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original article

Role of Intestinal Ultrasonography in Assessment of Disease Activity in Ulcerative Colitis Patients

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Abstract

Background: Intestinal ultrasound [IUS] has been reported to be accurate in the diagnosis of ulcerative colitis and can also be applied to determine the extent, severity and location of inflammation. The aim of this study was to evaluate the usefulness of bowel US in comparison to colonoscopy for assessing disease extent and activity of ulcerative Colitis. **Methods:** This cross sectional study included 60 patients with ulcerative colitis who attended Gastroenterology outpatient clinics and IBD unit of National Hepatology and Tropical Medicine Research Institute. Participants were divided into 2 groups of patients according to Truelove and Witt's criteria for classification of severity of ulcerative colitis. Group I (n= 30) active ulcerative colitis patients. Group II (n= 30) inactive ulcerative colitis patients (in remission). Selected patients were subjected to laboratory investigations, colonoscopic and intestinal ultrasound examination (IUS). **Results:** In the present study, bowel wall thickness can be used to discriminate between active and inactive ulcerative colitis patients at a cut off level of > 3.5(P<0.001). The mean BWT was significantly thicker in active group of patients (5.2±0.7 mm, P<0.001) than of inactive (2.6±0.2 mm, P<0.001) while fat creeping and reactive lymph nodes (LNs) has no role in discrimination of ulcerative colitis patient's activity (P=0.150). Doppler signal increased (P=0.057), while wall layer stratification was disturbed in patients with active ulcerative colitis (P=0.002). **Conclusion:** IUS may represent a useful first-line, non-invasive tool for assessing activity, severity and extent of ulcerative colitis.

Key words: Intestinal Ultrasonography - Disease Activity - Ulcerative Colitis

Introduction:

Inflammatory bowel disease (IBD) comprises of two chronic intestinal disorders: Ulcerative colitis (UC) and Crohn's disease (CD). CD and UC are characterized by a course of remission and relapse with complex interactions among genes, the environment, and immunity ***(1).***

IBD have always seemed to be rare in the Middle East and Northern Africa. No accurate registry or cohort of patients had ever studied the exact prevalence of CD and UC in these populations. In Mediterranean countries, the prevalence of UC was estimated at 5/100000 in urban areas. The incidence of IBD seems tobe rising in Egypt with UC to CD ratio of 6:1 ***(2).***

Colonoscopy is the gold standard for the assessment of disease activity in UC patients. Therefore, it is increasingly being implemented to guide treatment decisions and to evaluate treatment outcomes in clinical trials. Several endoscopic activity scores have been developed and validated and can be used to assess endoscopic disease activity ***(3).*** For optimal monitoring of disease activity in UC patients, colonoscopy should be performed on a regular basis. However, repeated colonoscopies represent a logistic and economicchallenge, as well as significant burden for the patients. Moreover, there is a small risk of bowel perforation and transmural or extra-luminal disease activity, and complications such as abscesses cannot be assessed ***(4).***

Biomarkers such as serum C-reactive protein (CRP) and fecal calprotectin have limited reliability for assessing and grading UC activity. Therefore, cross-sectional imaging modalities, such as trans-abdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are increasingly being used in the management of IBD (5).

The use of US to assess gastrointestinal tract disorders is a recent development and has been focused primarily on the assessment of acute and chronic inflammatory conditions, such as appendicitis, diverticulitis, UC and CD ***(6).*** Over the past few years, the technical evolution of US equipment, combined with the use of oral and intravenous (IV) contrast agents and increased operator expertise, has led to greater enthusiasm for assessment of the gut by means of US ***(7).***

The aim of this work was to evaluate the usefulness of bowel US in comparison to colonoscopy for assessing disease extent and activity of Ulcerative Colitis.

Patients and Methods

This cross sectional study included 60 patients with ulcerative colitis who attended Gastroenterology outpatient clinics and IBD unit of National Hepatology and Tropical Medicine Research Institute. The study period was from June 2021 to May 2022.Included patients more than 18 years old with newly discovered or with flare-up of UC and documented diagnosis (endoscopic and histologic) of UC.

While patients with proctitis alone, pregnant females and complicated cases were excluded. The patients had been enrolled and subdivided into 2 groups of patients according to Truelove and Witt's criteria for classification of severity of ulcerative colitis.

- ***Group I*** (n= 30) active ulcerative colitis patients.
- ***Group II*** (n= 30) inactive ulcerative colitis patients (in remission).

Prior to treatment, all eligible patients were subjected to the following:

A. Proper history for each patient subjected to the study.

B. Clinical examination.

Thorough general and abdominal examination.

C. Laboratory investigations.

Including CBC (Hb level gm/dl, WBCs m/mm^3 Platelet count m/mm^3), ESR (mm/hr), CRP (mg/l) and Fecal Calprotectin (µg/g).

D. Radiological Examination:

The examination was performed using ultrasound machine LOGIQ 500 (GE, Yokogawa Medical System Ltd, Tokyo, Japan) within 3 days of endoscopy and all patients were instructed to fast the night prior to the examination using a 3.5 MHz

convex transducer then with a 7 MHz linear transducer for detailed examination of the bowel wall structure. The recorded US parameters included:

- Bowel wall thickness (BWT): The normal intestinal tract thickness in the terminal ileum, cecum, and right and left colon is <2 mm ***(9).***
- Doppler signal (DS) (categorized as absent, small spots or largespots/stretches).
- Colonic haustrations and wall layer stratification (WLS) either disturbed or normal.
- Fat creeping either present or absent.
- Reactive mesenteric lymph nodes either present or absent.

E. <u>Endoscopic Examination</u>:

Disease activity was categorized according to the endoscopic Mayo score.

Table (1): Truelove and Witt's criteria for classification of severity of ulcerative colitis

	Mild	Moderate	Severe
Bloody stools per day	<4	4-6	**> 6**
Pulse (bpm)	<90	≤ 90	**> 90**
Temperature (°C)	< 37.5	≤ 37.8	**> 37.8**
Hemoglobin (gm/dL)	> 11.5	≥ 10.5	**< 10.5**
ESR (mm/h)	< 20	≤ 30	**> 30**
CRP (mg/dL)	**Normal**	**≤ 30**	**> 30**

ESR: erythrocyte sedimentation rate.
CRP: C-reactive protein.*(8).*

Table (2): Mayo Score / Endoscopic Activity Index (EAI) for Ulcerative Colitis:

Endoscopic Findings:
Normal or inactive colitis seen (0 points)
Mild colitis: mild friability, erythema, decrease in vascularity (1 point)
Moderate colitis: friability, marked erythema, absent vascular pattern, erosions seen (2 points)
Severe colitis: ulceration and spontaneous bleeding (3 points)

(10)

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Ethical consideration:

All patients had informed consent that they were involved in the study. An approval from the research ethics committee in Benha Faculty of Medicine was obtained.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Data were tested for normal distribution using the Shapiro Walk test.

Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data.

Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. Repeated measures ANOVA test was used to compares means across one or more variables that are based on repeated observations of normally distributed variables. While Friedman test was used for non- normally distributed variables.

All statistical comparisons were two tailed with significance Level of P-value ≤
0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates Non-significant difference.

Using Roc curve, it shows that: Fecal calprotectin can be used to discriminate between active and inactive patients at a cut off level of >222, with 76.7% sensitivity, 96.7% specificity, 95.9% PPV and 80.6% NPV (AUC = 0.91& p-value < 0.001).
Bowel wall thickness can be used to discriminate between active and inactive patients at a cut off level of >3.5, with 100% sensitivity, 100% specificity, 100% PPV and 100% NPV (AUC = 1.0& p-value < 0.001).

Table (3): Demographic and clinical data of the studied groups.

		Group I (Active ulcerative colitis) (N = 30)		Group II (Inactive ulcerative colitis) (N = 30)		Stat.test	P-value
Age(years)	**Mean**	38.7		40.3		T = 0.65	**0.517 NS**
	±SD	9.9		9.8			
Sex	**Male**	20	66.7%	20	66.7%	X^2 = 0.0	**1.0 NS**
	Female	10	33.3%	10	33.3%		
Smoking	**No**	26	86.7%	24	80%	X^2 =0.48	**0.488 NS**
	Yes	4	13.3%	6	20%		
Residence	**Rural**	19	63.3%	14	46.7%	X^2 =1.68	**0.194 NS**
	Urban	11	36.7%	16	53.3%		
Occupation	**Working**	27	90%	17	56.7%	**X^2 = 8.5**	0.004 S
	Not working	3	10%	13	43.3%		
Family history of IBD	**No**	23	76.7%	24	80%	X^2 =0.098	**0.754 NS**
	Yes	7	23.3%	6	20%		
Age at diagnosis (years)	**Mean**	36.8		38.1		T =0.49	**0.622 NS**
	±SD	9.9		9.8			
Duration (years)	**Median**	2		2		MW =	**0.061 NS**
	IQR	1 - 3		2 - 3		330.5	
Pulse (beat/min)	**Median**	86		78		**MW =**	0.04 S
	IQR	80.3 - 94.5		74 - 94		**311.5**	
Temp (C^o)	**Median**	37		37		MW =404	**0.493 NS**
	IQR	36.7 - 37.3		36.7 - 37.2			
Abdominal tenderness	**No**	7	23.3%	25	83.3%	**X^2 =21.7**	< 0.001 HS
	Yes	23	76.7%	5	16.7%		
Intestinal sounds	**Normal**	8	26.7%	24	80%	**X^2 =17.1**	< 0.001 HS
	Exaggerated	22	73.3%	6	20%		
Abdominal distension	**No**	11	36.7%	25	83.3%	**X^2 =13.6**	< 0.001 HS
	Yes	**19**	**63.3%**	**5**	**16.7%**		

T: independent sample T test.
S: significant.
X^2: Chi-square test
NS: non-significant.
MW: Mann Whitney U test.
HS: highly significant.
IQR: Interquartile range.
Temp: temperature

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	IQR	1 - 3		2 - 3			
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	IQR	80.3 - 94.5		74 - 94			
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Abdominal tenderness	**No**	7	23.3%	25	83.3%	**X^2 =21.7**	< 0.001 HS
	Yes	23	76.7%	5	16.7%		
Intestinal sounds	**Normal**	8	26.7%	24	80%	**X^2 =17.1**	< 0.001 HS
	Exaggerated	22	73.3%	6	20%		
Abdominal distension	**No**	11	36.7%	25	83.3%	**X^2 =13.6**	< 0.001 HS
	Yes	**19**	**63.3%**	**5**	**16.7%**		

T: independent sample T test. S: significant.
X^2: Chi-square test. NS: non-significant.
MW: Mann Whitney U test. HS: highly significant.
IQR: Interquartile range. Temp: temperature

Table (4): Laboratory findings of the studied groups.

		Group I (Active ulcerativecolitis) (N = 30)	Group II (Inactive ulcerativecolitis) (N = 30)	T	P-value
Hb(g/dl)	**Mean**	11.3	12.8	**5.03**	< 0.001 HS
	±SD	1.2	1.0		
WBCs(x10^3/µl)	**Mean**	11.9	7.2	**9.5**	< 0.001 HS
	±SD	2.1	1.7		
ESR(mm/h)	**Mean**	33.6	16.2	**4.5**	< 0.001 HS
	±SD	20.3	6.3		
CRP(mg/L)	**Mean**	31.9	5.4	**10.7**	< 0.001 HS
	±SD	13.3	2.3		
Fecal Calprotectin(µg/g)	**Mean**	250.6	116.9	**8.1**	< 0.001 HS
	±SD	**73.5**	**51.8**		

T: independent sample T test. HS: highly significant.
Hb: hemoglobin. WBCs: white blood cells.
ESR: erythrocyte sedimentation rate. CRP: C-reactive protein.

Table (5): Intestinal ultrasound examination of the studied groups.

		GroupI (Active ulcerative colitis) (N = 30)		Group II (Inactive ulcerative colitis) (N = 30)		Stat. test	P-value
Bowel wall thickness (mm)	**Mean ±SD**	5.2 0.7		2.6 0.2		**T= 18.9**	<0.001 HS
Doppler signal	**Absent**	17	56.7%	27	90%^	**X2= 16.6**	<0.001 HS
	Small spots	7	23.3%	2	6.7%		
	Large spots	6	20%	1	3.3%		
Wall layer stratification	**Normal**	12	40%	27	90%	**X^2= 16.5**	<0.001 HS
	Disturbed	18	60%	3	10%		
Fat creeping	**Absent**	30	100%	30	100%	------	------
	Present	0	0%	0	0%		
Reactive LNs	**Absent**	28	93.3%	30	100%	X^2 = 2.06	**0.150 NS**
	Present	**2**	**6.7%**	**0**	**0%**		

LNs: lymph nodes. NS: non-significant.
T: independent sample T test. S: significant.
X2: Chi-square test. HS: highly significant.

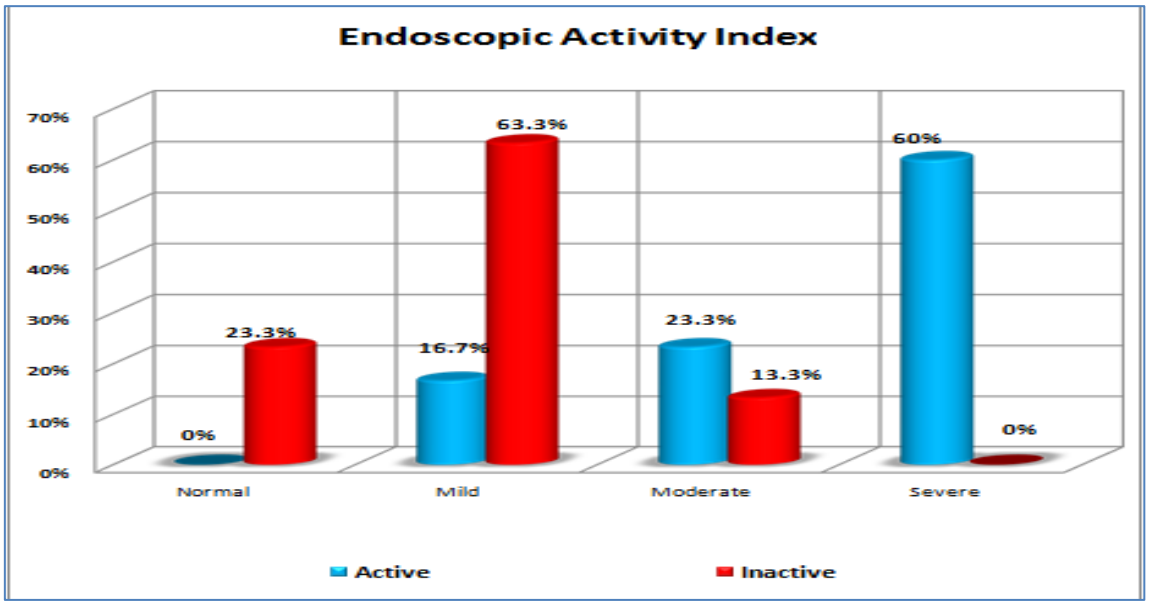

Figure (1): Endoscopic Activity Index of the studied groups.

Table (6): Endoscopic Activity Index and intestinal ultrasound examination of the studied groups.

		Group I (Active ulcerative colitis)								Group II (Inactive ulcerative colitis)							
		EAI						**Stat. test**	**P-value**	**EAI**						**Stat.test**	P-value
		Mild (n = 5)		**Moderate (n = 7)**		**Severe (n = 18)**				**Normal (n = 7)**		**Mild (n = 19)**		**Moderate (n = 4)**			
Bowel wall thickness	**Mean**	5.6		5.2		5.2		F =0.9	0.418 NS	2.6		2.5		2.8		F =2.26	**0.123 NS**
	±SD	0.8		0.7		0.6				0.2		0.1		0.3			
Doppler signal	**Absent**	5	100%	1	14.3%	1	61.1%	X^2 = 9.1	0.057 NS	7	100 %	19	100 %	1	25 %	**X^2 = 21.7**	< 0.001 HS
	Small spots	0	0%	3	42.9%	4	22.2%			0	0%	0	0 %	2	50 %		
	Large spots	0	0%	3	42.9%	3	16.7%			0	0%	0	0 %	1	25 %		
Wall stratification	**Normal**	5	100%	4	57.1%	3	16.7%	**X^2= 12.4**	**0.002 S**	7	100 %	19	100 %	1	25 %	**X^2 = 21.6**	< 0.001 HS
	Disturbed	**0**	**0 %**	**3**	**42.9%**	**15**	**83.3 %**			**0**	**0%**	**0**	**0 %**	**3**	**75 %**		

X2: Chi-square test. HS: highly significant.
F: F value of ANOVA test. NS: non-significant.
EAI: Endoscopic Activity Index. S: significant.

Table (7): Diagnostic performance of fecal calprotectin and bowel wall thickness in discrimination of active and inactive patients.

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Calprotectin	**>222**	**0.91**	**76.7%**	**96.7%**	**95.9%**	**80.6%**	< 0.001
Bowell wall thickness	>3.5	1.0	100%	100%	100%	100%	< 0.001

PPV: positive predictive value. AUC: Area under curve
NPV: negative predictive value.

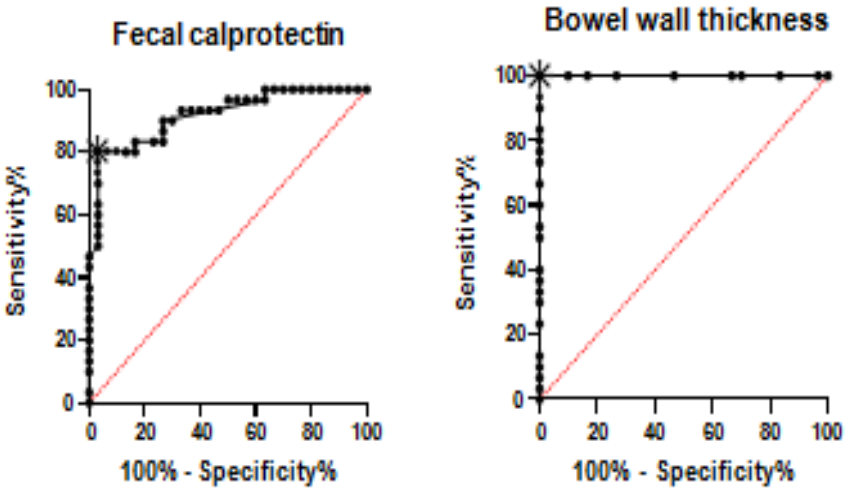

Figure (2): ROC curve of active and inactive patients as regard fecal calprotectin and bowel wall thickness.

Discussion

In this cross sectional study, we examined the role of IUS in assessment of disease activity in ulcerative colitis patients. The mean patient age at diagnosis was 38.7 (±9.9 SD) in active ulcerative colitis patients and 40.3 (±9.8 SD) in inactive ulcerative colitis patients (Table 3). This finding was in agreement with ***(11)***, ***(12)*** and ***(13)*** as; they found that the most affected age group was 30-40 years old. Clinical features of the studied patients in the current study revealed that; tachycardia, abdominal tenderness, exaggerated abdominal sounds and abdominal distension increased in patients of active group with high statistical significant difference, but no statistical significant difference between studied groups as regards body temperature (Table 3).

Compared to our findings, ***(14)*** found that 85% of patients complained from abdominal tenderness, and 50% of patients complained from bleeding per rectum, also 60% of patients were complaining of chronic diarrhea. Also, ***(15)*** reported that UC patients typically present with rectal bleeding, diarrhea, tenesmus. As regard to laboratory findings, there were high statistical significant difference between the studied groups as regard presence of anemia, leukocytosis and increased ESR, CRP and fecal calprotectin (Table 4).

These results were in agreement with ***(16), (17), (18), (11), (19)*** and ***(12).*** Against our study, ***(20)*** concluded that, ESR and CRP were not useful in predicting clinical, endoscopic, or histologic UC disease activity. They examined role of both markers in diagnosis of IBD and its correlation with clinical, endoscopic, histological, and radiographic disease activity during follow-up. Normal ESR and CRP values in their study were observed in up to 42% of patients with UC at diagnosis. The difference between the results of the present study and the previous one could be explained by the finding that correlation of ESR and CRP with clinical, endoscopic, and histologic activity during follow-up depended on their value at diagnosis and mode of analysis. Also, ***(21)*** observed that patients with normal CRP at time of diagnosis did not have abnormal CRP levels again with clinical disease activity or with colitis. This finding may suggest that elevation of CRP is an individual genetic trait. As regard to intestinal ultrasound examination, there were highly statistical significant difference between the studied groups regarding bowel wall thickness, doppler signal and wall layer stratification (Table 5).

The most characteristic feature of inflammation in UC is thickening of the bowel wall. The advantages of transabdominal ultrasonography include the rapid evaluation of bowel wall thickness, as well as wall layer stratification that reflects alterations in histopathology in UC. Visualization of the vascularization of the bowel using color Doppler sonography is the second advantage of IUS. The third major advantage, in comparison to other cross-sectional imaging modalities, includes the direct visualization of motility ***(22).*** The present study demonstrated that; there were statistically significant correlation between Endoscopic Activity Index and wall layer stratification in active group, but no statistical significant relation between

Endoscopic Activity Index on one hand and bowel wall thickness & doppler signal on the other hand (Table 6). ***(23)*** also showed that an US index with BWT, vascular signal, and wall layer stratification strongly correlated with ileocolonoscopy activity signs. It is noted that, the main goal of treatment is mucosal healing in patients with IBD ***(24),*** as well as mucosal healing is important for efficacy of treatment and long-term prognosis of the disease ***(25).***

In the present study, there were high statistical significant differences between the studied groups regarding the ultrasound examination. The mean BWT was significantly thicker in active group of patients (5.2±0.7 mm) than of inactive (2.6±0.2 mm). This was in line with ***(14)*** who reported that in the control group, the mean BWT was 2 mm with a range from 1–3 mm, but in the patient group, the mean BWT was 7.5±1.0 mm. Also, ***(26)*** study verified that ultrasound abnormalities (thickness of bowel wall) differentiate IBD patients from non-IBD controls. ***(27)*** reported that with the use of high-resolution US, the cutoff between normal and pathological wall thickness is typically 3 mm. Another study, ***(28)*** who found that, the median thickness of the colon wall in the most involved sites was 4.3 mm in acute phase and 4.4 mm in the inactive phase. The median number of the color signals in the active phase at the most involved site, distal part of descending colon, and sigmoid was higher than that of the color signals in the inactive phase.

Also, there were highly statistical significant difference between the studied groups regarding doppler signal and wall layer stratification**.** Bowel wall inflammation in IBD causes significant changes in resistance and velocity in the mesenteric blood supply. Hyperdynamic blood flow in IBD has been shown by different invasive methods. Early angiographic and histopathologic studies revealed increased vascularity within the mucosa and submucosa but reduced muscularis blood flow in active disease, which tend to decrease further in the late fibrosing stage ***(29).*** Sonography can be useful in analyzing the bowel wall and obtaining functional information about most of the affected bowel in CD and UC ***(30).***

Also, ***(31)*** reported that stratification of the bowel wall is preserved early in the disease process. Similar results were obtained by ***(32) and. (33)*** who reported that Doppler signal correlated with disease activity. In ***(28)*** study, estimation of macroscopic vessel density in diseased bowel loops, based on the number of color signals, showed that patients with active disease had higher vessel density, whereas those with quiescent disease had no vessel density. This finding was significant in the most involved site, distal part of the descending colon, and sigmoid but not in the middle part of the descending colon. In addition, the more severe the disease was, the higher number of the color signals was detected.

Altogether, these findings indicated that increased intramural flow reflected the clinical activity in patients with UC. Moreover, these results are parallel to the characteristic of the UC, that is, hypovascularized bowel wall ***(34).***In our study, we demonstrated that; fecal calprotectin can be used to discriminate between active and inactive patients at a cut off level of >222 and bowel wall thickness can be used to discriminate between active and inactive patients at a

cut off level of >3.5 (Table 7). Similar results were obtained by ***(35)*** who reported that fecal calprotectin ≤250 μg/g demonstrated strong prognostic value in predicting Week 52 disease remission, irrespective of treatment. Thus, early fecal calprotectin assessment may identify patients who are benefitting from treatment despite not having yet achieved endoscopic or histologic improvements in disease activity. ***(36)*** included thirty patients with moderate to severe UC (endoscopic Mayo score [EMS] ≥2) starting tofacitinib treatment. Patients were evaluated at baseline and after 8 weeks of tofacitinib induction, 27 patient completed follow-up. Endoscopic remission was defined as EMS = 0 and improvement as EMS ≤1. The most accurate cutoff values for BWT were 2.8 mm for endoscopic remission and 3.9 mm for improvement.

Conclusion:

IUS may represent a useful first-line, non-invasive tool for assessing activity, severity and extent of UC, and may be helpful to determine in a rapid manner whether a significant flare has occurred and to guide the management of UC patients, delaying or avoiding colonoscopy when it is not needed. In addition, IUS may be preferred in clinical practice for monitoring disease course and for assessing short-term treatment response, reducing the necessity of repeated colonoscopies, although further specific data on monitoring will be needed.

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