Original article

Serum Amyloid A as a Biomarker of Ulcerative Colitis Disease Activity

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Abstract

Background: Ulcerative colitis is a chronic inflammatory disease characterized by episodes of remission and exacerbation. Patients typically presented by bloody diarrhea, abdominal pain and loss of weight. Various pro-inflammatory cytokines are currently known to play an important role in the pathogenesis of IBD. Serum amyloid A belongs to the family of acute-phase reactants. **Objectives:** the study aimed to assess the clinical usefulness of serum amyloid A in predicting the disease activity in ulcerative colitis patients in comparison to fecal calprotectin and C-reactive protein. **Patients and methods:** A total of 90 patients with UC presented for colonoscopy were included. Socio-demographic, clinical and laboratory data were recorded and patients were classified into inactive, mild, moderate and severe according to The Simple Clinical Colitis Activity Index and Mayo endoscopic sub score. FC, CRP and SAA were measured, and their association with endoscopic scores was evaluated. **Results:** Serum amyloid A and fecal calprotectin were significantly lower in remission than activity. Serum amyloid A at cut off value >3.97µg\ml could discriminate active from remittent patients, the sensitivity, specificity, PPV, NPV and accuracy were (84.44, 55.56, 65.5, 78.1 and74.2% respectively). Regarding fecal calprotectin; at cut off value >100µg\mg it could distinguish between activity and remission with sensitivity, specificity, PPV, NPV and accuracy were (88.89, 86.67, 87.0, 88.6 and 93.9% respectively). However, both marker showed no significant difference between the different grades of activity. **Conclusion:** Serum amyloid A level was significantly higher in active cases than remittent cases, however it could not differentiate between the different grades of ulcerative colitis activity.

Key Words: Ulcerative colitis, serum amyloid A, C-reactive protein, fecal calprotectin

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) are chronic diseases of unknown etiology. Dysregulation of host immune response to intestinal microbiome in genetically susceptible individuals is proposed as an underlying pathogenic mechanism [1].

Ulcerative colitis (UC) is limited to the colon with major involvement of mucosa. Patients with ulcerative colitis (UC) typically manifest symptoms such as rectal bleeding, persistent bloody diarrhea, increased stool frequency, abdominal pain and loss of weight [2]. Typically, patients with IBD follow a disease course consisting of alternating exacerbations and periods of remission [3].

The diagnosis of ulcerative colitis is best made with endoscopy and mucosal biopsy for histopathology. Laboratory studies are helpful to exclude other diagnoses and assess the patient's nutritional status, but serologic markers can assist in the diagnosis of inflammatory bowel disease [4]. Various pro-inflammatory cytokines are currently known to play an important role in the pathogenesis of IBD [5]. Cytokines have been shown to modulate the intestinal immune system by increasing the expression of adhesion factors on endothelial cells enabling transmigration of phagocytes and lymphocytes to sites of inflammation [6 & 7].

Serum amyloid A (SAA) is an apolipoprotein of high-density lipoproteins (HDL) and belongs to the family of acute-phase reactants. It is produced predominantly by hepatocytes, besides it has been reported that it is also produced extra hepatically (Intestinal epithelium) upon enhanced serum levels of pro-inflammatory cytokines, such as TNF- α and IL-6, and is enhanced in several chronic inflammatory diseases [8 & 9].

Its concentration increases dramatically during acute inflammation and injury, within 5-6 hours levels that are 1000-fold greater than normal and slowly return to normal within several days [10] .These proteins have several roles, including the transport of cholesterol to the liver for secretion into the bile, the recruitment of immune cells to inflammatory sites, and the induction of enzymes that degrade extracellular matrix, and also implicated in several chronic inflammatory diseases, such as amyloidosis, atherosclerosis, and rheumatoid arthritis [11]

Irrespective of its role in disease development, SAA has been shown to be the most sensitive acute-phase protein in IBD (when compared to other acute phase

proteins, such as alpha-1antichymotrypsin (alpha-1-ACT) and alpha-1-acid glycoprotein (alpha-1-AGP), or even CRP [12]. Therefore, SAA may be of added value as inflammatory biomarker in monitoring the acute phase reaction, besides CRP [13].

Fecal calprotectin (FC) and serum C-reactive protein (CRP) levels are widely used and considered predictive markers for the degree of inflammation, but also show inconsistent correlation with mucosal inflammation when compared to endoscopy [14, 15 & 16]

CRP is limited by the lack of specificity to inflammation within the gut. Although fecal calprotectin (FC) correlates with disease activity status in IBD patients [17], the low compliance of collecting stool samples and/or the difficulty of collecting diarrhea samples frequently disturbs/interferes adversely with clinical monitoring [18]

Therefore, novel serum biomarkers with high diagnostic accuracy for detection of mucosal inflammation are still needed. Furthermore, these serum biomarkers should be validated and routinely available in daily practice.

Aim of the study:

The current study aimed to assess the value of serum amyloid A in the prediction of ulcerative colitis disease activity in

comparison to other biomarkers such as CRP and fecal calprotectin.

Patients and methods

Study design:

This study was designed as a cross sectional observational study conducted on 90 consecutive patients with UC attending the inflammatory bowel disease (IBD) clinic at Benha University Hospital and Mahalla Hepatology Teaching Hospital for colonoscopy from January 2021 to February 2022. All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study protocol was approved from the ethical committee of scientific research of Benha faculty of medicine. (Study no. Ms.22.6.2021)

Study population:

The studied patients were presented with different grades of ulcerative colitis disease activity. Patients were classified into mild, moderate, severe and remission according to The Simple Clinical Colitis Activity Index (SCCAI) and Mayo endoscopic sub score. All studied patients were subjected to the following; clinical assessment by full history taking (age, sex, residence,

occupation, special habits, medications, operations) and thorough clinical examination to detect signs of inflammatory bowel disease. Laboratory investigations were done including CBC (Sysmex, XF-5100, USA), C-reactive protein (CRP) by turbidity method (Biosystem, spain), fecal calprotectin by ELISA kit catalog. No CAL35-K01 (Eagle Biosciences, Inc.), stool analysis and serum level of amyloid A.

Serum amyloid A measurement:

A venous blood sample of 5 ml was obtained from each patient to be put into a plain vacutainers and was left for about 20-30 mins to coagulate. All samples were centrifuged and the sera were separated and kept frozen at -20° C for further analysis. All sera samples were subjected

to serological detection of amyloid A by enzyme linked immunosorbent assay (ELISA) according to the manufacturer's instructions of (Sun Red Biotechnology company -China) ®.

Clinical activity assessment:

Clinical activity was assessed by The Simple Clinical Colitis Activity Index (SCCAI). The score was determined by asking the person with colitis questions regarding: bowel frequency at day/night, urgency of defecation, blood in stool, general health, extra intestinal manifestations. The calculated score ranges from 0 to 19, where active disease is a score of 5 or higher[19].

Table 1. The simple clinical colitis activity index (SCCAI).

Bowel frequency (number of stools per day)	0-3 = 0 points 4-6 = 1 points 7-9 = 2 points >10 = 3 points
Number of stools per night	0 = 0 points 1-3 = 1 point >4 = 2 points
Urgency of stool	None = 0 points Hurry = 1 point Immediately= 2 points Incontinence = 3 points
Blood in stool	None = 0 points Trace = 1 point Occasionally (<50% of stool) = 2 points Usually (>50% of stool) = 3 points
General well-being	Very well = 0 points Slightly below = 1 points Poor = 2 points Very poor = 3 points Terrible = 4 points
Extra colonic features	Arthritis = 1 point Uveitis = 1 point Erythema nodosum = 1 point Pyoderma gangrenosum = 1 point

Endoscopic assessment:

Degree of mucosal inflammation was evaluated by endoscopic examination by use Mayo endoscopic sub score that is a hybrid between clinical and endoscopic variables; stool frequency, bleeding, inflammatory activity on sigmoidoscopy, overall physician assessment and daily activities of the patient are assessed. According to colonoscopy, mucosal appearance is classified into mild disease (erythema, decreased vascular pattern, mild friability), moderate disease (marked erythema, absent vascular pattern, friability, erosions) and severe disease (spontaneous bleeding, ulceration). Mucosal healing is diagnosed with an endoscopic sub score of 0 or 1[20]

Histological examination:

Biopsies of the colon are confirmatory for diagnosis when specimens showing findings consistent with chronic inflammatory changes. In most cases, pathologic examination reveals disease limited to the mucosal layers with paneth cell metaplasia, mucin depletion, and distortion of crypt architecture, crypt abscess and infiltrates of the mucosa with lymphocytes, plasma cells and granulocytes [21]

Statistical analysis:

Statistical presentation and analysis of the present study was conducted by SPSS V20. The numerical data was expressed in the form of the mean and standard deviation. The categorical data was presented as numbers and percentage. Analysis of our study depended on student t- test, paired t-test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests. ROC-curve; Receiver Operating Characteristic curve analysis also was used to evaluate the diagnostic performance of serum amyloid A (SAA) in prediction of activity of ulcerative colitis.

Results

Baseline characteristics:

A total of 90 colonoscopies were performed in 90 UC including 34 males and 56 females. Their mean age was 35.8 ± 9.3 years. The baseline characteristics of the patients. Regarding the U.C. activity assessed by mayo score; mild, moderate, severe and remission were presented in (5.56, 18.89, 25.56, 50%)respectively. For treatment, 34.44, 28.89, 26.67 and 10% of the patients were administrated with mesalazine, corticosteroids, immunomodulators and biologics respectively. Anemia, thrombocytosis and leukocytosis were significantly higher in active group especially moderate and severe cases than inactive group. Stool analysis data are shown in Table 2. Also, CRP was significantly higher in activity

especially moderate and severe than in remission (inactive) as shown in Table 3. Fecal calprotectin was significantly lower inactive group than moderate and severe activity groups and its level increases with higher grades of disease activity as shown in Table 4. Serum amyloid A was significantly lower in remission group

than in cases with moderate and severe activity as shown in Table 5. There was a statistically significant positive correlation between the different grades of ulcerative colitis activity and CRP, fecal calprotectin and serum amyloid A as shown in Table 6.

Table 2. laboratory investigations in the different grades of ulcerative colitis.

		Groups											ANOVA	
		Mild			Moderate			Severe			Inactive			F	P-value
Hb (g/dl)	**Range**	9.8	-	11.6	7.7	-	14.1	8	-	15.9	9.5	-	14.5	3.620	0.016*
	Mean ±SD	10.860	±	0.744	10.647	±	1.907	10.739	±	2.126	11.834	±	1.204		
PLT (x10³/cc)	**Range**	221	-	328	222	-	407	194	-	696	147	-	325	6.145	0.001*
	Mean ±SD	275.000	±	48.974	297.941	±	62.893	360.435	±	145.294	265.444	±	51.061		
WBCS (x10³/cc)	**Range**	5.2	-	13.5	4.96	-	12.8	3.8	-	19.6	4	-	10.1	7.100	<0.001*
	Mean ±SD	8.220	±	3.179	8.516	±	2.351	9.561	±	3.838	6.642	±	1.630		
Chi-Square		N	%		N	%		N	%		N	%		X²	P-value
Stool analysis	**Normal**	4	80.00		14	82.35		15	65.22		44	97.78		13.404	0.004*
	Abnormal	1	20.00		3	17.65		8	34.78		1	2.22			
						TUKEY'S Test									
	MI&MO		**MI&S**			**MI&I**			**MO&S**			**MO&I**			**S&I**
Hb (g/dl)	0.994		0.999			0.577			0.998			0.054*			0.046*
PLT (x10³/cc)	0.955		0.200			0.996			0.120			0.559			<0.001*
WBCS (x10³/cc)	0.996		0.717			0.565			0.585			0.058			<0.001*

Hb Hemoglobin, PLT Platelets, WBCS white blood cells, CRP C-reactive protein, MI Mild, MO Moderate, S Severe, I Inactive.

Table 3. Serum level of CRP in different grades of ulcerative colitis .

		Groups											ANOVA	
		Mild			Moderate			Severe			Inactive			F	P-value
CRP (mg/L)	**Range**	4	-	48	2.4	-	96	5	-	96	1	-	6	17.865	<0.001*
	Mean ±SD	16.200	±	18.171	29.612	±	25.065	39.609	±	33.781	3.267	±	1.684		
						TUKEY'S Test									
	MI&MO		**MI&S**			**MI&I**			**MO&S**			**MO&I**			**S&I**
CRP (mg/L)	0.579		0.106			0.547			0.433			<0.001*			<0.001*

MI Mild, MO Moderate, S Severe, I Inactive.

Table 4. Fecal calprotectin (ug/mg) different grades of Ulcerative Colitis.

		Groups											ANOVA	
		Mild			Moderate			Severe			Inactive			F	P-value
Fecal calprotectin	**Range**	55	-	340	65	-	1169	37	-	1108	1.7	-	172	16.253	<0.001*
	Mean ±SD	151.800	±	117.259	371.824	±	322.723	396.696	±	321.759	57.095	±	44.022		
						TUKEY'S Test									
	MI&MO		**MI&S**			**MI&I**			**MO&S**			**MO&I**			**S&I**
Fecal calprotectin	0.202		0.111			0.793			0.984			<0.001*			<0.001*

MI Mild, MO Moderate, S Severe, I Inactive.

Table 5. Serum amyloid A in different grades of Ulcerative Colitis.

		Mild			Moderate			Severe			Inactive			F	P-value
							Groups							ANOVA	
Serum amyloid A (µg/ml)	Range	3.8	-	10.9	3.19	-	15.6	3.04	-	14.9	2.32	-	9.6	5.224	0.002*
	Mean ±SD	6.002	±	2.827	6.882	±	2.937	6.563	±	3.783	4.444	±	1.638		
TUKEY'S Test															
	MI&MO		**MI&S**		**MI&I**		**MO&S**			**MO&I**			**S&I**		
Serum amyloid A (µg/ml)	0.914		0.973		0.598		0.982			0.009*			0.013*		

MI Mild, MO Moderate, S Severe, I Inactive.

Correlation between serum amyloid A and laboratory variables:

There was a positive correlation between serum amyloid A and fecal calprotectin, CRP, PLT. Also we found that there was only negative correlation between serum amyloid and WBCs but not significant as shown in Table 6 and Figures 1 and 2.

Table 6. Correlation of serum amyloid A with laboratory variables and SCCAI.

Correlations		
	Serum amyloid A	
	r	**P-value**
CRP (mg/L)	0.342	0.001*
Hb (g/dl)	-0.095	0.371
PLT (x10³/cc)	0.246	0.020*
WBCS (x10³/cc)	-0.021	0.844
Fecal calprotectin (µg/mg)	0.431	<0.001*
SCCAI score	0.392	<0.001*

CRP C-reactive protein, HB hemoglobin, PLT platelets, WBCS white blood cells, SCCAI Simple Clinical Colitis Activity Index.
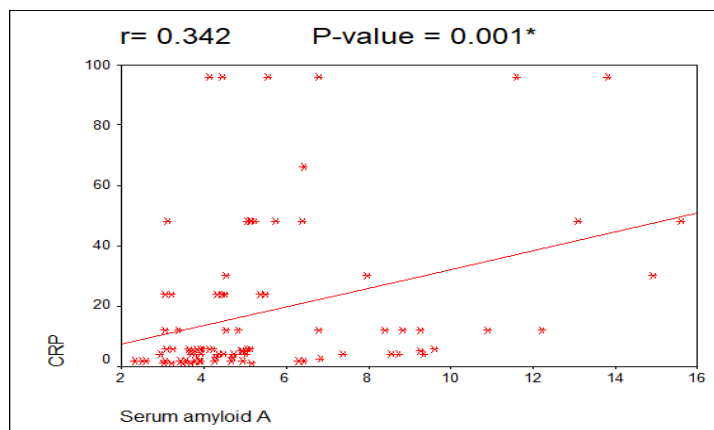

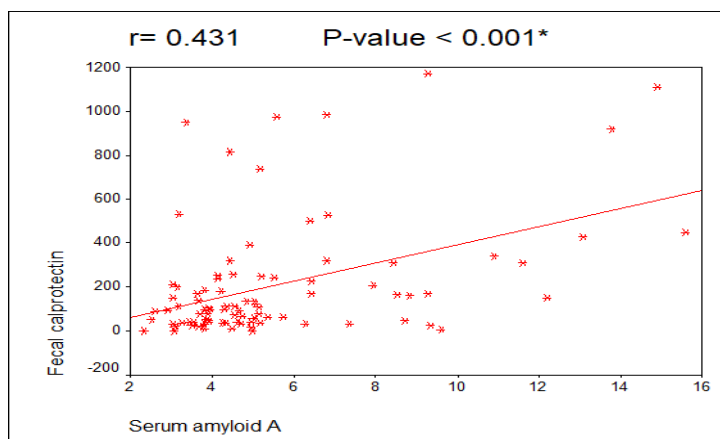**Figure 1:** Correlation between serum amyloid A and CRP

Figure 2: Correlation between serum amyloid A and fecal calprotectin

Diagnostic performance of serum amyloid A and fecal calprotectin for prediction of mucosal inflammation and remission.

The predictive value of SAA and fecal calprotectin to identify mucosal inflammation in clinical activity using the ROC curve is shown in Figure 3. Regarding serum amyloid A; at cut off value >3.97 µg\ml could discriminate active from remittent patients, the sensitivity, specificity, PPV, NPV and accuracy were (84.44, 55.56, 65.5, 78.1 and 74.2% respectively). Regarding fecal calprotectin; at cut off value >100µg\mg could distinguish activity from remission, the sensitivity, specificity, PPV, NPV and accuracy were (88.89, 86.67, 87.0, 88.6 and 93.9% respectively). The area under the ROC curve (AUC) of SAA was 0.742, whereas that of fecal calprotectin was 0.939.

Comparison of ROC curves for both SAA and fecal calprotectin showed that fecal calprotectin had a higher sensitivity and specificity than serum amyloid A. Serum amyloid A may be added value but not superior to fecal calprotectin in diagnosis of mucosal inflammation and UC activity.

The predictive value of SAA and fecal calprotectin in differentiation between different grades of ulcerative colitis disease activity using the ROC curve is shown in Figure 4. Regarding serum amyloid A; at cut off value ≤4.45 µg\ml could discriminate severe activity from mild to moderate activity, the sensitivity, specificity, PPV, NPV and accuracy were (43.48, 86.36, 76.9, 59.4 and 59.7% respectively). Regarding fecal calprotectin; at cut off value >243 µg\mg could distinguish severe activity from mild to moderate activity, the sensitivity, specificity, PPV, NPV and accuracy were (60.87, 63.64, 63.6, 60.9 and 58.1% respectively). The area under the ROC curve (AUC) of SAA was 0.597, whereas that of fecal calprotectin was 0.581.

Comparison of ROC curves for both SAA was higher than fecal calprotectin in specificity but fecal calprotectin showed that SAA   low in sensitivity.
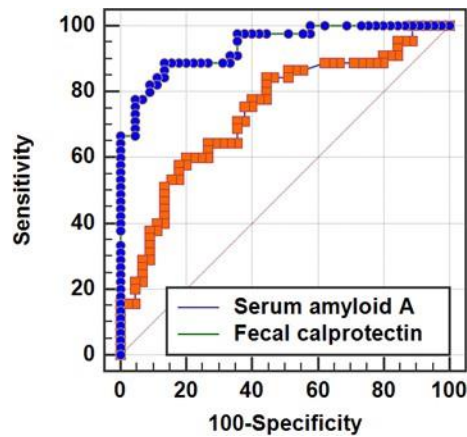

Figure 3: ROC curve for predictive ability of SAA and fecal calprotectin to identify mucosal inflammation in clinical activity
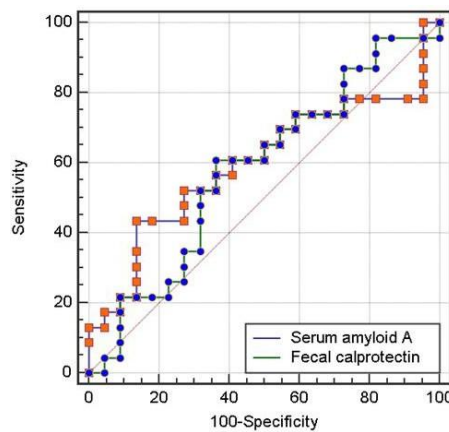

Figure 4: ROC curve for predictive ability of SAA and fecal calprotectin to identify mucosal inflammation in clinical activity

Discussion

Ulcerative colitis (UC) is a chronic, relapsing, immune-mediated disease characterized by continuous colonic mucosal inflammation essentially involves the rectum and may extend proximally to the entire colon. There is currently no single gold standard for diagnosis of UC or prediction of disease activity. So, diagnostic assessment relies on a panel of clinical data, endoscopic findings, fecal and serological markers and histological criteria [22].

Serum amyloid A (SAA) is a sensitive acute phase protein that is highly expressed in response to inflammation and tissue injury. SAA is present in the blood of healthy subjects at generally quite low levels, but during the acute-phase response (APR), SAA hepatic production leads to remarkable increased serum values within

the initial 24 hours with very lower levels after the acute phase [23].

The patients in the current study were 34 males and 56 females (37.8% vs 62.2%). Their mean age at time of inclusion was 35.8 ± 9.3 years and range from 18-65 years. The total colonoscopies performed along the study were 90 and the findings of colonoscopy were graded according to Mayo sub score; into grade 0 (inactive or remission), 1 (mild), 2 (moderate), 3 (severe). Most of the patients were from urban areas (58.89 %) and 85.56 % of them were non-smokers.

This is in agreement with a study that evaluated 80 UC patients where male to female percentage was (42.5% to 57.5%) of all the studied patients with mean age [24].

In the present study, the most common clinical symptoms in the studied patients were diarrhea (57.78 %), bleeding per rectum (43.33%), urgency (44.44 %), tenesmus (42.22 %), crampy abdominal pain (45.56 %) and loss of weight (43.33 %). Simple Clinical Colitis Activity Index (SCCAI) score was (Mean ±SD= 4.711 ± 5.303). This is consistent with a study that evaluated SAA level in UC as a new predictor of disease activity where diarrhea (40%), stomach discomfort (80%), bloody stool (36%) and weight loss (60%) were the most common symptoms of UC [25]

In the present study, the most frequent colonoscopic findings among the patients during activity were mucosal erythema (56.67 %), fine granularity (50 %), erosions (44.44 %), ulcers (44.44 %), loss of vascular marking (40 %) and spontaneous bleeding (28.89 %) but the luminal narrowing with pseudopolyps was the least frequent finding (16.67 %). This came in agreement with a study that stated the typical endoscopic findings in patients with UC include edematous mucosa, erythema, loss of vascular markings, and mucosal friability. More severe cases may be associated with erosions, ulcers, and spontaneous bleeding. Luminal narrowing and pseudopolyps may occur due to chronic inflammation, which results in mucosal atrophy [26].

Also, in the current study the most frequent histological findings in between patients were acute cryptitis (56.67 %), crypt abscess (45.56 %) and mucosal ulcers (43.33 %), but the least frequent findings were pseudopolyps (17.78 %) and dysplasia (4.44 %). This may come in line with a study in which histological findings of UC observed are not specific and include diffuse inflammatory cell infiltration, cryptitis, crypt abscess, structural abnormalities of crypts, erosion, and goblet cell depletion and loss. Screening for

dysplasia and cancer is thus particularly important [27].

Regarding the laboratory findings in the present study, anemia, thrombocytosis, leukocytosis and CRP were significantly higher in active patients especially moderate and severe grade than inactive patients (P = 0.016, 0.001 and < 0.001 respectively).

This is consistent with a study which also found that active UC patients showed significantly greater WBC, absolute neutrophilic count, absolute monocytic count, CRP, and ESR than inactive UC patients and controls (P < 0.01) [25]. Also, another study that found the serum CRP and ESR levels in the control group were considerably less than different grades of UC groups [28]. Furthermore, findings in the current study were backed up by a study which discovered that patients of UC had lower levels of hemoglobin, albumin, and total protein than normal people (P = 0.001). Also severe UC patients had lower hemoglobin, albumin, and total protein levels than mild-to-moderate UC patients (P= 0.001) [29].

In the present study, the fecal calprotectin was significantly lower in the inactive group than moderate and severe activity groups (P < 0.001) and its level increases with increase in the grade of disease activity. This agrees with a study

that concluded the level of fecal calprotectin identifies patients with UC who have endoscopic and histologic features of mucosal healing and correlates with endoscopic and histologic inflammatory activity [30].

In the current study, SAA was significantly higher in the moderate and severe activity groups than inactive group (P = 0.002) and there was a positive correlation between SAA and the different grades of activity of UC.

This comes in line with the results of a study that found in UC patients, there was a positive correlation between mucosal inflammation and SAA, with the correlation being stronger than that of CRP, and SAA level was found to more accurately reflect the degree of the mucosal inflammation [31].

In the current study, the CRP was significantly higher in moderate and severe activity than inactive group (P < 0.001). This is consistent with a study which found that the CRP level increased in patients with active disease (p < 0.0001) [32].

There is another study which assessed the usefulness of selected laboratory markers in UC in 45 patients. Whereas, fecal calprotectin was found to be correlated closely with the Mayo endoscopic score (r = 0.880, P <0.001), and

might be used to evaluate the severity of UC in the clinical setting[33]. This observation is in line with previous reports indicating that fecal neutrophil derived protein as useful surrogate marker of mucosal disease activity in IBD [34]. However, the CRP levels in that study were not statistically correlated (r = 0.273, P = 0.299).

Regarding the fecal calprotectin at cutoff >100 in the current study, the sensitivity, specificity, PPV, NPV and accuracy were (88.89, 86.67, 87.0, 88.6 and 93.9% respectively). In another study, the ROC curve analysis showed that the best cutoff point for calprotectin concentration was obtained at a threshold of 79.5 µg/g, predicting endoscopically active disease (MES ≥1) with 97% sensitivity and 80% specificity (PPV = 91%, NPV = 80%) [33]. There was another study that suggested a threshold of 100 µg/g or higher [35].

In the current study, there were significant positive correlations between SAA and fecal calprotectin, CRP, PLT and SCCAI score (P = 0.001, 0.020, < 0.001 and 0.001 respectively). Regarding the predictive value of SAA, it was found to be at cut off >3.97, the sensitivity, specificity, PPV, NPV and accuracy were (84.44, 55.56, 65.5, 78.1 and 74.2% respectively). So, the fecal calprotectin was higher than SAA in sensitivity and specificity. SAA

may be added value but not superior to fecal calprotectin in diagnosis of mucosal inflammation and UC activity.

This may come in agreement with a study which concluded that fecal calprotectin correlated better with endoscopic disease activity than clinical activity, CRP, platelets, hemoglobin, and blood leukocytes. The strong correlation with endoscopic disease activity suggests that FC represents a useful biomarker for noninvasive monitoring of disease activity in UC patients [36].

This came in disagreement with the results of another study in which SAA levels < 5.8 could discriminate mucosal inflammation from mucosal healing with sensitivity of 0.722, specificity of 0.850, PPV of 0.760, NPV of 0.823, and accuracy of 0.799. On the contrary, CRP levels < 0.060 could distinguish mucosal inflammation from mucosal healing with sensitivity of 0.620, specificity of 0.758, PPV of 0.628, NPV of 0.752, and accuracy of 0.704. The results indicate that SAA could be an excellent marker in predicting mucosal healing in clinical remission patients than CRP [31].

Also, there was a study which found that the best combination of predictive inflammatory biomarkers consists of serum SAA, IL-6, IL-8, and Eotaxin-1. In the ROC analysis, serum levels of Eotaxin-1 (pg/ml) and SAA (mg/l) presented the best

discriminative capacity regarding binary ordered, composite IBD endoscopic disease activity (area under the receiver operating characteristics curve (AuROC) 0.75 (SE: 0.06, 95% CI: 0.62–0.87, P < 0.001) for both serum Eotaxin-1 and SAA levels while serum CRP levels with an AuROC of 0.57 (95% CI: 0.43–0.72, P = 0.32) [37].

To the best of our knowledge, there is no enough report examining the correlation between SAA and endoscopic findings of UC yet. In the present study, SAA was found to have a strong correlation with endoscopic findings and may be a possible useful marker for predicting endoscopic activity in UC patients in clinical remission. In UC patients, there was a positive correlation between mucosal inflammation and SAA and SAA was found to more accurately reflect the state of the mucosa. SAA was proved to be of added value for predicting mucosal inflammation in clinical remission patients besides CRP and fecal calprotectin.

Conclusion

Serum amyloid A can be used for prediction of remission in patients with ulcerative colitis in spite of being not superior to fecal calprotectin. However it could not differentiate between the different grades of activity.

References

1. **Khor, B.; Gardet, A.; Xavier, R.J. (2011)** Genetics and pathogenesis of inflammatory bowel disease. Published online.

2. **Colombel, J.F.; Rutgeerts, P.; Reinisch, W.; Esser, D.; Wang, Y.; Lang, Y. et al (2011)** Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology, 141 (4) pp.1194-1201.

3. **Sartor, R.B. (2006)** Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol, 3 (7) pp.390-407.

4. **McNamara D (2018)** Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol, 105(3) pp. 501-23.

5. **Neurath, M.F. (2014)** Cytokines in inflammatory bowel disease. Nat Publ Gr. Published online.

6. **Neuman, M.G. (2007)** Immune dysfunction in inflammatory bowel disease. Transl Res, 149 (4).

7. **Jump, R.L.; Levine, A.D. (2004)** Mechanisms of natural tolerance in the intestine: Implications for inflammatory bowel disease. Inflamm Bowel Dis, 10 (4) pp.462-478.

8. **Hwang, Y.G.; Balasubramani, G.K.; Metes, I.D.; Levesque, M.C.; Bridges, J.r. S.L.; Moreland, L.W. (2016)** Differential response of serum amyloid A to different therapies in early rheumatoid arthritis and its potential value as a disease activity biomarker. Arthritis Res, 18 (1) pp.1-8.

9. **Wilson, P.G.; Thompson, J.C.; Shridas, P.; McNamara, P.J.; de Beer, M.C.; de Beer, F.C. et al (2018)** Serum amyloid A is an exchangeable apolipoprotein. Arterioscler Thromb Vasc Biol, 38 (8) PP.1890-1900.

10. **Nakamura T (2011)** Amyloid A Amyloidosis Secondary to Rheumatoid Arthritis: Pathophysiology and Treatment. Clinical and Experimental Rheumatology, 29(5) pp. 850–57.

11. **Zhang N, Ahsan MH, Purchio AF and West DB (2005)** Serum Amyloid A-Luciferase Transgenic Mice: Response to Sepsis, Acute Arthritis, and Contact Hypersensitivity and the Effects of Proteasome Inhibition. The Journal of Immunology, 174 (12) pp. 8125-34.

12. **Wakai, M.; Hayashi, R.; Tanaka, S.; Naito, T.; Kumada, J.; Nomura, M. et al (2020)** Serum amyloid A is a better predictive biomarker of mucosal healing than C-reactive protein in ulcerative colitis in clinical remission. BMC Gastroenterol, 20 (1).

13. **Plevy, S.; Silverberg, M.S.; Lockton, S.; Stockfisch, T.; Croner, L.; Stachelski, J. et al (2013)** Combined serological, genetic, and inflammatory markers differentiate non-IBD, Crohn's disease, and ulcerative colitis patients. Inflamm Bowel Dis, 19 (6) pp.1139-1148.

14. **Lewis, J.D. (2011)** The Utility of Biomarkers in the Diagnosis and Therapy of Inflammatory Bowel Disease. Gastroenterology, 140 (6) pp.1817.

15. **Langhorst, J.; Elsenbruch, S.; Koelzer, J.; Rueffer, A.; Michalsen, A.; Dobos, G.J. (2008)** Noninvasive Markers in the Assessment of Intestinal Inflammation in Inflammatory Bowel Diseases. Am J Gastroenterol, 103(1) pp.162-9.

16. **Vermeire, S.; Van, Assche, G.; Rutgeerts, P. (2006)** Laboratory markers in IBD: Useful, magic, or unnecessary toys? Gut, 55 (3) pp.426-431.

17. **Mosli, M.H.; Zou, G.; Garg, S.K.; Feagan, S.G.; MacDonald, J.K.; Chande, N.; Sandborn, W.J. et al (2015)** C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol, 110 (6) PP. 802-819.

18. **Luisa, A. ; Mechie, N.C. ; Petzold, G. ; Ellenrieder, V. ; Kunsch, S. ; Amanzada, A. (2019)** Impact of faecal calprotectin measurement on clinical decision-making in patients with Crohn's disease and ulcerative colitis, Plos One 14 (10).

19. **D'Haens, G.; Sandborn, WJ.; Feagan, B.G.; Geboes, K.; Hanauer, S.B.; Irvine, E.J. et al (2007)** A Review of Activity Indices and Efficacy End Points for Clinical Trials of Medical Therapy in Adults With Ulcerative Colitis. Gastroenterology, 132 (2) pp. 763–86.

20. **Moran, C.P.; Neary, B. and Doherty, G.A. (2016)** Endoscopic Evaluation in Diagnosis and Management of Inflammatory Bowel Disease. World Journal of Gastrointestinal Endoscopy, 8 (20) pp. 723.

21. **Danese, S.; Fiorino, G.; Peyrin-Biroulet, L.; Lucenteforte, E.; Virgili, G.; Moja, L. et al (2014)** Biological Agents for Moderately to Severely Active Ulcerative

Colitis. Annals of Internal Medicine, 160 (10) pp. 704–11.

22. **Schoepfer, A.M.; Vavricka, S.; Zahnd-Straumann, N.; Straumannd, A.; Beglinger, C. (2012)** Monitoring inflammatory bowel disease activity: clinical activity is judged to be more relevant than endoscopic severity or biomarkers. J Crohns Colitis, 6 (4) pp.412-8.

23. **Sack, G.H. (2018)** Serum Amyloid A: A Review. Molecular Medicine,24(1).

24. **Okba, A.M.; Amin, M.M.; Abdelmoaty, A.S, Ebada, H.E.; kamel, A.H.; Allam, A.S. et al (2019)** Neutrophil/lymphocyte ratio and lymphocyte/monocyte ratio in ulcerative colitis as non-invasive biomarkers of disease activity and severity. Auto Immun Highlights, 10 (1) pp. 4.

25. **Elnagdy, M.; Mansour, R.; Abd El Aziz, S.; Gaafar, A. (2022)** Evaluation of Serum Amyloid (A) Level in Ulcerative Colitis as a new Predictor of Disease Activity. Al-Azhar International Medical Journal, 3 (5) pp.35-39.

26. **Choi, C.H. ; Jung, S.A. ; Lee, B.I. ; Lee K.M. ; Kim, J.S. ; Han, D.S. et al (2009)** Diagnostic Guideline of Ulcerative Colitis. The Korean Journal of Gastroenterology, 53 (3) pp. 145–60.

27. **Mitsuishi, T. (2018)** Correlation between histological findings and endoscopic findings in patients with ulcerative colitis: Basal plasmacytosis is an important finding suggesting active inflammation. JGH Open, 3 (2) pp. 100-104.

28. **Xia, D. and An, J. (2018)** Serum folic acid, PCT, CRP and ESR detection as biomarker in differentiation ulcerative colitis activity. Pteridines, 29 (1) pp.179-86.

29. **Zhang, MH.; Wang, HG.; Shi, YT.; Zhou, JF.; Yan, W.; Ma, TH. et al (2020)** Efficacy of Serum Total Bilirubin in Predicting the Severity of Ulcerative Colitis: A Cross-Sectional Study. Ann Clin Lab Sci, 50 (2) pp. 228-232.

30. **Theede, K.; Holck, S.; Ibsen, P.; Ladelund, S.; Nordgaard-Lassen, I.; Nielsen, AM. (2015)** Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. Clinical Gastroenterology and Hepatology, 13 (11) pp. 1929-36.

31. **Wakai, M.; Hayashi, R.; Tanaka, S.; Naito, T.; Kumada, J.; Nomura, M. et al (2020)** Serum Amyloid A Is a Better Predictive Biomarker of Mucosal Healing than C-Reactive Protein in Ulcerative Colitis in Clinical Remission. BMC Gastroenterology, 20 (1) pp. 85.

32. **Karoui, S.; Laz, S.; Serghini, M.; Bibani, N.; Boubaker, J.; Filali, A. (2011)** Correlation of C-reactive protein with clinical and endoscopic activity in patients with ulcerative colitis. Dig Dis Sci, 56 (6) pp. 1801-1805.

33. **Mańkowska-Wierzbicka, D.; Swora-Cwynar, E.; Poniedziałek, B.; Adamski, Z.; Dobrowolska, A.; Karczewski, J. (2015)** Usefulness of selected laboratory markers in ulcerative colitis. Eur Cytokine Netw, 26 (2) pp. 26-37.

34. **Karczewski, J.; Swora-Cwynar, E.; Rzymski, P.; Poniedziałek, B.; Adamski, Z. (2015)** Selected biologic markers of inflammation and activity of Crohn's disease. Autoimmunity, 48 (5) pp. 318-27.

35. **D'Haens, G.; Ferrante, M.; Vermeire, S.; Baert, F.; Noman, M.; Moortgat, L. et al (2012)** Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflammatory Bowel Disease, 18 (12) pp. 2218-24.

36. **Schoepfer, A.M.; Beglinger, C.; Straumann, A.; Safroneeva, E.; Romer, Y.; Armstrong, D. et al (2013)** Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflammatory Bowel Diseases, 19 (2) pp. 332-41.

37. **Bourgonje, A.R.; von Martels, J.Z.H.; Gabriëls, R.Y.; Blokzijl, T.; Buist-Homan, M.; Heegsma, J. et al. (2019)** A Combined Set of Four Serum Inflammatory Biomarkers Reliably Predicts Endoscopic Disease Activity in Inflammatory Bowel Disease. Front Med (Lausanne), 6 pp. 251.