable for up to 7 days at room temperature and resistant to degradation [10]. Compared with conventional serum markers, FC is a more promising marker for assessing intestinal activity with endoscopy as a reference [11]. FC has a good diagnostic precision for the differentiation of organic and functional intestinal diseases. A high concentration of calprotectin in feces represents a strong argument to carry out a colonoscopy in order to rule out the presence of IBD or other organic pathologies. Parallelism between FC levels and IBD activity has been confirmed, although this fecal marker appears to better

reflect the disease activity in UC than in CD. The capacity of FC's to predict relapse of IBDs is promising. It has been suggested that, in IBD patients receiving treatment, a normalization or decrease in FC concentrations is an accurate indicator of endoscopic healing. Greater FC concentration has been found in asymptomatic first-degree relatives of patients with IBD, suggesting that there is a high prevalence of subclinical intestinal inflammation in them [12].

2. SUBJECTS AND METHODS

2.1 Study Subjects

Thirty patients with UC and five as control were included at AL-Quwayiyah General Hospital, Riyadh, KSA. The study was carried out for six months from August – 2015 to January – 2016. The included patients attended the gastrointestinal endoscopy clinic of the departments of internal medicine in AL-Quwayiyah General Hospital, Riyadh, KSA. Twenty five patients came presented with manifestations of active UC mainly in the form of bleeding per rectum, chronic dysentery, chronic diarrhea with mucous and five patients were asymptomatic and came for follow up. All patients underwent lower GI fiberoptic endoscopy (proctosigmoidoscopy, ES450WE5-Fujinon and colonoscopy EC 530 WL-Fujinon) with multiple biopsies from each patient, from the site of the lesions. Sterile biopsy forceps were used and the flexible endoscopies and biopsy forceps were sterilized by cidex for at least 20 minutes, then washed with sterile saline. The biopsies preserved in formaline 10% and sent to histopathology laboratory in the regional laboratory and blood bank, Riyadh, KSA. The patients' disease activities were assessed according to Montreal classification which assesses the extent of disease and severity of symptoms, both of which have important prognostic value. The extent of disease is classified as mucosal changes on endoscopy limited to the rectum (E1), the left side of the colon, (E2) and beyond the splenic flexure (E3). The symptom severity score ranges from none (S0) to severe systemic manifestations (S3) [13]. Also the disease activity assessed by Mayo subscore, while the clinical remission defined as total subscore < 1 with no rectal bleeding [14]. Of the patients, 25 were hospitalized.

Control group consisted of five healthy subjects who showed no evidence of clinical manifestation or laboratory investigation suggesting UC and no

abnormalities detected under sigmoidoscopy and colonoscopy.

Demographic characteristics were shown in Table 1.

2.2 Stool Collection and Measurement of Fecal Calprotectin

Fecal samples were taken within one week before or after endoscopic examination and the stool samples were stored at -70°C until the time of measurement.

Calprotectin was measured by enzyme linked immunosorbent assay (ELISA) method (Calprotectin ELISA Kit, Immundiagnostik AG, Bensheim, Germany). CRP and ESR were measured in the clinical laboratory, AL-Quwayiyah General Hospital, Riyadh, KSA, based on the instructions provided by the reagent manufacturer.

2.3 Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 16 soft ware (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean \pm standard deviation, median and range. Chi square test (X²), or Fisher's exact test (FET), "Z" test were used to analyze categorical variables. Quantitative data were tested for normality using Kolomogrov Smirnov test, and proved to be non parametric. So, Mann Whitney U (MWU) test, Krauskal Wallis test (KWT) was used at 0.05 level of significance. Significant KWT was followed by post hoc multiple comparisons using Bonferroni adjusted Mann Whitney U test at adjusted P=0.017 to detect significant pairs. ROC curve was used to determine cutoff value of FC, CRP & ESR with optimum sensitivity and specificity in prediction of UC activity.

P value >0.05 is non significant (NS)

P<0.05 is significant (S)

P≤0.001 is highly significant (HS)

3. RESULTS

In this study 30 patients with UC and 5 as controls were allocated and the main demographic variables of the included patients are presented in (Table 1). The mean age was 41.8 \pm 13 in the UC patients and was 32.9 \pm 8.92 in the control group, and 19(63.33%) were males

among the UC patients. The mean duration of the UC was 13.6 ± 9.4 years.

3.1 Colonoscopic Findings

Of the patients 25 presented by active UC ranging from mild to severe picture and 5 patients were in remission. According to endoscopic Mayo score: 5(16.67) showed Mayo score 0 (remittent patients); 8(26.67%) showed Mayo score 1; 13(43.33%) showed Mayo score 2; 4(13.33%) showed Mayo score 3.

The extent of UC according to Montreal classification was total (extensive) colitis 6(24%); left-sided colitis, 12(48%); and proctitis, 7(28 %).

3.2 Concentrations of Fecal Calprotectin, CRP and ESR in Patients with UC and in Controls

There was a high significant difference in the fecal calprotectin concentration between the patients with active UC and the patients with inactive UC ($P < 0.001$) (Table 2, Fig. 1).

The FC concentration was significantly greater in the patients with inactive UC than in the controls ($P < 0.001$).

As regard CRP and ESR; the patients with active UC had higher levels of CRP and ESR than the patients with inactive UC and the controls ($P < 0.001$), but there was no significant difference between the patients with inactive UC and the controls.

3.3 The Concentrations of Fecal Calprotectin, CRP and ESR with the Disease Activity (Mayo Score) in UC Patients

As shown in Table 3 and Fig. 2, the concentrations of fecal.

Calprotectin had a good correlation with the disease activity that the concentration was greater in severe cases than in moderate and mild cases and this difference was highly statistically significant ($P < 0.001$).

Also CRP concentration in severe cases was greater than in moderate and mild cases and in comparison the difference was statistically significant ($P < 0.002$).

ESR concentration was higher in severe cases than moderate and mild cases but there was only statistical significant difference as regard severe and mild cases not between moderate and mild cases.

3.4 Results of Receiver-operator Characteristic Analyses

Fig. 3 shows the ROC graphs for FC, CRP and ESR values. The AUC with 95% confidence interval (CI) of all biomarkers is shown in Table 4. Specificity was highest for fecal calprotectin, and lowest for ESR. The specificity rates for fecal calprotectin, CRP and ESR were 90%, 80% and 70% respectively. The sensitivity for fecal calprotectin was relatively high, but was relatively low for CRP and was lowest for ESR. The sensitivity rates for fecal calprotectin, CRP and ESR were 96%, 88% and 84%, respectively. The ROC curves showed the trade-off between specificity and sensitivity for fecal calprotectin (the area under the curve, AUC, 0.954; 95%CI 0.89-1.0; $P < 0.001$), for CRP (AUC, 0.944; 95%CI 0.87-1.0; $P < 0.001$) and for ESR (AUC, 0.812; 95%CI 0.63-0.99; $P < 0.001$). The AUC of fecal calprotectin was relatively greater than that of CRP and was more greater than ESR.

4. DISCUSSION

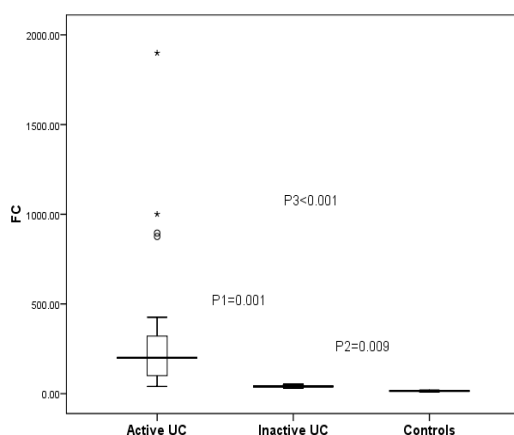
Chronic remission and exacerbation of inflammation of the gastrointestinal tract is the hallmark of UC. Infiltration of the neutrophils into the inflamed mucosa at an early stage of inflammation is considered one of the most prominent histological features observed in UC. Neutrophils are a major source of inflammatory cytokines one of them is the fecal calprotectin [15,16].

Routine colonoscopy in patients with UC is costly, invasive and has associated morbidity and mortality. Serum markers of inflammation such as C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in isolation are not sufficiently sensitive or specific for the diagnosis of UC [17].

In the current study the mean age was 41.8 ± 13 in the UC patients and most of the patients were males 19/30 (63.33%) and this is in agreement with Yamaguchi. [18] who found that mean age was around 45 and most of patients were males in his study.

Table 1. Demographic data of the subjects

Variable	UC (n=30)	Control (n=5)	Test of sig	P
Gender (NO.male /female)	19/11	5/0	FET	0.26 (NS)
Age (yr. mean, range)	41.8±13.1 (25-64)	32.9±8.92 (28-40)	MWU=1.23	0.22 (NS)
Disease duration (yr. mean, range)	13.6±9.4 (0-32)	-	---	---
Active smoker	8/30 (26.67%)	1/5 (20%)	Z=0.32	0.75 (NS)
Family history	5/30 (16.67)	2/5 (40)	Z=1.2	0.22 (NS)
Extra-intestinal manifestations	4/30 (13.33)	0.0	Z=0.89	0.38 (NS)
Extent of disease (montreal classification) (n=25)				
E1	7 (28%)	--		
E2	12 (48%)	---		
E3	6 (24%)	---		
Mayo score (endoscopic item): 0 (healthy & inactive)	5 (16.67%)	5 (100%)	X ² =14.6	0.002 (S)
1	8 (26.67%)	0.0		
2	13 (43.33%)	0.0		
3	4 (13.33%)	0.0		

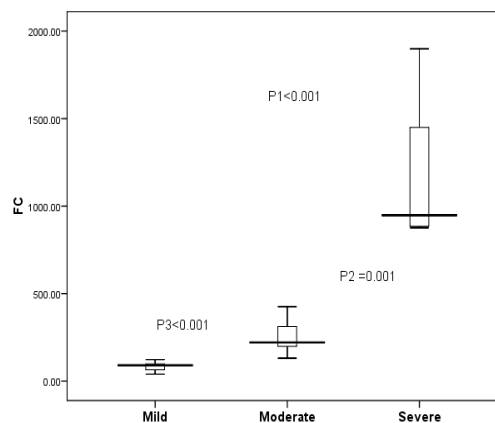
**Fig. 1. Concentration of FC in the UC patients and controls**

P1 between active and inactive, P2 between inactive and controls and P3 between active and controls

In the present study according to endoscopic Mayo score: 5(16.67) showed Mayo score 0 (remittent patients); 8(26.67%) showed Mayo score 1; 13(43.33%) showed Mayo score 2; 4(13.33%) showed Mayo score 3 this was similar to a study carried out by Takashima et al. [19] who found that most of cases with active UC were Mayo score 2 followed by Mayo score 1 then lastly Mayo score 3.

The extent of UC in this study was total (extensive) colitis 5(20%); left-sided colitis, 9(36%); and sigmoidoproctitis, 11(44%) and this was similar to the results of Langholz et al. [20],

who found that approximately 45% of patients have colon inflammation limited to the rectosigmoid, 35% have inflammation extending proximal to the sigmoid, and 20% have extensive colitis.

**Fig. 2. Concentration of FC in UC patients as regard grades of activity**

P1 between mild and severe, P2 between moderate and severe and P3 between mild and moderate

The presence of active gut inflammation in patients with IBD is associated with an acute phase reaction and migration of leucocytes to the gut, and this is translated into the production of several proteins, which may be detected in serum or stools [3]. On resolution of the event which triggered the production of these proteins, their concentrations will return to normal levels but not all with the same speed [21].

Table 2. Comparing the studied groups regarding FC, CRP and ESR

Variable	Active UC (N=25)		Inactive UC (N=5)		Controls (N=5)		KWT	P
	Mean \pm SD	Median (range)	Mean \pm SD	Median (range)	Mean \pm SD	Median (range)		
FC	346.6 \ddagger \pm 417.6	200.2 (39.88-1899.19)	42 \pm 10.3 \dagger	40 (30-55)	14.8 \pm 4.3	15 (10-20)	20.6	<0.001 (HS)
CRP	22.3 \ddagger \pm 19.5	19 (5-100)	6.6 \pm 2.4	6(4-10)	4 \pm 1.2	4 (2-5)	17.3	<0.001 (HS)
ESR	31.4 \ddagger \pm 14.5	25 (12-60)	10.2 \pm 3.4	11(6-15)	6.2 \pm 2.6	5 (4-10)	20.7	<0.001 (HS)

 \dagger →Sig in comparison with controls \ddagger → Sig in comparison with inactive

KWT→Kruskal Wallis Test (Posthoc multiple comparisons were done using Bonferroni adjusted Mann Whitney U test at adjusted P at 0.017)

Table 3. Comparing FC, CRP and ESR among active UC patients according to Mayo score

Variable	Mild active UC (N=8)		Moderate active UC (N=13)		Severe active UC (N=4)		KWT	p
	Mean \pm SD	Median (Range)	Mean \pm SD	Median (Range)	Mean \pm SD	Median (Range)		
FC	83.8 \pm 25.8	90.6 (39.88-122.43)	255.6 \pm 92.3	220.8 (131.17-425.81)	1167.8 \ddagger \pm 490.6	948 (876.12-1899.18)	19.8	<0.001 (HS)
CRP	10.4 \pm 4.7	9.5 (5-18)	20.7 \pm 8.9	20 (7-35)	51.3 \ddagger \pm 34.2	40 (25-100)	12.5	0.002 (S)
ESR	20.1 \pm 6.3	18.5 (15-35)	32.5 \pm 13.5	30 (12-55)	50 \pm 7.1 \dagger	47.5 (45-60)	10.9	0.004 (S)

 \dagger →Sig in comparison with mild \ddagger → Sig in comparison with moderate

KWT→Kruskal Wallis Test (Posthoc multiple comparisons were done using Bonferroni adjusted Mann Whitney U test at adjusted P at 0.017)

Table 4. Specificity and sensitivity for fecal calprotectin, CRP and ESR

Score (cut-off)	Sens%	Spec%	PPV%	NPV%	Accuracy%	AUC	95%CI	P
FC> 57.76 μ g/g	96%	90%	96%	90%	94.3%	0.954	0.89-1.0	<0.001 (HS)
CRP>7.5 mg/l	88%	80%	91.7%	72.7%	85.7%	0.944	0.87-1.0	<0.001 (HS)
ESR>15.5 mm/h	84%	70%	87.5%	63.6%	80%	0.812	0.63-0.99	0.004 (S)

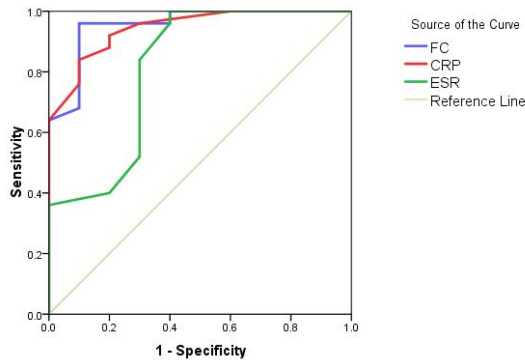


Fig. 3. ROC curve for the validity and predictivity of FC, ESR and CRP in prediction of active UC

ESR depends on the plasma concentration and on the number and size of the erythrocytes [22]. Compared with CRP, ESR will peak much less rapidly and may also take several days to decrease, even if the clinical condition of the patient or the inflammation is ameliorated [20]. The ESR is a crude assessment of disease activity. In ulcerative colitis (UC), where clinical, endoscopic and histological activity is used to assess the overall disease, the correlation between ESR and disease activity is good. However, it may be normal in proctitis and proctosigmoiditis [23].

In the present study the patients with active UC had higher levels of CRP and ESR than the patients with inactive UC and the controls ($P < 0.001$), but there was no significant difference between the patients with inactive UC and the controls and this was in agreement with Xiang et al., 2008 who found that The patients with active UC had higher levels of CRP and ESR than the patients with inactive UC and the controls ($P < 0.05$), but there was no significant difference between the patients with inactive UC and the controls [24]. Elevated ESR and CRP values in patients with active UC have been reported by other studies [17,24]. Moreover, Canani et al. [25] and Langhorst et al. [26] reported high specificity, both for CRP and ESR, although with a markedly lower sensitivity than fecal markers in the diagnosis of disease activity in IBD.

In the current study, there was a highly significant increase in the mean value of fecal calprotectin in the patients with active UC in comparison with the patients with inactive UC and control. Also There was a highly significant increase in the mean value of fecal calprotectin

in the patients with inactive UC in comparison with the controls. This results was supported by Xiang et al. [24] who found the same results, also supported by Watanabe et al. [27] who found in his study that the Fecal Cal. level was significantly higher in UC group than in the control group (Cal, UC $P < 0.05$).

In the current study, Calprotectin had a good correlation with the disease activity that the concentration was greater in severe cases than in moderate and mild cases and this difference was highly statistically significant ($P < 0.001$), this was in agreement with Watanabe et al., 2013 who found that all fecal biomarkers were significantly correlated with disease activity in UC (Cal, $r = 0.789$), Fecal Cal. levels were significantly higher in the active phase than in the inactive phase (Cal, $P < 0.001$), also Watanabe et al. [27] found that endoscopically active UC patients showed significantly higher fecal Cal. levels than inactive UC patients by Mayo endoscopic subscore (Cal, $P < 0.001$). A study by Zittan et al. [28] observed that in UC, FC correlated with clinical Mayo score ($r = 0.63$, $P < 0.0001$). This correlation was strengthened by adding the endoscopic subscore ($r = 0.90$, $P < 0.0001$). The endoscopic subscore also independently correlated with FC ($r = 0.96$, $P < 0.0001$). Also Xiang et al. [24] found that the concentrations of fecal calprotectin, CRP and ESR in UC had a good correlation with disease activity index. The correlation coefficient between disease activity index and the concentrations of fecal calprotectin, CRP and ESR were 0.866, 0.492 and 0.433 respectively. This association was strongest for fecal calprotectin and weakest for ESR [23]. Similarly Lobatón and colleagues evaluated the ability of FC to predict endoscopic activity according to the Mayo score in 123 patients with UC. They found that FC was an accurate marker of endoscopic remission in UC [29].

In the present study, Specificity was highest for fecal calprotectin, and lowest for ESR. The specificity rates for fecal calprotectin, CRP and ESR were 90%, 80% and 70% respectively. The sensitivity for fecal calprotectin was relatively high, but was relatively low for CRP and was lowest for ESR. The sensitivity rates for fecal calprotectin, CRP and ESR were 96%, 88% and 84%, respectively.

This was relatively in agreement with Xiang et al. [24] who found that the fecal calprotectin had a 91.9% sensitivity and a 79.4% specificity for

making a differentiation between active UC and inactive UC. These results were significantly better than those obtained with CRP and ESR.

In the present study, The ROC curves showed the trade-off between specificity and sensitivity for fecal calprotectin (the area under the curve, AUC, 0.954; 95%CI 0.89-1.0; $P < 0.001$), for CRP (AUC, 0.944; 95%CI 0.87-1.0; $P < 0.001$) and for ESR (AUC, 0.812; 95%CI 0.63-0.99; $P < 0.001$). The AUC of fecal calprotectin was relatively greater than that of CRP and was more greater than ESR. This was in agreement with Schoepfer and colleagues who evaluated the correlation between endoscopic activity and FC, CRP, PLT, TLC, and the clinical score (Lichtiger Index). They found that endoscopic disease activity correlated best with FC, followed by the Lichtiger Index, CRP, TLC, and PLT count. FC was the only marker that could discriminate between different grades of endoscopic activity. FC with a cut-off of 57 $\mu\text{g/g}$ had a sensitivity of 91% and a specificity of 90% to detect endoscopically active disease [30]. Also a study by Lin et al. [31], the AUC for fecal calprotectin in UC was 0.93 (0.89-0.97).

Similarly Mohamed et al. 2013 carried out a study on 40 patients. Twenty of these patients had UC and 20 patients as controls, he found that there was a highly significant increase in the mean value of fecal calprotectin in active UC patients in comparison with the inactive UC patients and controls. Also, there was a highly significant increase in the mean value of fecal calprotectin in the inactive UC patients in comparison with the controls. There was also a highly significant positive correlation between fecal calprotectin and UCAI, CRP, ESR, total leukocyte count, and platelets count. At the cutoff value of 131 $\mu\text{g/g}$, fecal calprotectin has 100% accuracy, sensitivity, specificity, positive predictive value, and negative predictive value in differentiating UC patients from other patients with lower gastrointestinal symptoms and at the cut-off value of 253 $\mu\text{g/g}$ fecal calprotectin has 95% accuracy, sensitivity, specificity, positive predictive value, and negative predictive [32].

Also Schoepfer and colleagues reported similar results in patients with IBD; endoscopic disease activity correlated best with FC ($R = 0.834$), followed by the Clinical Activity Index ($R = 0.672$), CRP ($R=0.503$), and blood leukocytes ($R = 0.461$). The overall accuracy of calprotectin in detecting endoscopically active disease was 89% and it was the only marker to discriminate

inactive, mild, moderate, and highly active disease value in differentiating active from inactive UC patients [33].

5. CONCLUSION

Evaluations of the activity of IBD is important for treatment. The present study demonstrated close associations between fecal biomarkers (FC) and ulcerative colitis activity. The results of this study suggests that fecal calprotectin reflects the degree of intestinal inflammation, and could be a promising noninvasive diagnostic tool for evaluation of the activity in patients with UC.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

Ethical clearance was obtained from the ALQuwayiyah General hospital's ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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