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Predictive value of trefoil factor 3 for identifying activity in ulcerative colitis patients: a comparison with fecal calprotectin and C-reactive protein

Internal Medicine

Ahmed A. Khairallah[1], Mohammed S. El-fayoumy[2], Ashraf A. El-sherbiny[1], Mohammed S. El-shorbagy[3], Fathy A. El-ghamry[2]

[1] Internal Medicine Department, National Research Centre, Cairo, Egypt.
[2] Internal Medicine Department, Faculty of Medicine for Boys, Cairo, Al-Azhar University, Egypt.
[3] Clinical Pathology Department, Faculty of Medicine for Boys, Cairo, Al-Azhar University, Egypt.

ABSTRACT

Background: Trefoil factor-3 (TFF3) is primarily expressed by small intestine and colon goblet cells. Several studies have revealed that it plays a crucial function in mucosal protection and gastrointestinal tract repair.

Objective: to evaluate the significance of TFF3 as a marker of disease activity in ulcerative colitis (UC) patients.

Methods: A hospital-based case control study was done on 40 active-UC patients, 40 patients in remission state who underwent colonoscopy and 40 non-ulcerative colitis healthy individuals as control group. Serum TFF3 was measured by ELISA and compared to C-reactive protein (CRP) and fecal calprotectin (FC) values. Clinical and endoscopic assessment was scored according to Lichtiger Index and ulcerative colitis endoscopic severity index (UCEIS).

Results: Serum TFF3 was significantly correlated with Lichtiger Index (r=0.671), UCEIS (r=0.642), FC (r=0.8048) and CRP (r=0.3759). Serum TFF3 cutoff point <4.25 ng/ml indicated remission with a specificity 69.2%, 69%; sensitivity 92%, 97% for endoscopic and clinical indices respectively. Also, TFF3 significantly differentiated between mild, moderate, and severe diseases. The AUC of TFF3+FC was significantly higher than that of TFF3 and FC alone for predicting UC remission.

Conclusion: Serum TFF3 is significantly correlated with clinical, endoscopic indices and FC in UC patients. Serum TFF3 is a powerful predictive biomarker of remission alone and in combination with FC in UC patients.

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Corresponding author: Ahmed A.A. Khairallah, Internal Medicine Department, National Research Centre, Cairo, Egypt, **Tel:** 01096098444. **E-mail:** ahmed.abdo.khairallah@gmail.com

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INTRODUCTION

Inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (UC), are characterised by chronic recurrent episodes of inflammation in and around the gastrointestinal tract. Previously, clinical remission was the primary therapeutic goal for UC patients, and treatment focused on symptom control, such as bleeding and diarrhea. However, there is mounting evidence that attaining clinical remission without mucosal healing (MH) is not associated with lower rates of hospitalisation or colectomy over time, but rather with a higher risk of relapse. As a result, MH has become the treatment target in UC patients, leading to better short- and long-term events [1].

To date, endoscopic evaluation is the most accurate way to assess disease activity in IBDs. The location, extent, and severity of IBDs can be established with this procedure but its use is prevented by several drawbacks, as it is invasive, burdensome to patients, time-consuming, and expensive. Moreover, a reliable assessment of mucosal lesions can hardly be performed in clinical practice. Therefore, several disease activity biomarkers have been tested and validated as C-reactive protein (CRP) and fecal calprotectin (FC). FC is a pioneer biomarker for intestinal inflammation frequently

used for the determination of mucosal activity in UC patients. FC correlates well with disease activity and is useful in assessing response of treatment. Although FC is a sensitive in IBD, it is not a specific and increased levels are also seen in gastrointestinal malignancies and infections. There is a lack of agreement between the results produced by different fecal calprotectin assays even though the manufacturer cut-off values for most fecal calprotectin assays are similar. There is also intra-individual inconstancy and age-dependent variability[2].

CRP is an inflammatory marker that is routinely used to assess and track disease activity in patients with IBDs. It is readily available and reasonably priced. The fundamental problem of this marker, however, is that it is neither specific nor sensitive to IBDs[3].

Trefoil factor 3 (TFF3) belongs to the family of trefoil factors, which are peptides with a distinct three-loop structure linked by cysteine disulfide bonds. TFF3 is primarily expressed by small intestine and colon goblet cells. TFF3 has been demonstrated to be up regulated at the site of mucosal injury and to be linked to gastrointestinal restitution and repair. TFF3 overexpression has been linked to impaired mucosal permeability and vulnerability to oxidants, as well as inadequate epithelial regeneration in animal models of ulcerative colitis [4]. Here, we investigated TFF3 as a biomarker of disease activity in UC patients and to compare it with FC and CRP.

PATIENTS AND METHODS

This case control hospital-based study was conducted in the gastroenterology unit of Al-Hussein University hospital between September 2020 and January 2023. All patients gave informed consent, and the study design was approved by the Ethics Board of Al-Azhar University.

Inclusion criteria were: (1) age of 18 years or older, (2) a confirmed diagnosis of UC based on accepted endoscopic, radiologic, and histologic criteria.
Exclusion criteria were: (1) pregnancy, (2) colon cancer or polyps, (3) infectious or ischemic colitis, (4) Crohn's disease, (5) previous bowel surgery, (6) use of non-steroidal anti-inflammatory drugs within the last 90 days, (7) immunodeficiency, (8) heavy smoker, and (9) presence of systemic illness like diabetes, chronic liver or renal disease.
Participants were divided into: 40 non-ulcerative colitis healthy individuals as a control group (group I), 40 patients with quiescent ulcerative colitis in remission (group II) and 40 patients with active ulcerative colitis (group III).

Disease severity was assessed clinically using Lichtiger clinical index, endoscopically using Ulcerative Colitis Endoscopic Severity Index (UCEIS) and histopathology using Robarts index. The Lichtiger Index is composed of 20-point clinical index; diarrhea (0-4), nocturnal diarrhea (0-1), abdominal pain (0-3), abdominal tenderness (0-3), bleeding (0-3), general well-being (0-5) and need for antidiarrheal drugs (0-1). Remission is defined as a score of 0-3; mild activity as a score of 4-8; moderate activity as a score of 9-14; severe activity as a score of >14[5]. The UCEIS score is composed of 8-point score; vascular pattern (0-2), bleeding (0-3) and ulcers and erosions (0-3). Remission is defined as a score of 0-1; mild activity as a score of 2-4; moderate activity as a score of 5-6; severe activity as a score of 7-8[6]. Robart's index is composed of 33-point clinical index; chronic inflammatory infiltrate (0-3), acute inflammatory infiltrate (0-3), crypts involved (0-3), erosion or ulceration (0-4) and correction factor is used. Remission is defined as a score of 0-3; activity as a score of >3[7].

Patients underwent colonoscopy or sigmoidoscopy and biopsies were taken from the rectum and proximal colon. The biopsies were preserved in formalin and stained with hematoxylin and eosin. Patients were needed to give a blood and stool samples before the endoscopy. Serum levels of CRP was quantified using enzyme-linked immunosorbent assay (ELISA), (Biovision co., Egypt). The serum levels of TFF3 were measured by ELISA (SinoGeneClon, China). Fecal levels of calprotectin was analyzed by means of sandwich ELISA, (Epitope Diagnostics, USA). Demographic and clinical data collection and examination was performed by direct patient interview.

Statistical analyses

All statistical tests were done using GraphPad Prism 8. One-way and two-way ANOVA, unpaired t-test, Tukey's post-test, chi square test, Pearson's correlation tests, receiver operating characteristic curve and DeLong's test were used in analysis of the data. $P \leq 0.05$ was considered significant.

RESULTS

Clinical and demographic characteristics of patients with UC are shown in Table 1. The mean duration of illness in active-UC was significantly lower than quiescent group. Most IBD patients belonged to urban residents, yet most of urban patients were in activity while most of rural UC-patients were in active disease.

The mean body mass index in active patients was significantly lower than that of quiescent patients. Most of the patients had negative family history. By comparing both quiescent and active UC groups regarding extra-intestinal complications, nutritional deficiency (regarding anemia and albumin deficiency) was the most noticeable complication, which was more common in active-UC group with a significant difference. Moreover, 40% of active patients and 32.5% of quiescent ones have arthralgia with a statistically significant difference. Further statistics revealed no significant statistical

difference in the other extra intestinal manifestations. As regards IBD-related medications, more patients with active-UC received steroids, immunosuppressive and biological treatment than quiescent-UC cases, whereas more quiescent UC patients responded to conventional treatment with mesalamine alone with a statistical difference.

Sixty percent of patients with active-UC had either mild or severe anemia compared to 27.5% of the quiescent group with significant statistical difference. Also, 27.5% of patients with active-UC has leukocytosis compared to only 7.5% of the quiescent group with statistically significant difference Moreover, 22.5% of patients with active-UC has thrombocytosis compared to none of the quiescent group. Furthermore, 80% of active-UC and 7.5% of quiescent patients had RBCs in their stool analysis, while 30% of active-UC and 2.5% of quiescent patients had pus cells in their stool analysis with statistically significant difference between both groups. In addition, the serum albumin for active patients was significantly lower than that of the quiescent and control group. Further statistics revealed no significant statistical difference in the other liver and kidney functions (tables 1, 2, supplementary file).

Table (1): Comparison between the groups as regard clinical data

Clinical data	Quiescent UC no. (%)	Active UC no. (%)	Significant test	p-value
Age (years)				
- <30	8 (29.0%)	9 (25%)	$\chi^2 = 18.73$	0.004*
- 30-	12 (32.3%)	16 (42.5%)		
- 40-	12 (16.1%)	15 (27.5%)		
- 50+	8 (22.6%)	0 (0%)		
Sex				
- Male	19 (47.5%)	16 (40%)	$\chi^2 = 1.4$	0.52
- Female	21 (52.5%)	24 (60%)		
BMI (Mean ± SD)	26.99 ± 3.23	24.73 ± 2.67	t .test	< 0.001*
Family History				
- No	38 (95%)	39 (97.5%)	$\chi^2 = 0.346$	0.556
- Yes	2 (5%)	1 (2.5%)		
Disease duration (Mean ± SD)	7.13± 3.28	4.83± 2.87	t .test	0.0013*
Residency				
- Urban	37 (92.5%)	28 (70%)	$\chi^2 = 6.646$	0.009*
- Rural	3 (7.5%)	12 (30%)		
Complications				
- Nutrient deficiency	11 (27.5%)	24 (60%)	$\chi^2 = 8.584$	0.003*
- Eye affection	1 (2.5%)	2 (5%)	$\chi^2 = 0.346$	0.556
- Joint affection	13 (32.5%)	16 (40%)	$\chi^2 = 1.127$	0.028*
- P. Sclerosing cholangitis	0 (0%)	1 (2.5%)	$\chi^2 = 1.013$	0.314
- Skin affection	1 (2.5%)	2 (5%)	$\chi^2 = 0.346$	0.556
Treatment				
- 5-ASA	27 (67.5%)	34 (85%)	$\chi^2 = 8.727$	0.048*
- CST	11 (27.5%)	21 (52.5%)		
- AZA	8 (20%)	17 (42.5%)		
- TNFI	1 (2.5%)	8 (20%)		
- No treatment	13 (32.5%)	6 (15%)		
Stool analysis				
- RBCs	3 (7.5%)	32 (80%)	$\chi^2 = 6.536$	<0.001*
- Pus Cells	1 (2.5%)	12 (30%)	$\chi^2 = 11.11$	<0.001*

χ^2: Pearson Chi-Square, t: student test, *: Significant at $p \leq 0.05$.

In the present study, CRP was significantly higher in clinically active patients (LCI<3) than patients in clinical remission and healthy volunteers. CRP levels were also significantly higher in patients not having mucosal healing (UCEIs<1) than those achieved mucosal healing. However, CRP showed no significant difference between histologic active patients (RHI<3) and those with histologic remission. By classifying activity group into mild, moderate, and severe clinical and endoscopic activity, CRP showed no significant difference between all groups (tables 3, 4).

Moreover, mean fecal calprotectin was significantly higher in clinically active patients (LCI<3) than patients in clinical remission and healthy volunteers. Fecal calprotectin levels were also significantly higher in patients not having mucosal healing (UCEIs<1) than those achieved mucosal healing. Also, fecal calprotectin was significantly higher in histologic active patients (RHI<3) than those with histologic remission. Interestingly, by classifying activity group into mild, moderate and severe clinical and endoscopic activity, fecal calprotectin showed a significant difference between all groups.

Table (2): Comparison between the groups as regard laboratory investigations

Laboratory investigations	Group 1 Control Mean ± SD	Group 2 Quiescent UC Mean ± SD	Group 3 Active UC Mean ± SD	p-value	Post hoc test
Hemoglobin	13.36 ± 0.86	12.49 ± 1.15	11.6 ± 1.21	< 0.001*	P1<0.01*, P2<0.01*
WBCs	7.8 ± 1.57	8.37 ± 2.2	9.68 ± 2.02	< 0.001*	P1=0.71, P2=0.01*
Platelet	240.3 ± 53.45	250.73 ± 63.68	335 ± 94	< 0.001*	P1=0.92, P2<0.01*
ALT	31.9 ± 13.2	26.1 ± 7.8	23.5 ± 8.4	0.02*	P1=0.15, P2=0.40
AST	32.0 ± 10.4	27.3 ± 7.6	25.1 ± 9.0	0.07	P1=0.28, P2=0.49
Total Bilirubin	0.12 ± 0.04	0.32 ± 0.29	0.24 ± 0.18	0.03*	P1=0.03, P2=0.24
Albumin	4.43 ± 0.36	4.15 ± 0.51	3.68 ± 0.56	<0.01*	P1=0.28, P2<0.01*
Creatinine	0.99 ± 0.19	1.01 ± 0.21	0.94 ± 0.16	0.24	P1=0.94, P2=0.22
Urea	42.4 ± 5.3	36.0 ± 10.1	32.7 ± 7.4	<0.01*	P1=0.09, P2=0.20
Sodium	138.5 ± 3.8	138.3 ± 4.5	138.6 ± 4.3	0.95	P1=0.99, P2=0.94
Potassium	4.08 ± 0.52	3.98 ± 0.44	4.02 ± 0.44	0.78	P1=0.78, P2=0.89

One-way ANOVA followed by Tukey's test, P: between groups P1; group 1-2, P2; group 2-3, *: Significant P value (≤0.05).

Table (3): Comparison of inflammatory markers between all groups

Inflammatory markers	Group 1 Control Mean ± SD	Group 2 Quiescent UC Mean ± SD	Group 3 Active UC Mean ± SD	p-value	Post hoc test
FC					
- LCI	16.3±10.7	71±50	442±241	P <0.001*	P1= 0.625, P2<0.001*
- UCEIs		72±52	411±255	P <0.001*	P1= 0.666, P2<0.001*
CRP					
- LCI	5.15±4.8	8.45±5.61	16±17	P 0.0034*	P1=0.691, P2=0.01*
- UCEIs		8.46±5.167	16±16	P 0.006*	P1=0.697, P2=0.019*
TFF3					
- LCI	1.614±0.97	3.59±2.36	7.6±2.6	P <0.001*	P1=0.050, P2<0.001*
- UCEIs		3.525±2.419	7.3±2.7	P <0.001*	P1=0.072, P2<0.001*

One-way ANOVA followed by Tukey's test, P: between groups P1; group 1-2, P2; group 2-3, *: Significant P value (≤0.05)

Interestingly, mean serum TFF3 was significantly higher in clinically active patients (LCI<3) than patients in clinical remission and healthy volunteers. Serum TFF3 was also significantly higher in patients not having mucosal healing (UCEIs<1) than those achieved mucosal remission. Also, TFF3 was significantly higher in histologic active patients (RHI<3) than those with histologic remission. Interestingly, by classifying activity group into mild, moderate, and severe clinical and endoscopic activity, TFF3 showed significant difference between all groups.

TFF3 showed a strong positive correlation with FC. Moreover, TFF3 showed significant but weak correlation with other laboratory markers; leucocyte and platelet counts showed weak positive correlation, while hemoglobin level and serum albumin showed weak negative correlation. Moreover, TFF3 showed positive agreement with severity indices; UCEIs showed strong correlation and moderate agreement, LCI moderate correlation and moderate agreement while RHI showed moderate correlation and weak agreement with TFF3 (table 5).

Using Roc analysis of UC patients, CRP predicted disease activity in UC patients at a cutoff point >8.6 (specificity 80%, 79%; sensitivity 65%, 67% for endoscopic and clinical indices respectively). (Table 6). Moreover, FC diagnosed disease activity in UC patients at a cutoff point >179 (specificity 91.2%, 91.9%; sensitivity 81%, 88% for endoscopic and clinical indices respectively).

Table (4): Comparison of inflammatory markers between different severity subgroups of active patients

Inflammatory markers	Group 3a Mild activity Mean ± SD	Group 3b Moderate activity Mean ± SD	Group 3c Severe activity Mean ± SD	p-value	Post hoc test
FC					
- LCI	248.05±82.28	452.68±260.63	598.09±190.15	P<0.001*	P1=0.001*, P2=0.002*
- UCEIs	201±106.8	426.6±190.6	719.4±250.9	P <0.001*	P1=0.001*, P2=0.001*
CRP					
- LCI	12.67±8.80	15.82±18.13	19.45±19.42	P <0.001*	P1=0.230, P2=0.428
- UCEIs	10.5±8.95	15.61±17.85	22.66±19.92	P <0.001*	P1=0.219, P2=0.128
TFF3					
- LCI	5.41±1.68	7.87±2.23	9.0±2.8	P <0.001*	P1=0.001*, P2=0.079
- UCEIs	5.08±1.364	7.403±1.675	11±2.2	P <0.001*	P1=0.002*, P2=0.001*

One-way ANOVA followed by Tukey's test, P: between groups P1; group 1-2, P2; group 2-3, *: Significant P value (≤0.05)

Table (5): Correlation between TFF3 and biomarkers and severity indices

Items	r	P-value	95% Confidence Intervals
TFF3 - CRP	0.3759	<0.001*	0.1658 - 0.5533
TFF3 - FC	0.8048	<0.001*	0.7018 - 0.8749
TFF3 - HB	-0.2817	0.013*	-0.4757 - 0.06163
TFF3 - TLC	0.2403	0.035*	0.01729 - 0.4406
TFF3 - PLT	0.3318	0.003*	0.1165 - 0.5174
TFF3 - Albumin	-0.3285	0.003*	-0.5146 - 0.1128
TFF3 - UCEIS	0.7201	<0.001*	0.5871- 0.8152
TFF3 - LCI	0.5852	<0.001*	0.4101 - 0.7187
TFF3 - RHI	0.4331	<0.001*	0.2252 - 0.6033

r: Pearson Correlation, *: Significant P value (≤0.05)

Table (6): Comparison of ROC curve for different biomarkers predicting remission

Items	AUC	P- value	Cut off	Specificity	Sensitivity
FC					
- UCEIs-1	0.906	<0.001*	> 179	91.2%	81.6%
- LCI-3	0.953	<0.001*	> 179	91.9%	88.6%
CRP					
- UCEIs-1	0.662	0.012*	> 8.60	80%	65%
- LCI-3	0.690	0.003*	> 8.60	79.1%	67.6%
TFF3					
- UCEIs-1	0.863	<0.001*	> 4.25	69.2%	92.3%
- LCI-3	0.878	<0.001*	> 4.25	69%	97.2%

Table (7): Comparison of ROC curve for combined biomarkers predicting remission

	AUC	P-value	Specificity	Sensitivity	DeLong's test
CRP+TFF3					
- UCEIs-1	0.870	<0.001*	74.4%	89.7%	P2<0.001*, P3=0.452
- LCI-3	0.885	<0.001*	69%	94.4%	P2<0.001*, P3=0.449
FC+TFF3					
- UCEIs-1	0.913	<0.001*	88.2%	84.2%	P1=0.044*, P3=0.017*
- LCI-3	0.954	<0.001*	89.2%	91.4%	P1=0.044*, P3=0.005*
CRP+FC					
- UCEIs-1	0.904	<0.001*	91.2%	84.2%	P1=0.483, P2<0.001*
- LCI-3	0.954	<0.001*	83.8%	97.1%	P1=0.448, P2<0.001*
CRP+FC + TFF3					
- UCEIs-1	0.932	<0.001*	94.1%	89.2%	P1=0.028*, P2<0.001*, P3=0.008*
- LCI-3	0.954	<0.001*	89.2%	91.4%	P1=0.048*, P2<0.001*, P3=0.005*

AUC: Areas under the ROC curve, DeLong's test; P1; compared with FC, P2; compared with CRP, P3; compared with TFF3, *: Significant P value (≤0.05)

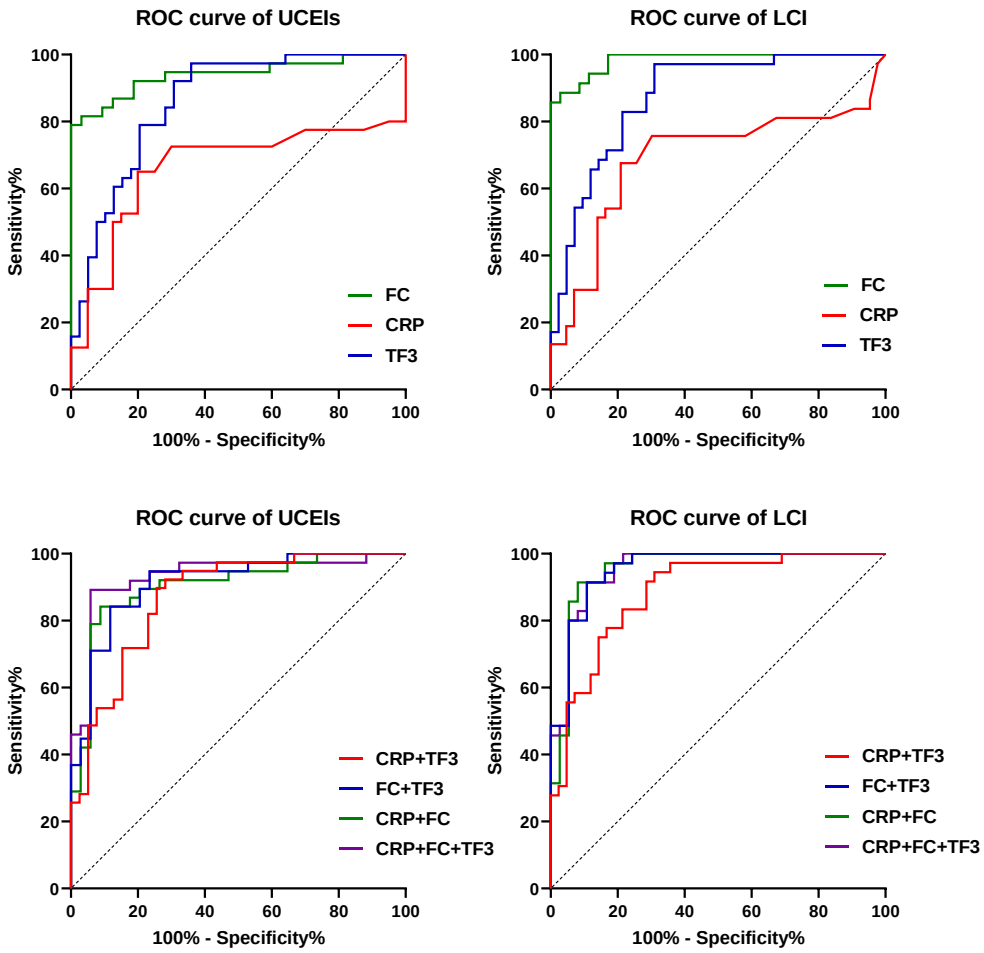

Figure (1): Comparison of ROC curve for different biomarkers predicting remission

AUC: Areas under the ROC curve, *: Statistically significant at $p \leq 0.05$.

Interestingly, TFF3 successfully diagnosed disease activity in UC patients at a cutoff point >4.25 (specificity 69.2%, 69%; sensitivity 92%, 97% for endoscopic and clinical indices respectively). All sensitivity and specificity values were higher than that of CRP and comparable to FC (higher sensitivity but lower specificity).

After combining of biomarkers, CRP+TFF3 diagnosed disease activity in UC patients with specificity of 74%, 69% and sensitivity of 89%, 94% for endoscopic and clinical indices respectively. FC+TFF3 gave a specificity of 88%, 89% and sensitivity of 84%, 91% for endoscopic and clinical indices respectively. Moreover, CRP+FC gave a specificity of 91%, 83% and sensitivity of 84%, 97% for endoscopic and clinical indices respectively. With combining all three markers, CRP+FC+TFF3, gave a specificity of 94%, 89% and sensitivity of 89%, 91% for endoscopic and clinical indices respectively (table 7, figure 1).

DISCUSSION

In the present study, CRP was significantly higher in active patients assessed clinically and endoscopically (but not histologically) than patients in remission. However, by classifying activity group into mild, moderate, and severe activity, CRP showed no significant difference. Moreover, CRP also showed week positive correlation with all severity indices; clinical, endoscopic, and histological. Using Roc analysis, CRP diagnosed disease activity in UC patients at a cutoff point >8.6 (with specificity of 80%, 79% and sensitivity of 65%, 67% for endoscopic and clinical indices respectively). Earlier reports were conflicting regarding the ability of CRP to diagnose activity in UC. Some of them showed no correlation, while others have reported a good correlation between CRP and disease activity assessed clinically or endoscopically. In a study by Tsampalieros[8], CRP showed no significant difference between different severity groups assessed clinically by Pediatric Ulcerative Colitis Activity Index (PUCAI) index. They showed that numerous patients with

moderate to severe UC still have normal CRP, ESR, albumin values and complete blood count. Also, Vermeire[9] reported that only 60% of active-UC patients had increased CRP levels compared with none of them with remission. Furthermore, Xiang[10] demonstrated that CRP (with a cutoff point > 5 mg/L) had a poor specificity (62%) and sensitivity (69%) in differentiating remission from activity as assessed by Mayo score. On the other side, in Egyptian study, data were collected from a database that included 200 patients, spanning an 8-year period, Header[11] assessed UC patients clinically by Truelove severity Index and endoscopically by Mayo score and found that 20% of the patients had mild, 41% had moderate, and 39% was in severely active disease and CRP showed significant difference between groups and better results was obtained when they used CRP/albumin ratio. This study, however, had some limitations including retrospective design of the study.

In the current study, FC was significantly greater in active-UC patients than patients in remission assessed clinically, endoscopically, and histologically. Moreover, FC showed strong positive correlation with clinical and endoscopic severity indices but moderate with histologic one. Furthermore, FC diagnosed disease activity in UC patients at a cutoff point >179 (with specificity of 91.2%, 91.9% and sensitivity of 81%, 88% for endoscopic and clinical indices respectively). These results were consistent with the study of Kawashima[12] on UC patients assessed endoscopically by Mayo endoscopic score (MES) which showed that 26% of the patients had remission, 24% of the patients had mild, 35% moderate, and 15% had highly active disease and FC showed significant difference between groups. Also, it showed a strong correlation between FC and Mayo endoscopic score (r= 0.86). In a similar study by Lee[13] on 181 UC patients, FC levels exhibited a strong inter-rater agreement with Mayo endoscopic score (k = 0.78) and UCEIS (k = 0.62). UCEIS exhibited a greater correlation with FC, compared to MES. Moreover, a study of Schoepfer [14], which included 152 patients with UC and exhibited a specificity of 71%, sensitivity of 93% using a FC cutoff point of 50 in differentiating remission and relapse assessed by clinical and endoscopic part of the Rachmilewitz Activity Index. Re-assessment with a higher cutoff point of 100 resulted in values of 88%, 86%, respectively. Its correlation with endoscopic index (r = 0.834) was stronger than that of with clinical index (r = 0.672). Again, FC was able to differentiate quiescent from mild, moderate, and severely disease with statistical difference. Similar study reported that a cutoff to detect clinical activity was 164µg/g with specificity of 73%, sensitivity of 85% and a cutoff point of 154.5µg/g indicated mucosal healing, with specificity of 85%, sensitivity of 72%[15]. Moreover, a systematic review by Boon [16] included 13 studies describing FC levels and its correlation with endoscopic severity in UC patients. In all studies, there was a significant correlation between FC levels and mucosal healing and inflammation. In contrast, an earlier study recorded a specificity of 34% only for FC with a cutoff point of 10, or 62% with a cutoff point of 20 for differentiating disease activity[17].

In the present study, TFF3 was significantly higher in active-UC individuals than those in remission assessed clinically, endoscopically, and histologically. Moreover, TFF3 showed strong positive correlation with endoscopic severity indices but moderate correlation with clinical and histologic ones. Furthermore, TFF3 showed strong positive correlation with FC. However, it showed only weak correlation with other less specific laboratory markers including CRP, serum albumin, hemoglobin level, leucocyte and platelet counts. Furthermore, TFF3 successfully diagnosed disease activity in UC patients at a cutoff point >4.25 (with specificity 69.2%, 69% and sensitivity 92%, 97% for endoscopic and clinical indices respectively). All sensitivity and specificity values were higher than that of CRP and comparative to FC (higher sensitivity but lower specificity). In the same line, Vestergaard[18] performed a study on 19 patients and reported that TFF3 was significantly higher in active individuals than those in clinical remission. Also, Conklin[19] reported that TFF3 levels exhibited a significant correlations with PUCAI index. Moreover, a study on 64 IBD patients assessed by UCEIS and Lichtiger Clinical Activity Index showed that TFF3 was remarkably higher in active patients than quiescent patients[20]. A similar study by Grønbaek[21] on 48 patients assessed by Activity Index (AI) showed that TFF3 was significantly elevated in active patients than those in clinical remission. Serum TFF3 levels showed significant correlations with serum albumin levels, ESR and CRP. The other laboratory values including hemoglobin, platelet and total leukocytic count showed lower correlations. TFF3 also exhibited a strong correlation with AI clinical score (r = 0.64). Moreover, a larger study by Nakov[3] on 128 patients assessed by UCEIS and Lichtiger Index showed that TFF3 was remarkably higher in active patients than quiescent patients. They reported a significant correlation between TFF3 and FC levels (r=0.473, p<0.001). There was also a significant correlation between TFF3 and UCEIS (r=0.662, p<0.001). Another study of Nakov[22] on 116 patients assessed by UCEIS, MES and Lichtiger Clinical Activity Index showed that TFF3 was remarkably higher in active patients than quiescent patients. They found a significant correlation between TFF3 and FC levels (r=0.473, p<0.001). Furthermore, TFF3 exhibited significant correlation with Lichtiger Index (r=0.736), MES (r=0.811) and UCEIS (r=0.820). They also reported that a serum TFF3 concentrations of < 6.74 ng/ml gave a high specificity of 86.9 %, sensitivity of 87.9%, in diagnosing complete MH defined by both UCEIS and EMS. Furthermore, Teng[23] recently assessed 51 IBD patients by PUACI and Baron's score and showed that TFF3 was significantly higher in patients with active UC-patients than quiescent patients. Also, TFF3 was correlated with PUCAI (r=0.994, p<0.001), but not with

CRP, or Baron's score. ROC curve analysis for TFF3 detected IBD activity with cutoff 6.01, 100% sensitivity and 76.2% specificity. In addition, Salama[24] recently assessed IBD patients and reported that TFF3 were significantly higher in active patients than in remission ones. They also reported TFF3 can predict IBD activity at a cutoff > 61.09 with a specificity and sensitivity of 77. 1% and 74.3 %, respectively. However, there were several limitations to this study as it was on a small sample size (25 patients) done in single center and the disease activity wasn't objectively assessed by activity indices. Another older study by Srivastava[25] on 74 patients assessed clinically by Simple Clinical Colitis Activity Index and endoscopically by Baron's score exhibited that TFF3 was significantly higher in active patients than those with mucosal healing. They reported that TFF3 were insignificantly higher in patients with extensive colitis than those with left-sided colitis. They also reported that a TFF3 concentrations of <1.27 gave a specificity of 68%, sensitivity of 70%, in identifying mucosal healing and endoscopic remission. Despite, this study also used single center design and used un-validated old activity indices.

In our study, after combining of biomarkers, specificity and sensitivity of CRP+TFF3 weren't significantly higher than TFF3 alone (p= 0.452). However, FC+TFF3 gave a specificity of 88%, 89% and sensitivity of 84%, 91% for endoscopic and clinical indices respectively. Values was significantly higher than FC and TFF3 alone (p=0.044; 0.017, respectively). With combining all three markers, values weren't significantly superior to FC+TFF3.

CONCLUSION

Our results reported that serum human TFF3 is significantly correlated with clinical activity, endoscopic severity indices and FC in UC patients. Moreover, TFF3 showed a highly sensitive and specific ability in identification of mucosal healing and was comparable to FC which gives an opportunity to avoid frequent stool sampling. Interestingly, the combination of TFF3 and FC exhibited higher predictability of mucosal healing than FC alone.

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الملخص العربي

القيمة التنبؤية لمعامل التريفويل الثلاثى لتحديد نشاط المرض في مرضى التهاب القولون التقرحي: مقارنة مع الكالبروتكتين البرازي و البروتين التفاعلي سى

أحمد عبده خيرالله[1]، محمد شحات الفيومى[2]، أشرف عبدالهادى الشربينى[1]، محمد سعيد الشوربجى[3]، فتحي عبدالرازق الغمرى[2]

[1] قسم الامراض الباطنة، المركز القومي للبحوث، القاهرة، جمهورية مصر العربية.

[2] قسم الامراض الباطنة، كلية طب بنين، جامعة الازهر، القاهرة، جمهورية مصر العربية.

[3] قسم الباثولوجيا الاكلينيكية، كلية طب بنين، جامعة الازهر، القاهرة، جمهورية مصر العربية.

ملخص البحث:

المقدمة: يتم التعبير عن معامل التريفويل الثلاثى (TFF3) بشكل أساسي بواسطة خلايا الأمعاء الدقيقة والقولون.ولقد كشفت العديد من الدراسات أنه يلعب وظيفة حاسمة في حماية الغشاء المخاطي وإصلاح الجهاز الهضمي.

الهدف: الهدف من الدراسة هو تقييم أهمية معامل التريفويل الثلاثى كمؤشر لنشاط المرض في مرضى التهاب القولون التقرحي (UC).

الطرق: يتضمن البحث 40 مريضًا نشطًا و 40 مريضًا في حالة خمول لمرضى القولون التقرحى خضعوا لمنظار القولون. تم قياس مصل معامل التريفويل الثلاثى بواسطة الاليزا و تم مقارنته بقيم البروتين التفاعلي سى (CRP) و الكالبروتكتين البرازي (FC). أُجري التقييم السريري التنظيرى وفقًا لمؤشر ليختر السريرى ومؤشر شدة التهاب القولون التقرحي بالمنظار (UCEIS).

النتائج: ارتبط مصل معامل التريفويل الثلاثى ارتباطًا وثيقًا بمؤشر ليختر (r = 0.671) ومؤشر شدة التهاب القولون التقرحي بالمنظار (r = 0.642) و الكالبروتكتين البرازي (r = 0.8048) و البروتين التفاعلي سى (r = 0.3759). وأشارت القيمة الحدية لمعامل التريفويل الثلاثى <4.25 نانوغرام / مل إلى خمول المرض مع خصوصية 69.2٪ ، 69٪ و حساسية 92٪ ، 97٪ للمؤشرات التنظيرية والسريرية على التوالي. أيضًا ، كما ميز معامل التريفويل الثلاثى بشكل كبير بين نشاط المرض البسيط والمتوسط والشديد. كان مؤشرالمنطقة الواقعة تحت المنحنى (AUC) لـمعامل التريفويل الثلاثى مضافا مع الكالبروتكتين البرازي للتنبؤ بخمول التهاب القولون التقرحي أعلى بكثير من معامل التريفويل الثلاثى او الكالبروتكتين البرازي كل على حدة.

الاستنتاجات: يرتبط مصل معامل التريفويل الثلاثى بشكل كبير بالمؤشرات السريرية والتنظيرية و الكالبروتيكتين البرازى في مرضى القولون التقرحى. يعتبر مصل معامل التريفويل الثلاثى مؤشر حيوي تنبؤية قوية لخمول المرض وحده او بالاقتران مع الكالبروتكتين البرازي في مرضى التهاب القولون التقرحي.

الكلمات المفتاحية: معامل التريفويل الثلاثى، الكالبروتكتين البرازي، مرضى القولون التقرحي، البروتين التفاعلي سى.

الباحث الرئيسى:

الاسم: أحمد عبده خيرالله، قسم الامراض الباطنة، المركز القومي للبحوث، القاهرة، جمهورية مصر العربية

الهاتف: 01096098444

البريد الالكترونى: ahmed.abdo.khairallah@gmail.com