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Changes in Serum Oncostatin M Levels during Treatment of Inflammatory Bowel Disease

Ghada Abdelrahman Mohamed, Hatem Abd El-Latif Mohamed, Ahmed Samir Abo Halima, Mohamed Elsayed Ali Elshaarawy, Abdelrahman Khedr*

Department of Internal Medicine, Faculty of Medicine – Ain Shams University, Egypt

***Corresponding author:** Abdelrahman Khedr, **Mobile:** (+20) 01005412601, **Email:** khedr76@hotmail.com

ABSTRACT

Background: Inflammatory bowel diseases (IBD) consist of Crohn's disease (CD) and ulcerative colitis (UC). They are characterized by a chronic relapsing and remitting disease course that results in intestinal symptoms but also frequently in extra-intestinal manifestations. Among potential targets and biomarkers, oncostatin M (OSM) has gained a lot of interest. OSM is a pleiotropic cytokine produced by activated T cells, monocytes, macrophages, and neutrophils. It is considered proinflammatory given its ability to promote leukocyte recruitment.

Objective: This study aimed to assess the value of oncostatin M as a potential biomarker in diagnosis, follow up and prediction of response to treatment of inflammatory bowel disease.

Patients and Methods: The study included 30 patients with IBD (15 with ulcerative colitis and 15 with Crohn's disease) from Outpatient Clinic of Gastroenterology Department of Ain Shams University Hospital as a study group. 30 healthy subjects were enrolled in this study as a control group.

Results: The mean Oncostatin M in IBD cases before treatment was 120.13 Pg/ml while after treatment was 91.17 Pg/ml with high significant difference. There was high statistical correlation in between fecal calprotectin level after treatment and oncostatin M after treatment. ROC curve for oncostatin level in diagnosis of IBD cases showed that the best cut off point between groups regarding the level of oncostatin was > 78.50 Pg/ml with sensitivity of 96.7%, specificity of 100%. ROC curve for oncostatin in prediction of response to treatment showed that the best cut off point between groups regarding the oncostatin level was found < 103.50 Pg/ml with sensitivity of 40%, specificity of 75%

Conclusion: Oncostatin M is a promising marker for the diagnosis and follow-up of IBD patients, however it has a limited predictive performance for the prediction of the response for IBD treatment.

Keywords: Inflammatory bowel diseases, Oncostatin M, Crohn's disease.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases characterized by periods of relapses and periods of remissions affecting the gastrointestinal tract and triggered by an abnormal immune response and they tend to affect young people [(1)]. IBD includes two forms Crohn's disease and ulcerative colitis. They affect GIT in different areas and different depth in a way unique for each type of them. Ulcerative colitis (UC) causes diffuse inflammation of the colonic mucosa with special tendency towards rectum, but it can affect the sigmoid or it affects the whole colon into the cecum. Crohn's disease (CD) causes transmural ulceration of any region of the gastrointestinal tract but terminal ileum is the most frequently affected area by the disease [(2)].

Various factors are included in the pathogenesis of IBD. These include genetic susceptibility, environmental factors, an inappropriate response to commensal microbes and abnormal immune reaction [(3)].

The introduction of biological agents such as infliximab and adalimumab for treatment of inflammatory bowel disease and their response rate ranging from 30 % to 50% necessitate the presence of new biological marker which can reflect disease activity, monitor treatment and predict the response for treatment [(4)]. Oncostatin M is a cytokine of interleukin 6 family, it is produced by hematopoietic cells especially T helper lymphocytes. It is involved in liver regeneration and bone metabolism. On other hand it is involved in some pathological conditions like chronic inflammation and cancer [(5)].

Beigel *et al.* [(6)] assumed a beneficial role for oncostatin M in patients with active IBD when he found high expression of oncostatin M in colonic lesions of those patients. He based his assumption on the ability of oncostatin to induce intestinal epithelial cell proliferation in vitro, while **Tan *et al.*** [(7)] tested the hazardous effects of overexpression of oncostatin M on the intestinal barrier function in a murine model of acute colitis that led to affection of tight junction integrity. **West *et al.*** [(8)] examined the histopathological intestinal lesions from patients with IBD to find high expression and upregulation of oncostatin that is directly proportional to the degree of severity of the disease

In this study we evaluated the changes in serum oncostatin M levels before and after treatment of inflammatory bowel disease to assess its role in diagnosis, monitoring and prediction of response to therapy in patients with IBD.

PATIENTS AND METHODS

30 patients with IBD confirmed by endoscopy and histopathological examination of endoscopic biopsies (15 patients with ulcerative colitis and 15 patients with Crohn's disease) from Outpatient Clinic of Gastroenterology Department, Ain Shams University Hospital. 30 healthy subjects were enrolled

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in this study as a control group. After patients' consents and ethical committee approval patients started treatment with one of the following steroids, infliximab or adalimumab. Oncostatin M level and fecal calprotectin were evaluated at baseline and one year following treatment in IBD group. Oncostatin M level was evaluated by ELISA TECAN Infinite F50ELIZA Reader singapore.

Exclusion criteria:

Patients under 18 years old or patients with any contraindication for biological therapy (patients with TB, cancer or severe infection).

Endoscopy and biopsies were done for histopathology evaluation of disease activity before treatment and after treatment. Full history taking, thorough clinical exam and laboratory data including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Urea, serum creatinine, total plasma proteins, serum albumin, total bilirubin, serum alanine transaminase (ALT), serum aspartate transaminase (AST), carcinoembryonic antigen **(**CEA), cancer antigen (CA 19.9), stool analysis and stool culture and sensitivity were done to all patients and controls. Disease activity and remission were assessed by the clinical activity scoring using Truelove-Witts scoring for ulcerative and Harvey-Bradshaw activity index (HBI) for Crohn's disease. Ulcerative colitis endoscopic index of severity (UCEIS) in case of ulcerative colitis and simple endoscopic score for Crohn's disease (SES-CD) in case of Crohn's disease were also used.

The UCEIS score is calculated as a simple sum from 0 to 8, which were stratified into four grades: remission (0–1), mild (2–4), moderate (5–6), and severe (7–8) based on endoscopic findings. SES-CD score is calculated as a simple sum, which were stratified into four grades: remission (0–2), mild (3–6), moderate (7–15), and severe (> 15) based on endoscopic findings. HBI score is calculated as a simple sum, which were stratified into four grades: remission (< 5), mild (5–7), moderate (8–16), and severe (> 16) based on severity of clinical data and presence or absence of clinical complications. Truelove-Witts scoring is based on clinical picture and ESR to differentiate activity into mild, moderate and severe. While, clinical remission in UC was defined as absence of blood in stools and normal bowel motions and ESR < 30.

Ethical consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Ain Shams University. Written informed consents were taken from all participants. The study was conducted according to the Declaration of Helsinki.

Statistical Analysis

Analysis of data was done using SPSS program version 25. Quantitative data were presented as mean and SD. Qualitative data were presented as count and percentage. Student t test was used to compare quantitative data between two independent groups while Chi square test was used for qualitative data. Paired samples t test was used to compare quantitative data for the same group at two different time points and marginal homogeneity test was used for qualitative data. One Way ANOVA test was used to compare quantitative data between more than two groups. Pearson's correlation test was used to measure correlation between different quantitative variables. ROC curve analysis was used to measure diagnostic validity of quantitative variables and determine the best cut off value. P value less than or equal to 0.05 was considered statistically significant.

RESULTS

Regarding demographic data, table (1) showed no significant difference between both groups.

Table (1): Demographic data

		Group				**t***	**P value**
		Cases		**Controls**			
		Mean	**SD**	**Mean**	**SD**		
Age		42.23	11.00	34.20	10.41	2.91	**0.01 HS**
		N	**%**	**N**	**%**	**X^{2**}**	**P value**
Gender	Male	17	56.7%	21	70.0%	1.15	0.28 NS
	Female	13	43.3%	9	30.0%		
Residence	Urban	16	53.3%	15	50.0%	0.07	0.80 NS
	Rural	14	46.7%	15	50.0%		
Smoking	No	19	63.3%	15	50.0%	1.09	0.30 NS
	Yes	11	36.7%	15	50.0%		

*Student t test **Chi square test

Table (2) showed that there was a highly significant difference between oncostatin levels in cases and control as the mean for cases was 120.13pg/ml and for controls was 19.75 pg/ml ($p<0.001$).

Table (2): Lab investigations

	Group				**t***	**P value**
	Cases		**Controls**			
	Mean	**SD**	**Mean**	**SD**		
Platelets ($10^3/mm^3$)	359.20	42.75	312.03	7.61	2.510	**0.02 S**
HB (g/dL)	10.65	1.79	12.60	0.98	5.226	**<0.001 HS**
WBCs ($10^3/mm^3$)	10.33	2.41	7.61	1.74	3.195	**0.002 HS**
ESR (mm/hr)	43.33	9.53	28.54	6.43	3.204	**0.003 HS**
CRP (mg/L)	74.90	7.41	4.77	0.87	5.226	**<0.001 HS**
Urea (mg/dl)	32.03	7.26	26.59	6.51	2.521	**0.01 HS**
Creatinine (mg/dl)	1.07	0.21	0.95	0.21	1.425	0.16 NS
ALT (U/L)	32.67	6.28	26.73	6.43	3.210	**0.002 HS**
AST (U/L)	31.57	6.12	29.57	6.43	1.234	0.22 NS
T. Proteins (g/dl)	7.07	0.64	6.97	0.56	0.642	0.52 NS
Albumin (g/l)	4.30	0.63	4.11	0.71	1.131	0.26 NS
Bilirubin (µmol/L)	0.82	0.19	0.79	0.17	0.364	0.72 NS
Carcinoembryonic Antigen (CEA) (µg/L)	1.88	0.36	1.85	0.32	0.131	0.90 NS
CA-19.9	17.87	4.32	15.77	3.73	1.603	0.11 NS
Oncostatin M (pg/ml)	120.13	28.43	46.90	10.64	9.952	**<0.001 HS**

*Student t test

The clinical data of patients are shown in table (3).

Table (3): Clinical data of cases

		Min.	**Max.**	**Mean**	**SD**
Illness Duration		1.00	4	1.6	0.37
No of exacerbations		1.00	5.00	2.13	0.41
No. of bowel motions		1.00	8.00	2.33	0.51
		N		**%**	
Type of IBD	UC	15		50.0%	
	CD	15		50.0%	
Family history	Negative	7		23.3%	
	Positive	23		76.7%	
Diarrhea	Negative	0		0.0%	
	Positive	30		100.0%	
Bloody diarrhea	Negative	10		33.3%	
	Positive	20		66.7%	
Abdominal pain	Negative	14		46.7%	
	Positive	16		53.3%	
Consistency	Formed	15		50.0%	
	Semi formed	15		50.0%	
Blood in stool	Negative	18		60.0%	
	Positive	12		40.0%	
Mucus in stool	Negative	16		53.3%	
	Positive	14		46.7%	

17 patients were treated with infliximab, 4 patients with adalimumab and 9 patients with prednisone as shown in table (4). There was a highly significant difference between fecal calprotectin levels before and after treatments as the mean before treatment was 343.37 ug/gm while after treatment was 147.63 ug/gm ($p<0.001$) (Table 5). Also, there was a highly significant difference between oncostatin M levels before and after treatments as the mean before treatment was 120.13 pg/ml while after treatment was 91.17 pg/ml ($p<0.001$) (Table 6).

Table (4): Treatment

		N	%
Treatment	Infliximab	17	**56.7%**
	Prednisone	9	30.0%
	Adalimumab	4	13.3%

Table (5): Fecal calprotectin before and after treatment

	Mean	SD	t*	P value
Fecal calprotectin level at baseline (µg/g)	343.37	82.70	4.82	**<0.001 HS**
Fecal calprotectin level after treatment	147.63	34.35		

*Paired samples t test

Table (6): Oncostatin before and after treatment

	Mean	SD	t*	P value
Oncostatin M at baseline (pg/ml)	120.13	28.31	6.40	**<0.001 HS**
Oncostatin M after Treatment	91.17	21.72		

*Paired samples t test

There was no significant relation between oncostatin levels and baseline laboratory investigations as shown in table (7).

Table (7): Correlation between baseline Oncostatin and lab investigations:

		Oncostatin M At Baseline
Platelets (mcL)	Pearson Correlation	.199
	P value	.293 NS
HB (g/dL)	Pearson Correlation	.073
	P value	.700 NS
WBCs (mcL)	Pearson Correlation	.087
	P value	.646 NS
ESR (mm/hr)	Pearson Correlation	-.100
	P value	.597 NS
CRP (mg/L)	Pearson Correlation	.319
	P value	.085 NS
Urea (mg/dl)	Pearson Correlation	-.247
	P value	.188 NS
Creatinine (mg/dl)	Pearson Correlation	-.249
	P value	.184 NS
ALT (U/L)	Pearson Correlation	-.340
	P value	.066 NS
AST (U/L)	Pearson Correlation	-.294
	P value	.115 NS
T. Proteins (g/dl)	Pearson Correlation	-.074
	P value	.697 NS
Albumin (g/l)	Pearson Correlation	.293
	P value	.116 NS
Bilirubin (µmol/L)	Pearson Correlation	.105
	P value	.581 NS
Carcinoembryonic Antigen (CEA) (ug/L)	Pearson Correlation	.107
	P value	.573 NS
CA-19.9	Pearson Correlation	.178
	P value	.346 NS
Fecal Calprotectin Level at Baseline	Pearson Correlation	.227
	P value	.227 NS

There was a highly significant correlation between oncostatin M levels and fecal calprotectin levels after treatment ($p<0.001$) as shown in figure (1). There was no significant relation between oncostatin levels and the degrees of severity of IBD before treatment as shown in table (8), while there was a highly significant relation between oncostatin levels and degrees of endoscopic severity of IBD after treatment ($p<0.001$) as well as a highly significant relation between oncostatin levels and degrees of clinical severity after treatment ($p<0.001$) as shown in table (9).

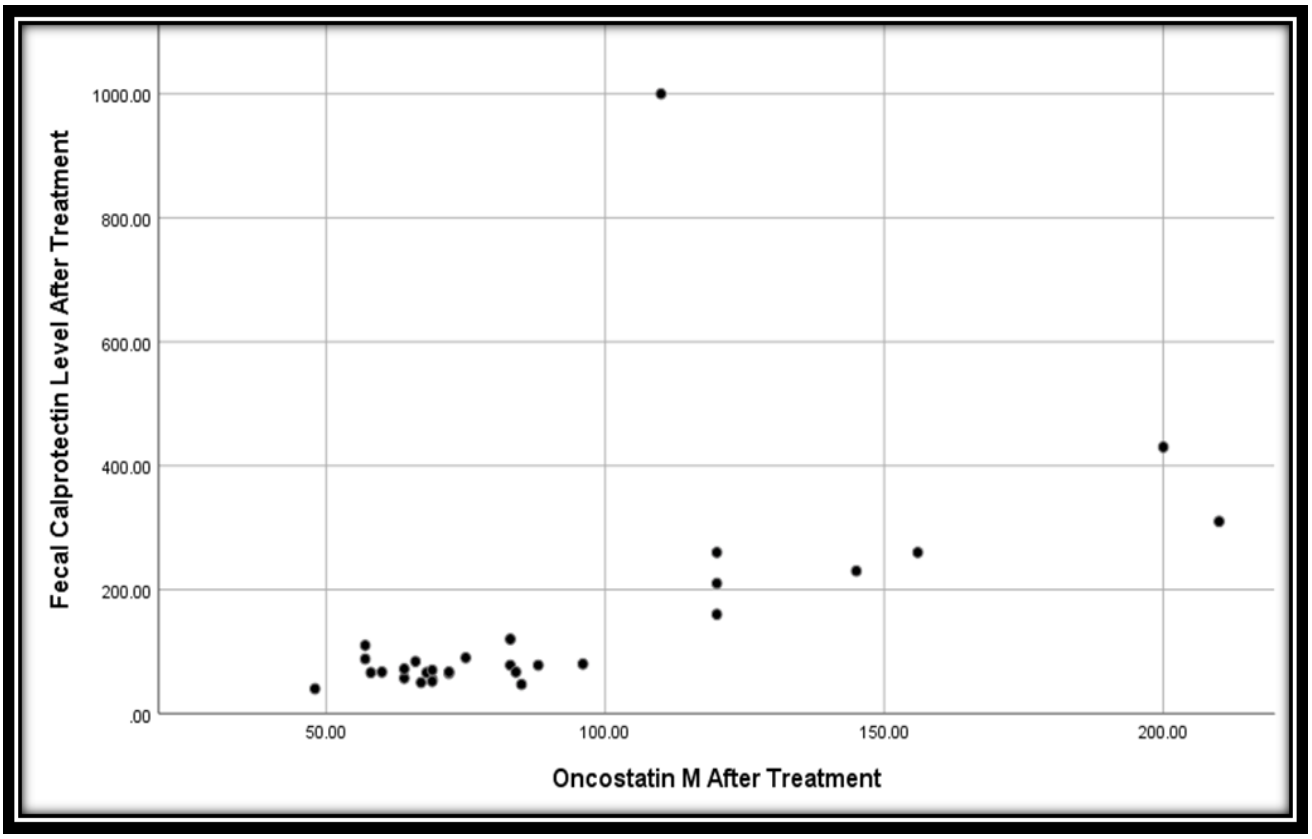

Figure (1): Correlation between Oncostatin and fecal calprotectin after treatment

Table (8): Relation between Oncostatin and severity scores before treatment:

		Oncostatin M at baseline		F*	P value
		Mean	SD		
Endoscopic scores before treatment	Mild	109.50	25.53	2.10	0.14 NS
	Moderate	116.19	27.63		
	Severe	144.83	33.50		
Clinical scores before treatment	Mild	112.00	25.03	2.01	0.15 NS
	Moderate	115.13	28.53		
	Severe	144.83	35.50		

*One Way ANOVA test

Table (9): Relation between Oncostatin and severity scores after treatment:

		Oncostatin M after treatment		F*	P value
		Mean	SD		
Endoscopic scores after treatment	Remission	110.10	24.98	12.87	**<0.001 HS**
	Mild	111.09	22.60		
	Moderate	137.33	67.69		
	Severe	144.83	32.50		
Clinical scores after Treatment	Remission	109.00	27.12	12.84	**<0.001 HS**
	Mild	111.27	22.14		
	Moderate	137.33	33.69		
	Severe	144.83	34.40		

*One Way ANOVA test

Receiver operating characteristic curve for the level Oncostatin in diagnosis of IBD cases showed that the best cut off point between groups regarding the level of oncostatin was > 78.50 pg/ml with sensitivity of 96.7%, specificity of 100% as shown in figure (2).

Validity of baseline Oncostatin for diagnosis of IBD:

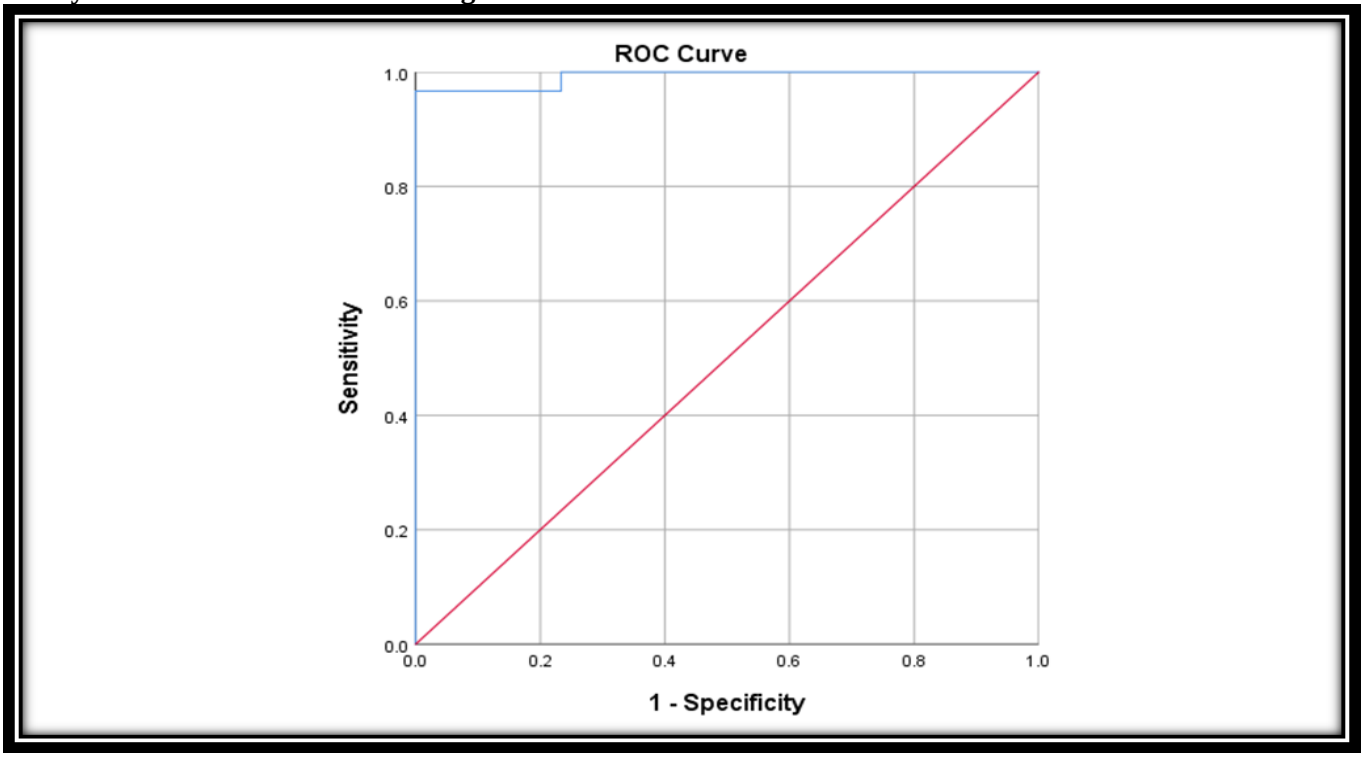

Figure (2): Validity of baseline Oncostatin for diagnosis of IBD.

Receiver operating characteristic curve for the level Oncostatin in diagnosis of IBD cases.
Best cut off value > 78.50 pg/ml. Sensitivity = 96.7%, and Specificity = 100%.

Receiver operating characteristic curve for the level of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) using Endoscopic Scores of Severity after Treatment showed that the best cut off point between groups regarding the level Oncostatin was < 103.50 pg/ml with sensitivity of 40% and specificity of 75%. The best cut off point between groups regarding the level of fecal calprotectin was < 232.00 ug/gm with sensitivity of 70% and specificity of 80% as shown in figure (3).

Validity of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) (using Endoscopic scores after treatment):

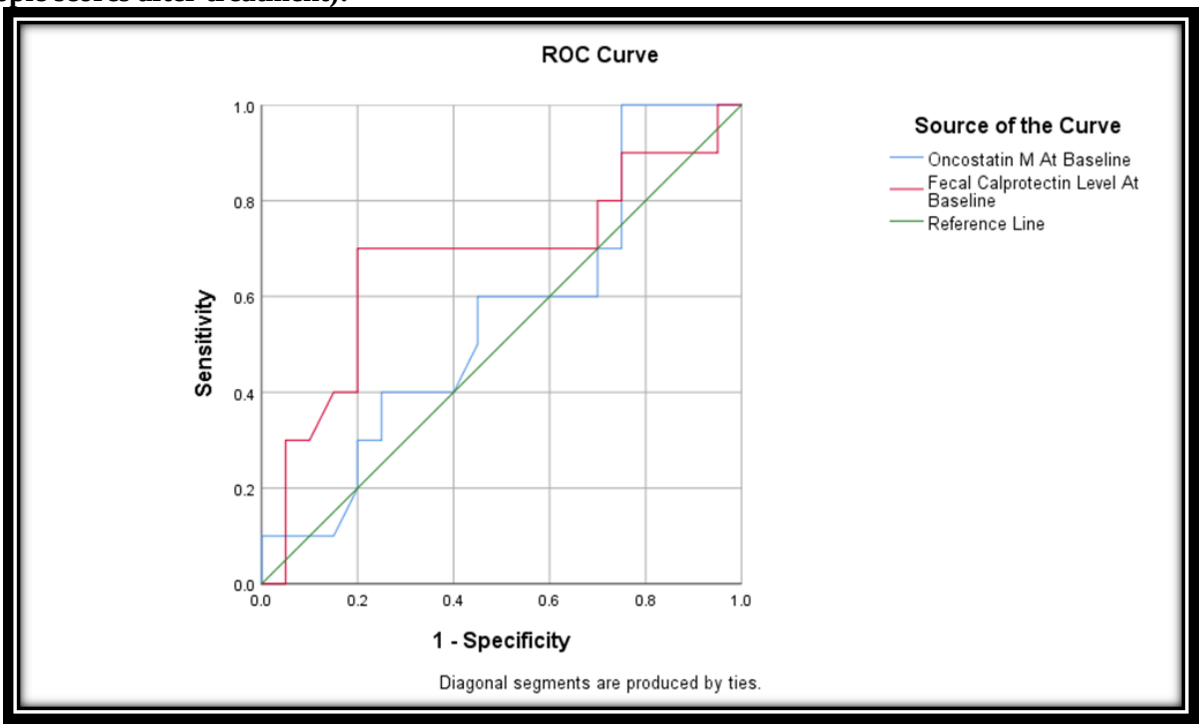

Figure (3): Validity of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) using Endoscopic Scores after Treatment.

Receiver operating characteristic curve for the level of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) (using endoscopic scores after treatment).

Area Under the Curve				
Area	**Std. Error**	**Asymptotic Sig.**	**Asymptotic 95% Confidence Interval**	
			Lower Bound	**Upper Bound**
0.992	0.008	**0.000 HS**	0.976	1

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error**	**Asymptotic Sig.**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
Oncostatin M At Baseline	0.555	0.111	0.628 NS	0.337	0.773
Fecal Calprotectin Level At Baseline	0.672	0.115	0.129 NS	0.446	0.899

- **Oncostatin:** Best cut off value < 103.50 pg/ml. Sensitivity = 40%, and Specificity = 75%.
- **Fecal calprotectin:** Best cut off value < 232.00 ug/gm. Sensitivity = 70%, and Specificity = 80%.

Receiver operating characteristic curve for the level of baseline Oncostatin and fecal calprotectin for prediction of response to treatment (remission) using Clinical Scores after Treatment showed that the best cut off point between groups regarding the level oncostatin was < 118.50 pg/ml with sensitivity of 66.7% and specificity of 54.2%. The best cut off point between groups regarding the level of fecal calprotectin was < 220.00 ug/gm with sensitivity of 66.7% and specificity of 75% as shown in figure (4).

Validity of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) (using Clinical scores after Treatment):

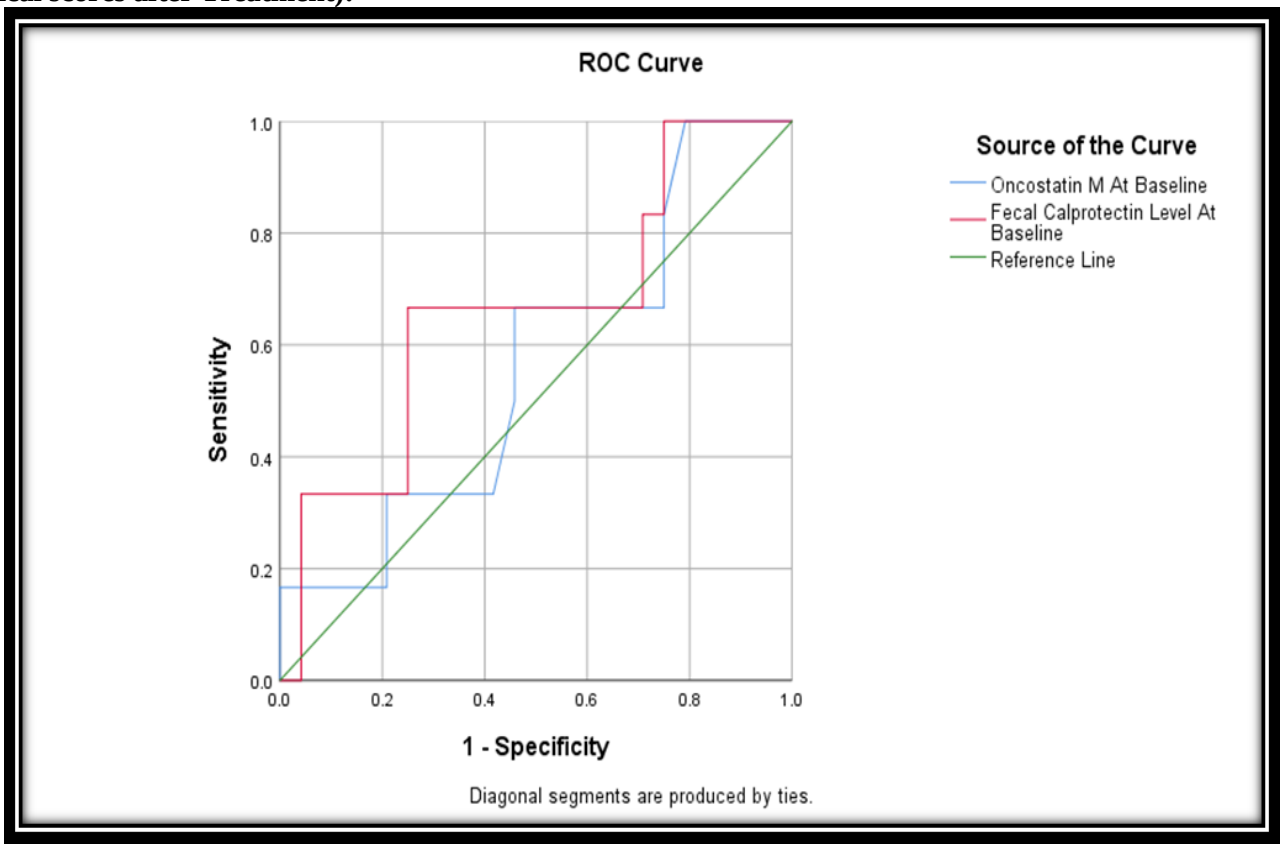

Figure (4): Validity of baseline oncostatin and fecal calprotectin for prediction of response to treatment (remission) using Clinical Scores after Treatment.

Receiver operating characteristic curve for the level baseline Oncostatin and fecal calprotectin for prediction of response to treatment (remission) (using Clinical scores after Treatment).

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Oncostatin M At Baseline	0.563	0.130	0.641 NS	0.307	0.818
Fecal Calprotectin Level At Baseline	0.660	0.131	0.233 NS	0.402	0.917

Oncostatin: Best cut off value < 118.50 pg/ml. Sensitivity = 66.7%, and Specificity = 54.2%.
Fecal calprotectin: Best cut off value < 220.00 ug/gm. Sensitivity = 66.7%, and Specificity = 75%.

DISCUSSION

This study was conducted mainly to evaluate the changes in serum oncostatin M levels during treatment of inflammatory bowel disease patients and its relation to clinical scoring and endoscopic scoring in inflammatory bowel disease patients and also to study the value of oncostatin as predictive marker of response to treatment in IBD patients.

In our study, we found a highly significant difference between oncostatin level in cases and oncostatin levels in control. We also found that the best cut off point value between groups regarding the level of oncostatin was found to be more than 78.50 pg/ml with high sensitivity of 96.7% and high specificity of 100%. These results signify the importance of oncostatin in the diagnosis of cases with active IBD and adding a valuable information to the literature. This result is supported by various studies as **West *et al.*** [8], **Verstockt *et al.*** [9] and **Kim *et al.*** [10] who studied tissue samples from intestinal lesions of patients with active IBD and found high expression of oncostatin M and oncostatin M receptor in tissue samples. **Verstockt *et al.*** [9] stated that the ROC analysis based on mucosal oncostatin showed a highly significant difference between patients with inflammatory bowel disease and control**s.** And another support comes from **Cao *et al.*** [11] who found a significant difference between serum oncostatin levels in inflammatory bowel disease patients and healthy subjects.

Our study showed a highly significant relation between oncostatin levels and severity scores after treatment using endoscopic scores of severity as inflammatory bowel disease patients without mucosal healing had higher levels of oncostatin so oncostatin may be used as marker for endoscopic activity. We also found a highly significant relation between oncostatin levels and severity scores after treatment using clinical scores of severity.

These results signify the precision of oncostatin as a future biomarker in follow up of inflammatory bowel disease. Our finding adds important evidence to **Cao *et al.*** [11] who provide the first evidence that serum oncostatin can be used to follow up inflammatory bowel disease patients.

Oncostatin is expressed in intestinal stromal cells in patients of inflammatory bowel disease and this leads to marked inflammatory response with production of chemokines that attract phagocytic cells and T lymphocytes. In an animal study with infliximab resistant intestinal inflammation, antagonism of oncostatin on genetic level leads to improvement of the disease [8]**.** These data can explain the highly significant relation in this study between oncostatin levels and severity scores after treatment using endoscopic index of severity

Fecal calprotectin use as a biomarker is universally popular clinically and shows superiority over CRP in diagnosis and follow up of inflammatory bowel disease [12]. In our study we found that there was highly significant difference between fecal calprotectin levels at baseline and after treatment of IBD. We also found a highly significant difference between oncostatin levels at baseline and after treatment of IBD. Also, there was highly significant correlation between fecal calprotectin levels and oncostatin levels after treatment of IBD. These results signify the importance and validity of oncostatin in follow-up of inflammatory bowel disease activity and detecting relapse and remission of the disease. Comparing fecal calprotectin levels to oncostatin levels before and after treatment is one of the strength points of this study.

In our study, although there was a significant difference between oncostatin levels in cases and oncostatin levels in healthy subjects, there was no significant relation between oncostatin levels in the different degrees of severity of IBD before treatment. As regards the literature there is good evidence that there is high expression and upregulation of oncostatin directly proportional to the degree of severity of the disease on tissue level provided by the famous study of **West *et al.*** [8].

This discrepancy between our results regarding the relation between serum oncostatin levels and severity of IBD before treatment and **West *et al.*** [8] results on tissue level may be explained by the relatively small number of cases in our study. **Cao *et al.*** [11] found a significant relation between oncostatin levels and degree of severity of IBD using the newly developed methodology of chemiluminescence immunoassay (CLIA) for detection of oncostatin levels, which appears to be more sensitive than the ELISA method used in our study.

As regards the use of oncostatin level for prediction of response to treatment, we found that the best cut off point was less than 103.50 pg/ml with sensitivity of 40%, specificity of 75% using Endoscopic scores of severity after treatment and the best cut off point less than 118.50 pg/ml with sensitivity of 66.7%, specificity of 54.2% using Clinical Score.

These results were disappointing regarding the use of oncostatin as a predictor of response to treatment in inflammatory bowel disease patients. **Cao *et al.*** [11] found that high levels of oncostatin predicts resistance to infliximab therapy. **Guo *et al.*** [4] confirmed the use of oncostatin as a predictor of response to treatment with infliximab in IBD patients. **West *et al.*** [8] stated that colonic oncostatin expression can predict the response to infliximab therapy. In another study of pediatric patients with Crohn's disease, there was significant correlation between high serum oncostatin levels and resistance to infliximab therapy [13]**. O'Connell *et al.*** [14] was the only available study to find that mucosal oncostatin M was not predictive of infliximab response in a small number of patients with severe ulcerative colitis**.** The discrepancy between our finding and the literature may be explained by our relatively small number of IBD cases.

In our study fecal calprotectin showed better prediction of response to treatment with best cut off point value less than 220.00 ug/gm with sensitivity of 66.7% and specificity of 75% using Clinical score and better prediction with best cut off point less than 232.00 ug/gm with sensitivity of 70% and specificity of 80% when using Endoscopic score of severity. This finding is supported by **Beltrán *et al.*** [15] who found that baseline levels of fecal calprotectin may predict the response to infliximab therapy.

In the current study, there was a high statistically significant difference in between cases and control group regarding CRP. Currently, CRP is used as clinical biomarker for Crohn's disease. High baseline CRP is associated with good response to infliximab treatment [16]**.**

We preferred fecal calprotectin over CRP to examine its correlation with oncostatin after treatment due to the high specificity of fecal calprotectin to IBD and its expression in mucosal intestinal lesions.

CONCLUSION

Oncostatin M is a promising marker for the diagnosis and follow-up of IBD patients, however it has a limited predictive performance for the prediction of the response for IBD treatment.

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Author contribution: Authors contributed equally in the study.

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