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Serum Trefoil Factor 3 as a Biomarker for Mucosal Healing in Ulcerative Colitis: Case Control Study

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ABSTRACT

Background: Ulcerative Colitis (UC) is a relapsing, long-lasting, and colon remitting inflammatory disease. UC is diagnosed through observation of symptoms, signs, endoscopy, and histology. Precise diagnosis and staging of the illness are crucial as they impact both treatment choices and prognosis.

Aim of the Work: This study aimed to assess serum Trefoil Factor 3 (TFF3) as a mucosal healing (MH) marker in UC cases.

Patients and Methods: The present study was conducted on 25 UC patients in activity, 25 patients in remission, and 25 control subjects with clinical, biochemical, and endoscopic evaluation. All patients had a comprehensive history, clinical examination, standard laboratory tests, ESR, CRP, CBC, fecal calprotectin (FC), TFF3, and colonoscopy.

Results: The best cut off point to TFF3 was determined by ROC curve to differentiate between remission and active groups was > 71 with sensitivity of 92.0%, AUC of 0.932, and 96.0% specificity. There was a significantly elevated CRP, FC and TFF3 among disease activity in relation to remission and control. However, hemoglobin level was significantly lower in activity and remission patients in comparison to healthy control. There was positive correlation between TFF3 and MES.

Conclusion: Serum trefoil factor 3 level increased during disease activity and decreased during remission and MH which makes serum TFF3 level can be utilized for MH prediction in UC and endoscopic remission.

Keywords: Serum Trefoil Factor 3, Mucosal Healing, Ulcerative Colitis, Endoscopic Remission.

INTRODUCTION

Lifelong chronic inflammatory bowel disease (IBD) identified as ulcerative colitis (UC) can be defined by times of remission and relapse. The precise pathogenesis of UC is unknown, however the disease is believed to be polygenic and multifactorial. The potential causes are immune dysfunction, environmental factors, and a probable genetic predisposition [1].

IBD is a condition that manifests in both genders at an early age. The IBD incidence and prevalence experienced a significant rise in the latter half of the 20th century. IBD has been acknowledged as one of the most prevalent gastrointestinal diseases since the turn of the 21st century, with an increasing prevalence in newly industrialized nations [2].

It is distinguished by inflammation that is limited to the mucosa and submucosa of the colon. The disease usually start in the rectum and advances distally in a continuous way [3]. Rectal urgency, tenesmus, crimson diarrhea with or without mucous, and varying degrees of abdominal discomfort comprise the classic presentation of UC [4].

Findings on endoscopy, negative stool examination, and biopsy, are used to clinically diagnose UC. Particularly throughout an acute exacerbation, laboratory evaluation typically reveals an elevation in inflammatory factors (ESR, CRP, leukocytosis) [3].

Management strategy relay on disease, severity and the disease course [3]. A paradigm shift in therapy goals has been facilitated by advancements in medical treatments, which have facilitated the transition from symptomatic alleviation to endoscopic and histological healing in order to achieve superior long-term outcomes [5].

A protein known as trefoil factor 3 (TFF3) is a member of the TFF family, which is composed of three stable secretory proteins that are expressed in conjunction with mucins from epithelial cells in the gastrointestinal tract. In the body, TFF1 usually appears in the gastroduodenal mucosa, whereas TFF2 is mainly expressed in the stomach antral glands and mucous neck cells **[5].**

Conversely, TFF3 is stated in intestine goblet cells and at significantly lesser levels in other organs, including the hypothalamus, salivary glands, respiratory tract, and breast. The TFF proteins are essential for the promotion of epithelial restitution following injury [5].

The TFF expression rise locally when the mucosal surface is discontinuous. This increased level aids in the injured tissue healing by protecting the mucosal surface from further harm and stimulating cell migration and proliferation **[5].** This study aimed to evaluate serum TFF3 as a MH marker in UC cases.

SUBJECTS AND METHODS

This case control study was performed on 50 UC cases divided into 25 in activity and 25 in remission treated in Ain Shams University Hospitals (Gastroenterology in patient Department and Outpatient Clinics) ranged in age from 18 to 68 years and 25 subjects as a control group with age ranged from 18 to 49.

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Inclusion criteria: Patients presented with UC disease during activity and remission. Patients more than 18 years old. Newly diagnosed patients with UC.

Exclusion criteria: Pregnant nursing females. Patients less than 18 years old. Patients who refuse to participate in the study. Patient with autoimmune disease as systemic lupus and rheumatoid arthritis. Patients with chronic diseases as DM, heart failure and renal failure. Other causes of serum TFF3 elevation (Peptic Ulcer Disease & Colorectal Cancer).

Study tools: All patients were subjected to the following: Age, sex, smoking status, number of bowel movements, abdominal pain, fever, weight loss, rectal hemorrhage, mucous in stool, tenesmus, urgency, nausea, vomiting, anorexia, and malaise are all included in the history-taking process. Detailed clinical examination including a comprehensive abdominal and general examination. Ten milliliters of venous blood were collected under complete aseptic precautions and then were divided into the following tubes: one Tri-potassium ethylene diamine tetra acetate (K3 EDTA) tube used for assay of CBC using hematology analyzers Sysmex (XN-1000), two tubes with clot activator. Blood in the tube with clot activator was allowed to clot for 30 to 45 minutes. After clotting, samples were centrifuged at 2000-3000 rpm (revolutions per minute) for 20 minutes. and the separated serum was used for assay of liver function tests and kidney function tests, which were performed on AU 680 chemistry analyzer (Beckman Instruments Inc., Scientific Instruments Division, Inc. 250 S. Kraemer Blvd. Brea, CA92634-3100, USA), while viral markers (HBsAg and HCVAb) and CRP were performed on Cobas e 411 immunoassay autoanalyzer using kits supplied by Roche Diagnostics (Roche Diagnostics GmbH, Sand Hofer Strasse 116, D-68305 Mannheim). The other tube was used for serum TFF3 assay. It was stored at -20 °C till analysis. Hemolysed samples were discarded. Repeated freezing/thawing of samples was avoided.
The separated serum was used to measure TFF3 level using enzyme linked immunoassay kit (Changsheng S Rd, Nanhu Dist, Jiaxing, Zhejiang, China).

Analytical method of measurement of TFF3:

This assay employs the quantitative sandwich immunoassay technique. These kits contain a micro-ELISA plate with an antibody specific to Human TFF3. Samples, standards and controls were added to the micro-ELISA plate wells and combined with the antibody. A biotinylated detection antibody specific for TFF3 and an Avidin Horseradish Peroxidase (HRP) conjugate were then added to each microplate well and incubated. The free components were washed away. Each well was filled with substrate solution. The reaction of the enzyme-substrate was stopped by putting stop solution. Optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value was directly proportional to the concentration of TFF3. A standard curve was constructed where concentration of TFF3 in the samples and controls were deduced.

The point-of-care desk-top Quantum Blue Reader® (POC Reader) method was employed to analyze calprotectin contained in stool samples. Quantum Blue® Calprotectin, Bühlmann Laboratories AG, Switzerland, is a lateral flow technology that adheres to the manufacturer's instructions and is based on ELISA techniques. We conducted an additional 1:10 dilution with extraction buffer in accordance with the manufacturer's instructions to achieve FC levels of up to 3000 µg/g. This was necessary because the POC device incorporates internal standards with a sensitivity of 300 µg/g and a range of 30-300 µg/g. 3000 µg/g was the value of FC that exceeded the upper limit of the tested ranges, while 30 µg/g was the value of FC that was below the lower limit.

Colonoscopy: The day prior to the examination, the patient adhered to a specific regimen that prohibited the consumption of substantial food. Beverages restricted to clear liquids, ordinary water, tea and coffee without milk or cream, bouillon, and carbonated beverages. Due to the potential for confusion with blood during the colonoscopy, it was advised to refrain from consuming red liquids and refrain from consuming any food or beverages after mid-night on the day prior to the procedure. The day before the procedure, the colon was cleared through repeated enemas. The day before the procedure, laxatives were also administered to the patient. To evacuate the colon in preparation for colonoscopy in adults sodium picosulfate (a stimulant laxative), magnesium oxide and anhydrous citric acid (which compose the FDA-approved magnesium citrate, an osmotic laxative) combination was used.

Lower GI endoscopy with intubation of terminal ileum and multiple biopsies were taken to confirm diagnosis, assess severity, extent of endoscopic involvement, Mayo Classification and visualization of any dysplastic changes or masses. Among endoscopic scores, Mayo Endoscopic Score (MES**)** was used during the study. It provides a numerical assessment, with higher points representing a more severe disease.

This study employed the Mayo score, which is a disease activity index that is frequently employed in placebo-controlled trials in UC. Four components comprise its entirety: physician evaluation, defecation frequency, rectal hemorrhage and endoscopy appearance. A cumulative score of 0 to 12 is the consequence of the ratings for each component, which range from 0 to 3. Mildly active disease is indicated by a score of 3 to 5 points, moderately active disease by a score of 6 to 10 points, and severely active disease by a score of 11 to 12 points.

Sample Size Calculation: Utilizing Power Analysis and Sample Size Software (PASS 15) (Version 15.0.

10) for sample size calculation, setting power at 99%, alpha error at 0.05, and reviewing previous study results. The resulting sample size of at least 50 UC patients (25 in activity and 25 in remission) and 25 healthy controls is required the sample size was estimated.

Ethical Approval: The investigation was conducted in accordance with Declaration of Helsinki . The Ethical Committee of Ain Shams University Hospitals approved the study prior to the study commencement. Each participant provided written consent. (Approval code: FWA 000017585).

Statistical Analysis

The statistical analysis was conducted utilizing SPSS version 27 (IBM©, Armonk, NY, USA). The normality of the data distribution was evaluated utilizing the Shapiro-Wilks test and histograms. Quantitative parametric data were analyzed using the ANOVA (F) test with a post hoc test (Tukey), depicted as mean and standard deviation (SD). The Kruskal-Wallis test and Mann-Whitney-U test were employed to evaluate the quantitative non-parametric data, which were presented as median and interquartile range (IQR) in order to compare each group. Qualitative variables were analyzed using the Chi-square test, which were presented as percentages and frequencies (%). Our definition of statistical significance was a two-tailed P value ≤ 0.05.

RESULTS

Table (1) showed that between groups regarding age there was statistically insignificant difference with p-value = 0.255.

Table (1): Comparison between studied groups regarding demographic data

			Subgroups		**Test value**	**P-value**
		Control group	**Remission**	**Active**		
		No.= 25	**No.= 25**	**No.= 25**		
Gender	Female	16 (64.0%)	17 (68.0%)	20 (80.0%)	1.672•	0.433
	Male	9 (36.0%)	8 (32.0%)	5 (20.0%)		
Age (years)	Mean ± SD	30.08 ± 7.2	29.2 ± 7.1	33.28 ± 8.1	1.394•	0.255

Data are presented as mean ± SD or frequency (%).

Table (2) showed that a statistically significant decrease was detected in hemoglobin level in patients in remission [11.61 ± 1.87] and patients in active status [11.08 ± 1.75] than control group [12.5 ± 0.82] with p-value = 0.007 and with insignificant difference between remission and active groups. Also, there was statistically insignificant difference between control group and patients subgroups regarding the other laboratory parameters.

Table (2): Comparison across studied groups according to laboratory parameters

		Control group	**Remission**	**Active**	**Test value**	**P-value**
		No.= 25	**No.= 25**	**No.= 25**		
TLC (10^3/uL)	Median (IQR)	6 (5 - 8)	7 (6 - 9)	7.7 (5 - 10.2)	3.390≠	0.184
Hb **(g/dL)**	Mean ± SD	12.5 ± 3.11	11.61 ± 1.87	11.08 ± 1.75	5.303•	0.007
Plt **(10^3/uL)**	Mean ± SD	305.32 ± 75.8	285.4 ± 70.47	293.6 ± 72.81	0.285•	0.753
Creat **(mg/dL)**	Mean ± SD	0.78 ± 0.189	0.74 ± 0.185	0.78 ± 0.188	0.269•	0.765
Na **(mmol/L)**	Mean ± SD	138.32 ± 1.63	138.08 ± 2.45	137.96 ± 1.74	0.216•	0.806
K **(mmol/L)**	Mean ± SD	3.86 ± 0.14	3.92 ± 0.3	4.07 ± 0.49	2.714•	0.073
AST **(IU/L)**	Median (IQR)	16 (12 - 22)	15 (12 - 21)	16 (13 - 20)	0.511≠	0.775
ALT **(IU/L)**	Median (IQR)	12 (11 - 16)	12 (10 - 15)	11 (10 - 15)	2.118≠	0.347
Total bilirubin **(mg/dL)**	Mean ± SD	0.37 ± 0.0911	0.37 ± 0.011	0.38 ± 0.012	0.039•	0.962
Direct bilirubin **(mg/dL)**	Mean ± SD	0.13 ± 0.05	0.14 ± 0.06	0.13 ± 0.06	0.275•	0.761
Total protein **(g/dL)**	Mean ± SD	6.92 ± 0.13	6.83 ± 0.43	6.89 ± 0.47	0.385•	0.682
Albumin **(g/dL)**	Mean ± SD	4.05 ± 0.41	3.86 ± 0.42	3.82 ± 0.56	1.728•	0.185

Parameters	**Control group VS Remission**	**Control group VS Active**
Hb (g/dL)	0.046	0.002

TLC: Total Leucocytic Count; Hb: Hemoglobin; Plt: Platelets; Na: Sodium; K: Potassium; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase. Data are presented as mean ± SD or frequency (%), and IQR: interquartile range Significant P-value < 0.05, Highly significant P-value < 0.01.

Table (3) showed that in terms of ESR level, there was a statistically significant difference between the control group and patient subgroups (p-value <0.001). The post-hoc analysis revealed that the level of ESR was significantly higher in patients in remission [50 (10 - 80)] and in active state [20 (11 - 30)] than in the control group, but there was no significant difference between the remission and active groups. Also, the table showed that there was statistically significant difference between groups regarding FC level with p-value <0.001. The post hoc analysis showed that the level of FC was significantly higher in patients in active state [2100 (900 - 2400)] than in remission [954.5 (406 - 2300)] and also in remission patients than control group [85 (73 - 110)]. Also, the table showed that there was statistically significant difference between the studied individuals in terms of CRP level with p-value <0.001. The CRP level was significantly higher in active state cases [8.1 (5.1 - 14.6)] than in remission [4.5 (2 - 9.6)] and also significantly higher in patients in remission than control group [0.9 (0.5 - 4)]. The level of TFF3 also significantly differed between the three groups with p-value <0.001. The TFF3 level was significantly elevated in active state cases [150 (126 - 180)] than in remission [36 (27 - 49)] and also significantly elevated in patients in remission than in control group [8 (7 - 10)].

Table (3): Comparison regarding inflammatory markers, fecal calprotectin, and TFF3

			Subgroups		**Test value**	**P-value**	**Sig.**
		Control group	**Remission**	**Active**			
		No.= 25	**No.= 25**	**No.= 25**			
ESR **(mm/h)**	Median (IQR)	6 (5 - 8)	50 (10 - 80)	20 (11 - 30)	23.352≠	0.000	HS
CRP **(mg/dL)**	Median (IQR)	0.9 (0.5 - 4)	4.5 (2 - 9.6)	8.1 (5.1 - 14.6)	17.977≠	0.000	HS
Fecal calprotectin **(ug/g)**	Median (IQR)	85 (73 - 110)	954.5 (406 - 2300)	2100 (900 - 2400)	43.498≠	0.000	HS
TFF3 **(ng/mL)**	Median (IQR)	8 (7 - 10)	36 (27 - 49)	150 (126 - 180)	65.729≠	0.000	HS

Post Hoc analysis by LSD and multi-comparison between groups			
Parameters	**Control vs Remission**	**Control vs Active**	**Remission vs Active**
ESR	0.001	0.001	0.196
CRP	0.039	0.001	0.022
Fecal calprotectin	0.001	0.001	0.021
TFF3	0.001	0.001	0.000

ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; TFF3: Trefoil Factor 3; AUC: Area under curve; +PV: Positive Predictive Value; -PV: Negative Predictive Value. Data are presented as mean ± SD or frequency (%), and IQR: interquartile range; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Table (4) showed that there was between the MES of the patients in the study and TFF3, a statistically significant positive correlation but between the TFF3 level and the other parameters statistically insignificant correlation was found.

Table (4): Correlation between TFF3 level and the other studied parameters

	TFF3	
	r	**P-value**
Age	0.143	0.320
TLC	-0.046	0.753
Hb	-0.034	0.814
Plt	-0.048	0.741
Creatinine	0.123	0.395
Na	-0.008	0.959
K	0.112	0.437
AST	0.024	0.868
ALT	-0.088	0.544
Total bilirubin	0.115	0.428
Direct bilirubin	0.014	0.922
Total protein	0.217	0.130
Albumin	0.098	0.500
ESR	-0.180	0.210
CR	0.228	0.111
Fecal calprotectin	0.126	0.387
Mayo endoscopic score	**0.781****	**0.000**

TFF3: Trefoil Factor 3; TLC: Total Leucocytic Count; Hb: Hemoglobin; Plt: Platelets; Creat: Creatinine; Na: Sodium; K: Potassium; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; AUC: Area under curve. Data are presented as mean ± SD or frequency (%), and IQR: interquartile range; P-value < 0.05: Significant; P-value < 0.01: Highly significant. R: Spearman correlation coefficient

The ROC curve indicates that the optimal cut-off point for TFF3 to differentiate between remission and active groups was >71 ng/ml, with a sensitivity of 92.0%, specificity of 96.0%, and AUC of 0.932 (Table 5 & figure 1).

Table (5): Receiver operating characteristics curve (ROC)

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
> 71	0.932	92.00	96.00	95.8	92.3

AUC: Area under curve

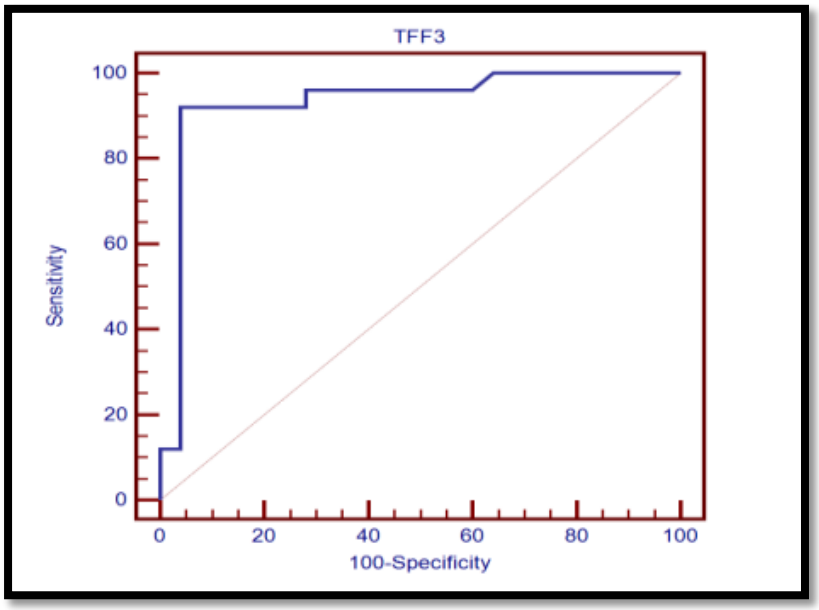

Figure 1: Receiver operating characteristics curve (ROC).

DISCUSSION

The chronic inflammatory condition is identified as UC that has variable degrees of impact on the rectum and colon. UC is generally regarded as a condition that arises in individuals who are genetically predisposed to environmental exposures. The microbiota, gut epithelial barrier abnormalities, and a dysregulated immune response are all closely associated. Applying a clinical, biochemical, endoscopic, and histological evidence, as bleeding diarrhea is a prevalent occurrence the diagnosis is established in patients **[6].** The fundamental objective of treating UC has been superseded by mucosal recovery, which has replaced clinical remission. Endoscopic examination is difficult for patients, necessitating the use of non-invasive indicators to assess MH. TFF3 expression is elevated subsequent to gastrointestinal tract injury [7].

MH is typically defined by MES of ≤ 1, while MES 0 represented complete endoscopic healing reflects significantly improved disease outcomes **[8].**

Regarding age & gender, a statistically insignificant difference was found between groups.

Patients in active status and those in remission exhibited a statistically significant decrease in hemoglobin levels than in control group in this study. This is consistent with prior research that has indicated that anemia is a prevalent complication in UC patients. **[9]** This case-control study included 40 UC patients in activity, 40 UC cases in remission, and 40 healthy controls.

In addition, the control group and patients' subgroups did not exhibit any statistically significant differences in albumin levels, which contradicted **Khairallah *et al.*** **[9]** findings that active UC cases are more likely to have an albumin deficiency. In terms of liver and kidney functions, between groups there was statistically insignificant difference that concurrs with **Khairallah *et al.*** **[9].**

In the CRP levels statistically significant differences were observed in the three groups in this study. Patients in the active state exhibited significantly higher CRP levels than those in remission, and patients in remission exhibited levels that were substantially higher than those in the control group. This discovery aligns with the findings of **Khairallah *et al.*** **[9]** who demonstrated that CRP levels were substantially elevated in active patients in comparison to healthy volunteers and patients in remission.

In the same vein, the investigation demonstrated a substantial disparity in the levels of FC among the three studied groups. The cases FC levels in the active state were significantly elevated than in remission, and the remission cases levels were significantly elevated than in the control group. This is in agreement with **Khairallah *et al.*** **[9]** findings who found that FC levels were significantly higher in active patients than in remission and healthy volunteers.

In our study, a statistically significant difference was observed regarding TFF3 levels between the three groups. Patients in the active state exhibited significantly higher levels than those in remission, and

patients in remission exhibited significantly higher levels than those in the control group. This result is in agreement with **Khairallah *et al.* [9]** who also discovered that serum TFF3 levels were substantially higher in patients who had not achieved MH compared to those who had achieved mucosal remission. Also, it aligns with the **Srivastava *et al.* [7]** who discovered that serum TFF3 levels were significantly greater in patients than in healthy volunteers. In addition, they discovered that patients who did not accomplish mucosal recovery exhibited significantly higher serum TFF3 levels than those who did.

These findings corroborate the theory that TFF3 levels are associated with inflammation in mucosa in the intestine and increase in the presence of mucosal injury [7]. This study demonstrated that there was a statistically significant positive correlation between the patients **MES** and TFF3, which aligns with **Khairallah *et al.* [9]. Srivastava *et al.* [7]** demonstrated in UC cases in clinical remission or with mild activity that serum TFF3 could recognize patients with MH with reasonable specificity and sensitivity. Nevertheless, the MH was defined as a Baron score of 0 or 1, and the latter did not accurately depict a complete MH**.**

The receiver operating characteristics curve was employed as the sensitivity of 92% and 96% as specificity. Remission was indicated by a cut-off value of less than 71. This is consistent with **Srivastava *et al.* [7]** who showed a < 1.27 ng/ml as serum TFF3 level had 68% specificity and 70% sensitivity for identifying patients with MH. Additionally, **Khairallah *et al.* [9]** demonstrated that a serum TFF3 threshold of less than 4.25 ng/ml in remission showed a 92% sensitivity and 69% specificity. In their study, **Nakov *et al.*** [10] demonstrated that TFF3 had a sensitivity of 92% at a threshold point of < 4.25 ng/ml, which in remission, and 69.2%.as specificity. We recommend that larger studies be conducted, and serum TFF3 can be used in conjunction with other inflammatory markers and endoscopic scores to predict disease activity. Additionally, serial measurements of TFF3 should be taken.

The surrogate marker was only evaluated once, which is the primary limitation of this study. In order to ascertain whether recurrent serum TFF3 measurements could be more beneficial in assessing improvements in endoscopic and clinical disease activity, further research is necessary. Serial measurements would be more valuable than the current study's singular cut-off if they exist. **[7].**

CONCLUSION

Serum TFF3 level was observed to be elevated during disease activity and decreasing during remission and MH. Consequently, the serum TFF3 level can be employed to predict MH in UC and endoscopic remission. The findings also indicated a strong correlation between serum human TFF3 levels and endoscopic severity scores and FC levels in UC patients. In addition, TFF3 revealed a high level of specificity and sensitivity in the detection of MH, which was comparable to FC, which mitigated the necessity for frequent stool samples.

List of Abbreviations

AST	Aspartate Transaminase
AUC	Area Under Curve
CBC	Complete Blood Count
CRP	C-Reactive Protein
DM	Diabetes Mellitus
ESR	Erythrocyte Sedimentation Rate
FC	Fecal Calprotectin
HBsAg	Hepatitis B Surface Antigen
HCVAb	Hepatitis C Virus Antibody
IQR	Interquartile Range
MES	Mayo Endoscopic Score
MH	Mucosal Healing
ROC	Receiver Operating Characteristic
SD	Standard Deviation
TFF3	Serum Trefoil Factor 3
UC	Ulcerative Colitis

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