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# Trefoil factor 3, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as predictor markers in ulcerative colitis activity

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**Abstract**
**Background:** The Trefoil factors 3 (TFF3) include a group of three peptides that are related to mucin and are released by goblet cells located in the mucosa of the intestines serve a crucial function in the preservation of mucosal barrier integrity and exhibit an upregulation response at the specific location of mucosal injury. The objective of this study was to assess the significance of Trefoil factor 3 and hematological indicators, namely the Neutrophil to Lymphocyte ratio (NLR) and Platelet to Lymphocyte ratio (PLR), in predicting the activity of ulcerative colitis.
**Methods:** The present research used a prospective cohort design, which included a sample of fifty patients diagnosed with ulcerative colitis (UC) in group I, and a control group (group II) consisting of twenty-five apparently healthy individuals. The patients were categorized into two distinct groups: group IA, consisting of active UC patients, and group IB, consisting of inactive UC patients. The serum levels of TFF3, NLR, PLR, and fecal calprotectin (FC) were evaluated.
**Results:** The statistical analysis revealed a significant rise in serum TFF3 levels in group I compared to group II, as well as in group IA compared to group IB. Additionally, there was a positive correlation seen between serum TFF3 levels and inflammatory indicators such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), FC, and endoscopic activity. There was an insignificant difference between group IA and group IB as regards total leukocyte count (TLC), NLR, and PLR. TFF3, FC, NLR, PLR detect remission and activity in UC patients at cut off value of 408.6, 57.5, 2.4, 102.1, AUC 0.9, 0.7, 0.6, 0.6, with sensitivity 92.5%, 87.5%, 55%, 67.5%, specificity 80%, 80%, 40%, 50%, The positive predictive values (PPV), 94.9%, 94.6%, 78.6%, 84.4% and the negative predictive values (NPV) was 72.7%, 61.5%, 18.2%, 27.8% respectively.
**Conclusions:** The potential use of serum TFF3 as a predictive marker for UC activity is evident since it demonstrates a positive correlation with other inflammatory indicators such as ESR, CRP, FC levels, and endoscopic activity.

**Keywords:** NLR, PLR, trefoil factor 3, ulcerative colitis

## 1. Introduction
Ulcerative colitis (UC) is a chronic inflammatory condition affecting the mucosal lining of the colon. Its etiology remains uncertain, and it is characterized by a pattern of recurring episodes of inflammation followed by periods of remission. The main objective of UC treatment has transformed, shifting from the initial focus on achieving and maintaining clinical remission to the current emphasis on facilitating mucosal healing. Accurate assessment of disease activity is crucial for the anticipation of treatment outcomes and assessments. The evaluation of UC activity often involves the use of a combination of serologic, endoscopic, and evidence clinical [1].
Non-invasive biomarkers of inflammatory bowel diseases (IBD), such as the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), are commonly employed in medical procedures to assess and monitor disease activity and the degree of inflammation. These biomarkers serve as supplementary measures, as no single method has been definitively established as the optimal approach for evaluating disease activity [2, 3].
The Trefoil Factor 3 (TFF3) includes a group of three peptides that are related to mucin and are released by goblet cells located in the intestinal mucosa.

They play a crucial function in the preservation of the integrity of the mucosal barrier and exhibit an upregulation response at the specific location of mucosal injury [4]. TFF3 is mostly released by goblet cells located in the large and small intestine. Its main function is protecting the gastrointestinal mucosa from various forms of harm. There has been a suggestion that the measurement of TFF3 serum levels may have a role in predicting the activity of intestinal illnesses [6, 7].

The calculation of PLR and NLR may be readily performed using the complete blood count (CBC), hence serving as more cost-effective and accessible biomarkers. The use of PLR and NLR as biomarkers has significant potential in the diagnosis and prediction of inflammatory conditions [8, 9]. However, the clinical consequences of PLR and NLR in patients with UC exhibit inconsistent findings. The use of biopsies and endoscopy in medical procedures is accompanied by substantial financial costs, significant time commitments, and inherent risks. Hence, it is crucial to establish the correlation between other disease activity markers and histological observations to effectively monitor disease activity and forecast therapy response in patients UC [10]. Therefore, the objective of this study was to evaluate the role of TFF3, PLR, and NLR in prediction of UC activity.

## Methods and Subjects

The present research obtained ethical clearance from the Ethical Committee of Tanta Faculty of Medicine, Egypt, with permission number 34891/9/21. The research started in October 2021 and concluded in October 2022. The present research used a prospective cohort design to investigate a sample of Fifty adult patients diagnosed with UC (Group I) This sample was then categorized into two distinct subgroups: Group IA, consisting of patients with active UC, and Group IB, consisting of patients with inactive UC. In addition, a control group (Group II) consisting of 25 apparently healthy people who had normal colonoscopy examination. Exclusion criteria were history of colorectal surgery, colorectal cancer or colon polyp, indeterminate colitis, infectious colitis, pregnancy, primary immunodeficiency, diabetic patient, chronic kidney disease, and neurological disorders.

All of them were subjected to CBC, PLR, NLR, CRP, ESR, FC, and stool analysis. The ELISA measurement of TFF3 concentration.

**Specimen collection, storage, and handling:** Seven ml of venous blood was collected from the antecubital vein was diluted as two ml on an EDTA tube for CBC (done on micros sixty), two ml on a tube with Na citrate for ESR, three were put on a plain tube, left for ten min to clot then centrifuged at three thousand r/min and serum was separated for TFF3and CPR assay. Samples for TFF3 were stored in a deep freezer until assay by ELISA technique.

**Colonoscopy with biopsy.** A high-definition video scope All exams were performed using an EPK I. Scan five thousand (Pentax Medical. Japan). The colonoscopy report included a remark on the segment or segments affected, the presence or absence of localized or widespread inflammation or ulceration, mucosal vascular pattern alterations, strictures, polyps, masses, anal fissure, perianal abscess, or fistulae, and other findings**.** Biopsies were obtained every ten cm from four quadrants, from stricture, mass lesion, or polyps with surrounding flat mucosa throughout the colon during colonoscopy. The tissue is fixed in formalin and sent for a histological analysis. The histopathological findings that are considered pathognomonic for active UC: inflammatory infiltrate in the mucosa, submucosa, and lamina propria, crypt destruction, erosion, or ulceration while in inactive disease there are resolving of all inflammatory cells while architectural changes may persist, and some crypts may appear branched and short [11].

## Statistical analysis

The data were analyzed using the IBM SPSS software program version 23.0, developed by SPSS Inc. in Chicago, IL, USA. The statistical tests used in this study included the Chi-square test, which was used to analyze categorical data and assess differences between various groups. The student's t-test is often used to compare two groups when the quantitative variables are regularly distributed. However, if the variables are not normally distributed, the Mann-Whitney test is more appropriate for comparing the two groups. The correlation between variables was examined using both the Pearson correlation coefficient and Spearman's rank correlation coefficient. The Receiver Operating Characteristic (ROC) curve was used to assess and evaluate the discriminatory power of variables in distinguishing across distinct patient groups. The sensitivity of a diagnostic test may be calculated by dividing the number of true positive results by the sum of true positive and false negative results. The specificity of a diagnostic test may be calculated by dividing the number of true negative results by the sum of true negative and false positive results. A significance level of less than 0.05 was deemed significant for a two-tailed P value.

## Results

There was an insignificant variant between all studied groups, as regards sex distribution and age. (Table 1)

A statistically significant difference was observed between group IA and group IB patients UC in terms of the presence of asymptomatic state, gaseous distension, bloody diarrhea, abdominal pain, erythematous mucosa, diffuse ulcerations with contact bleeding, healed mucosa (with prominent vascular markings), and Mayo score. However, no significant variance was found between the two groups in terms of fever, other symptoms, disease distribution, pseudo-polyps' presence, and medications used. (Table 2)

**Table 1:** The demographic statistics related to the groups under investigation.

| Parameters | | Group IA Active UC *(N=40)* | Group IB Inactive UC *(N=10)* | Group II Control *(N=25)* | P |
|---|---|---|---|---|---|
| **Age (years)** | | 35.45 ± 13.16 | 30.9 ± 12.87 | 40.12 ± 11.51 | 0.117 |
| **Gender** | **Male** | 20 (55.6%) | 4 (11.1%) | 12 (33.3%) | 0.852 |
| | **Female** | 20 (51.3%) | 6 (15.4%) | 13 (33.3%) | |

* Significant < 0.05

**Table 2:** Clinical data, distribution of the disease, and colonoscopic results in UC patients.

| Parameters | | Group IA (N=40) | Group IB (N=10) | P |
|---|---|---|---|---|
| **Asymptomatic** | | 0 (0%) | 6 (60%) | < 0.001** |
| Symptomatic | Abdominal pain | 36 (90%) | 4 (40%) | < 0.001** |
| | Gaseous distention | 31 (77.5%) | 2 (20%) | < 0.001** |
| | Bloody diarrhea | 34 (85%) | 0 | < 0.001** |
| | Fever | 4 (10%) | 0 | 0.297 |
| Other symptoms | No | 28 (70%) | 10 (100%) | 0.557 |
| | Arthralgia | 6 (15%) | 0 | |
| | Arthritis | 3 (7.5%) | 0 | |
| | Autoimmune thyroiditis | 1 (2.5%) | 0 | |
| | DVT | 1 (2.5%) | 0 | |
| | Growth retardation | 1 (2.5%) | 0 | |
| Distribution of the disease | Left-sided colitis | 14 (35%) | 3 (30%) | 0.723 |
| | Pancolitis | 16 (40%) | 3 (30%) | 0.751 |
| | Proctitis | 10 (25%) | 4(40%) | 0.345 |
| Colonoscopic Findings | Erythematous mucosa | 38 (95%) | 2 (20%) | < 0.001** |
| | Diffuse ulcerations with contact bleeding | 37 (92.5%) | 0 | < 0.001** |
| | Healed mucosa (Prominent vascular markings) | 0 | 10(100%) | < 0.001** |
| | Pseudo-polyps | 3 (7.5%) | 0 | 0.372 |
| Mayo score | Mild (3 - 6) | 16 (40%) | 0 (0%) | < 0.001** |
| | Moderate (7 - 10) | 11 (27.5%) | 0 (0%) | |
| | Severe (> 10) | 13 (32.5%) | 0 (0%) | |
| | Remission (0 - 2) | 0 (0%) | 10 (100%) | |
| Medications | 5-ASA | 29 (72.5%) | 10 (100%) | 0.06 |
| | Steroids | 25 (62.5%) | 5 (50%) | 0.123 |
| | Azathioprine | 16 (40%) | 6 (60%) | 0.254 |
| | Biological treatment | 5 (12.5%) | 1 (10%) | 0.828 |

* Significant < 0.05

**Table 3:** Complete blood count among studied groups.

| Parameters | Group IA (N=40) | Group IB (N=10) | Group II (N=25) | P |
|---|---|---|---|---|
| HB (g/dL) | 9.51 ± 1.4 | 12.75 ±1.95 | 12.48±1.89 | P1 < 0.001**<br>P2 < 0.001**<br>P3= 0.008* |
| Platelets (10^3/mm$^3$) | 310.52±104 | 232.5±28.29 | 191 ±34.77 | P1 < 0.001**<br>P2 < 0.001**<br>P3 < 0.001** |
| TLC (10^3/mm$^3$) | 9.32 ± 3.34 | 8.37 ± 2.81 | 6.22 ± 1.28 | P1 < 0.001**<br>P2= 0.413<br>P3 < 0.001** |
| NLR | 2.417(2.04) | 2.357 (1.72) | 1.657 (1.7) | P1= 0.013*<br>P2= 0.610<br>P3= 0.004* |
| PLR | 139.06 (112.22) | 98 (112.22) | 81.6 (56.73) | P1= 0.004*<br>P2= 0.286<br>P3= 0.002* |

* Significant p< 0.05
** TLC, NLR, PLR.
*** P1: Comparing between groups, P2: Comparing between (IA and IB), P3: Comparing between (IA+IB and group II).

The Hemoglobin (HB) level was statistically significant decline in group I compared to group II. Also, it was a statistically significantly declined in group IA compared to group IB (p-value < 0.001). Platelet count was statistically significantly elevated in group IA and group IB compared to group II (p-value less than 0.001).

There was a statistically significant elevated NLR, TLC, and PLR in group I compared to group II with no important variance between group IA and group I B as regards NLR, TLC, and PLR. (Table 3)

**Table 4:** The groups under investigation included the FC analysis and TFF3.

| Groups Parameters | Group IA (N=40) | Group IB (N=10) | Group II (N=25) | P |
|---|---|---|---|---|
| FC (mg/kg) | 48 – 997 | 42 – 198 | 25 – 170 | P1 < 0.001** |
| Median (IQR) | 252.5 (608) | 145.5 (122) | 83 (74) | P2= 0.038* |
| | 180.5 (540) | | | P3 < 0.001** |
| TFF3 (pg/ml) | 295.7 - 1690.7 | 289.3 - 942.6 | 225.5 - 1472.6 | P1 < 0.001** |
| Median (IQR) | 993.3 (460.4) | 617 (397.65) | 411 (330.1) | P2 < 0.001** |
| | 729.25 (423.4) | | | P3 < 0.001** |

* Significant less than 0.05
** P1: Comparing between groups, P2: Comparing between group (IA and IB), P3: Comparing between group (IA+IB and group II).

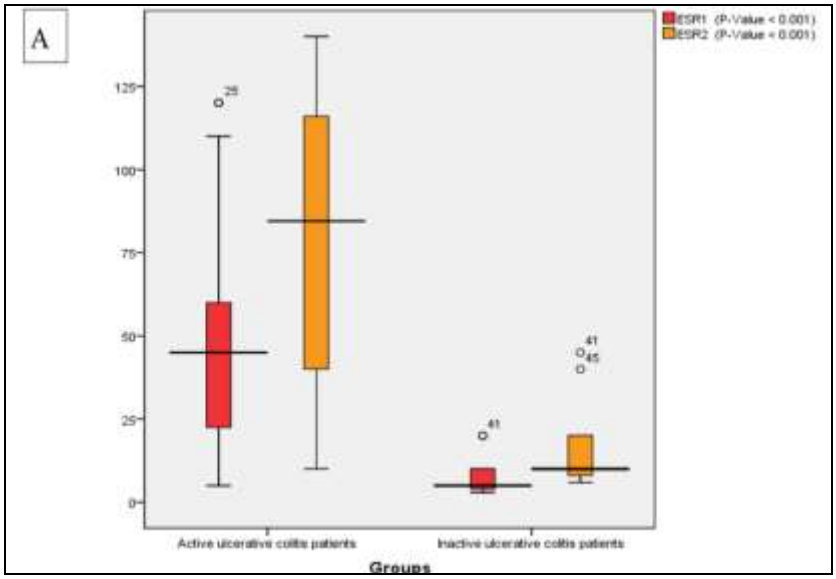
The levels of FC and TFF3 exhibited a statistically significant rise in group I when compared to group II, as well as in group IA when compared to group IB. Nevertheless, there was no statistically significant difference observed between group IB and group II. (Table 4)

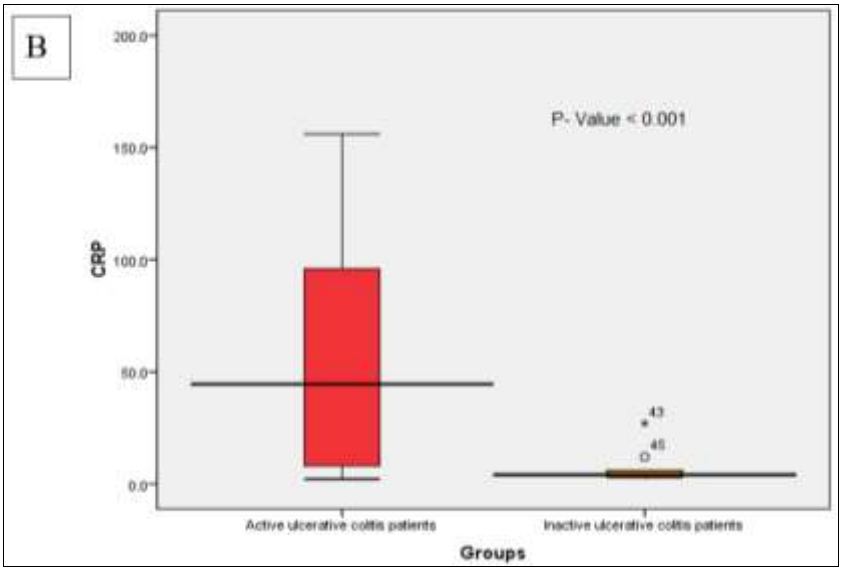
**Table 5:** The present study examines the associations between the TFF3 biomarker and several factors.

| Variables | TFF3 biomarker | |
|---|---|---|
| | R | P |
| Age | 0.068 | 0.561 |
| Sex | -0.080 | 0.498 |
| HB | -0.310 | 0.007* |
| Platelets | 0.443 | < 0.001** |
| TLC | 0.330 | 0.004* |
| NLR | 0.199 | 0.088 |
| PLR | 0.291 | 0.011* |
| CRP | 0.439 | < 0.001** |
| ESR1 | 0.442 | < 0.001** |
| ESR2 | 0.456 | < 0.001** |
| Mayo Score | 0.477 | < 0.001** |
| FC | 0.326 | 0.004* |

* Significant < 0.05
**TFF3, TLC, ESR, CRP, NLR, PLR, FC.

There was a statistically important elevated between UC patients as regard ESR 1 hour, ESR 2 hour, and CRP level. There was a statistically important elevate between studied groups as regard FC, and TFF3 by using post hoc test there was a significant elevate between group IA and group IB and group IA and group II. However, there was no significant variance between group IB and group II. (Figure 1).



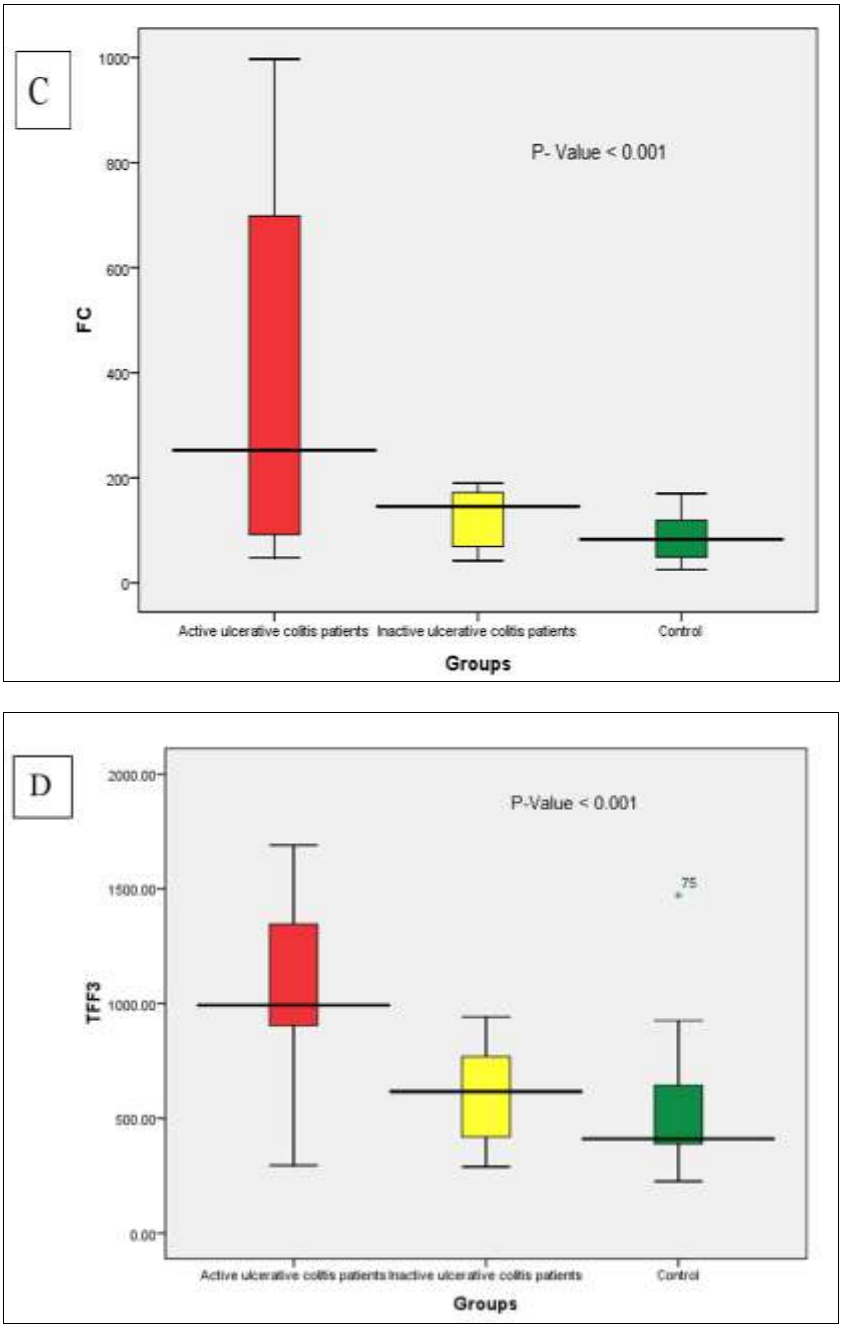
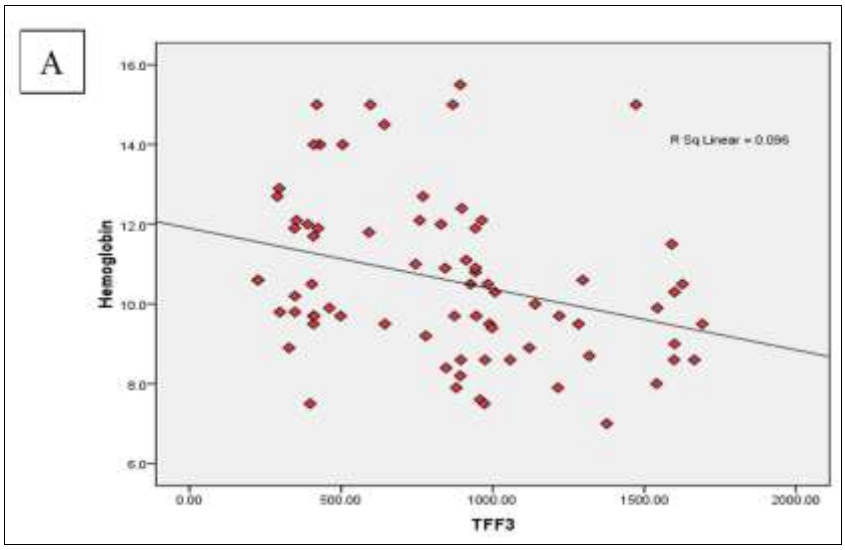



**Fig 1:** Box plots among UC patients show (A) ESR 1h, ESR 2h. (B), CRP (C), FC (D) and TFF



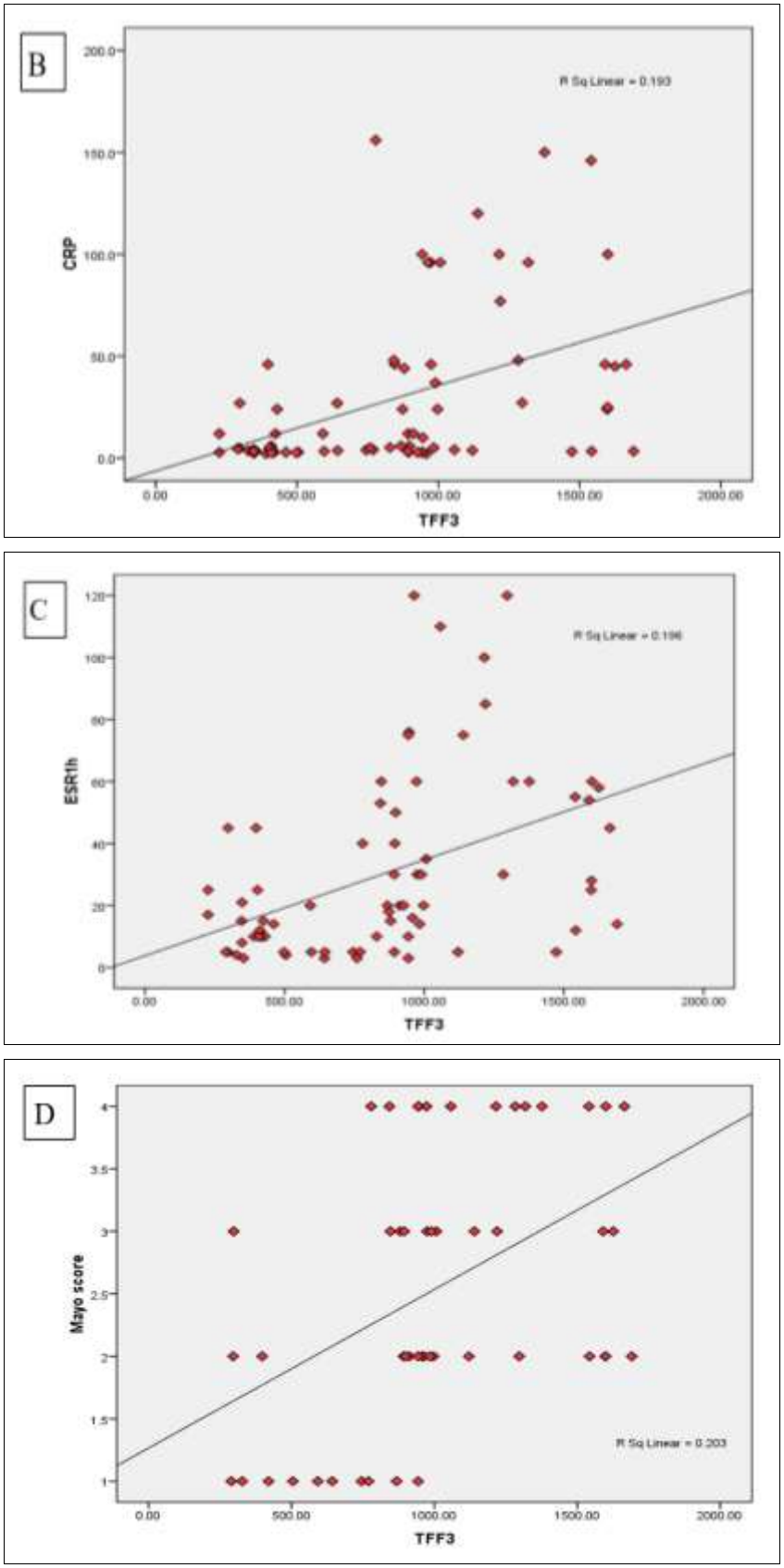



**Fig 2:** Correlation between TFF3 and HB level (A), CRP (B), ESR1h (C), and Mayo score (D)

**Table 6:** Regression analysis for predictor factors affecting UC patients.

| Independent variables | Odds Ratio (95%) CI | P |
|---|---|---|
| Age | 0.981 (0.917 – 1.049) | 0.571 |
| Gender | 0.837 (0.2 – 3.504) | 0.807 |
| HB | 0.966 (0.642 – 1.453) | 0.867 |
| Platelets | 1.00 (1.00 – 1.00) | 0.004* |
| TLC | 0.664 (0.453 – 0.974) | 0.036* |
| NLR | 2.336 (0.521 – 10.477) | 0.268 |
| PLR | 0.965 (0.923 – 1.01) | 0.123 |
| CRP | 0.977 (0.866 – 1.10) | 0.700 |
| ESR1 | 1.033 (0.864 – 1.235) | 0.719 |
| ESR2 | 0.968 (0.860 – 1.088) | 0.581 |
| FC | 0.991 (0.983 – 0.999) | 0.019* |
| TFF3 | 0.990 (0.983 – 0.997) | 0.003* |

* Significant < 0.05
** TFF3, TLC, ESR, CRP, NLR, PLR, FC.

TFF3 was positively correlated with CRP, ESR, Mayo score, and FC. Also, TFF3 was negatively correlated with HB level. (Table 5, Figure 2) By logistic regression (FC, TFF3) are predictors that affecting UC patients. (Table 6)
TFF3, FC, NLR, PLR for detect activity and remission UC patients at cut off value of 408.6, 57.5, 2.4, 102.1, AUC 0.9, 0.7, 0.6, 0.6 with sensitivity 92.5%, 87.5%, 55%, 67.5% and specificity 80%, 80%, 40%, 50% PPV, 94.9%, 94.6%, 78.6%, 84.4% and NPV 72.7%, 61.5%, 18.2%, 27.8% respectively. (Figure 3)

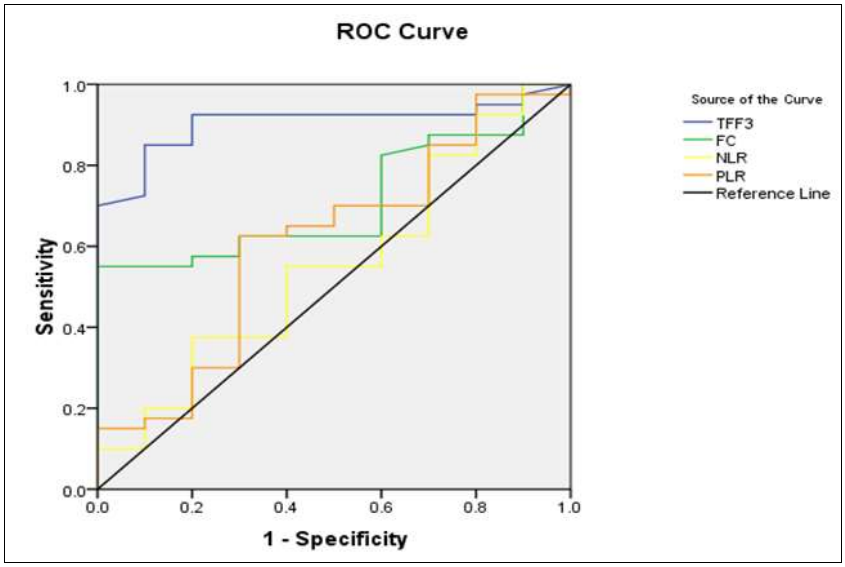



**Fig 3:** ROC curve for detection of remission and activity patients with UC.

## Discussion

UC is a chronic inflammatory disorder characterized by a persistent and recurring pattern of inflammation in the colon, which lasts throughout an individual's lifetime. There has been an increasing need for the development of surveillance and diagnostic technologies [12]. In the present research, HB level was statistically significantly declined in group I compared to group II. Also, it was a statistically significant decline in group IA compared to group IB (p value < 0.001). Platelet count was statistically significantly increased in group IA and group IB compared to group II (p-value < 0.001). There is a correlation between platelet counts and both iron deficient anemia and disease activity in patients with UC. The reversal of thrombocytosis in these individuals may be facilitated by the control of inflammation and the management of iron deficiency anemia [13]. Yusuf and Coşkun (2019) observed similar findings, indicating a substantial rise in platelet counts in patients with active UC compared to those in remission [14]. In their study, Akpinar *et al*. (2018) observed a statistically significant elevation in platelet count among patients with active UC compared to those in remission. Also, the study found that individuals with UC who achieved endoscopic remission had a high HB level compared to both control subjects and those with ongoing endoscopic illness [8]. Anemia is a common extraintestinal symptom of UC and has a significant influence on patients' quality of life [15]. The possibility of anemia in UC as a result of disease progression and blood loss [16].

In this research, there was a statistically important elevated in NLR in group I compared to group II with no significant variance between group IA and group IB. NLR was shown to be higher in those with active UC compared to those with inactive UC by Demir *et al*. (2015), Overall accuracy was 59.1% when using an NLR cutoff point of 2.39 to diagnose active UC, with a sensitivity of 48.6% and a specificity of 77.5% [17]. The serum NLR of active patients was shown to be considerably greater than that of inactive UC patients by Celikbilek *et al*. (2013) [18].

In this research, there was a statistically significant elevate in PLR in group I compared to group II with no significant variance between group IA and group IB. For detecting

active versus inactive UC, a PLR cut-off value of 102.1 showed an AUC of 0.6, sensitivity of 67%, specificity of 50%, PPV 84.4%, and NPV was 27.8%. Fidan and Kocak, (2017) found that the PLR in patients with active UC was significantly higher than in patients in remission [19]. Akpinar *et al*. (2018) found that PLR values in the endoscopically active disease group were higher than in the endoscopic remission group [8]. The difference between results in these studies may influenced by the number of enrolled patients and may be due to CBC (especially absolute neutrophil counts) was affected by drugs such as azathioprine, steroids, and anti-TNF, we did not exclude all patients who took these drugs. Also, this may be due to the inclusion of a relatively small number of patients on these medications, and those with an abnormal CBC had previously adjusted the drug dose or changed the medication.

In this study, active UC patients were shown to have higher levels of CRP and ESR1/ESR2 than patients in remission. Jeong *et al*. (2021) revealed similar results, seeing a significant elevation in CRP level and ESR in patients with active UC compared to patients in remission [20].

In this research, FC was statistically significantly elevated in group I compared to group II and in group IA compared to group IB. However, there was no significant variance between group IB and group II. For detecting active UC, an FC cut-off value of 57.5; AUC was 0.7, the sensitivity was 87.5%, specificity was 80%, PPV was 94.6%, and NPV was 61.5%. Nakov *et al*. (2019) also reported a statistically significant elevate in FC level in active UC patients compared to inactive patients and the control group, with a cutoff sensitivity of 97% and specificity of 98% [7]. Stevens *et al*. (2021) found lower median FC values in patients with deep remission and clinical compared to those with ongoing disease activity [21].

D'Amico *et al*. (2020) indicated that there was a high statistically significant elevate in FC findings among active UC patients and patients in remission state [22]. Grgić *et al*. (2022) reported significantly higher median FC in active UC patients (382,5 ug/g) versus inactive patients (44 ug/g) [23].

In this research, TFF3 was statistically significantly elevated in group I compared to group II and in group IA compared to group IB. However, there was no significant variance between group IB and group II. TFF3 median value was 993.3 pg/ml in group IA, 617 pg/ml in group IB, and 411 pg/ml in group II. TFF3 cut off stage 408.6 pg/ml (AUC), 905:95% CI, (0.819-0.991), sensitivity 92.5% and specificity 80%. Grønbaek *et al*. (2006) found serum TFF3 levels correlated with UC disease activity, with declining levels accompanying clinical development after steroid therapy [24].

We found a significant correlation between endoscopic activity, TFF3, and FC levels because in active UC the mucus epithelium is always affected, the mucus barrier is impaired, and the inflammation affects the superficial submucosa and mucosa [25]. Instead of being a marker for inflammation, TFF3 may be more accurately described as a biomarker for mucosal injury that may result from an inflammatory process. Thus, TFF3 may be utilized to distinguish between UC in its active and quiescent states and as a predictor of disease activity.

## Conclusions

The potential use of serum TFF3 as a predictive marker for UC activity is evident since it demonstrates a positive correlation with other inflammatory indicators such as ESR, CRP, FC levels, and endoscopic activity.

## Recommendation

Further studies should be done on a large number of UC patients to confirm the role of serum TFF3 in the evaluation of UC activity and determine its pathophysiological role in UC.

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**Author contributions:** All authors contributed equally to this work

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