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Correlation between fecal biomarkers and the presence of antineutrophil cytoplasmic antibodies with ulcerative colitis disease activity

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ABSTRACT

Background: Although colonoscopy remains the gold standard for Ulcerative colitis (UC) diagnosis due to its invasive and costly nature, non-invasive biomarkers are gaining importance in disease activity monitoring and diagnosis. In our study, we aimed to evaluate the correlation of fecal calprotectin (FC) and fecal lactoferrin (FL) levels with the disease activity according to 3 different disease activity indices and to investigate the relationship between the presence of peri-nuclear anti-neutrophil antibody (p-ANCA) and disease activity.

Methods: Our study was planned as a prospective cohort study and 80 patients diagnosed with UC who were admitted to the Gastroenterology department between 01.05.2023 and 01.09.2023 at Ondokuz Mayıs University Hospital were included in the study. 'Truelove and Witts' (TLW) activity index, SEO index and Mayo Score were applied. FC and FL levels in stool samples were analysed by Enzyme-Linked ImmunoSorbent Assay (ELISA), while p-ANCA presence in blood samples was examined using the Indirect Immunofluorescent Antibody (IIFA) method.

Results: It has been demonstrated that both faecal biomarkers can distinguish severe disease, but according to ROC analysis, the discriminatory power of FC is higher than that of FL. The cutt-off values calculated for severe disease were found above 300µg/g for FC and above 130µg/g for FL. Also ANCA positivity and formalin-resistant ANCA positivity in the severe disease group were statistically higher than mild disease group.

Conclusions: In addition to the relationship between faecal biomarkers and disease activity, our results demonstrated that patients with severe disease exhibited high rates of ANCA positivity and formalin resistance.

Keywords: ANCA, calprotectin, disease activity, lactoferrin

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INTRODUCTION

UC is a chronic IBD with multifactorial etiology and progresses with periods of remission and activation. UC often presents with bloody diarrhea and abdominal pain [1]. The diagnosis of UC is made by evaluating clinical findings, radiological examination and laboratory results together. Colonoscopy is used as the gold standard diagnostic method and histological evaluation of the biopsy sample is performed. Since this method is quite invasive and costly, it has become important to investigate non-invasive biomarkers both in the diagnosis of diseases and in the measurement of disease activity [2]. In recent years, biomarkers that are excreted in feces from active neutrophils and monocyte cells have been investigated. Of these, fecal calprotectin (FC) and fecal lactoferrin (FL) have been shown to better determine colon retention, provide results that are more compatible with activity indices, and are more specific for intestinal inflammation. FC has the best correlation with the activity of endoscopic inflammation in UC patients and is currently the most frequently preferred marker for the evaluation of UC activity as an alternative to colonoscopy [3,4]. FL is also a biomarker found in neutrophils and in case of intestinal inflammation, its level increases in the stool by leaking into the mucosa. It has been shown that FL level can be used in the diagnosis of IBD and in demonstrating disease activity [4]. Biomarkers are priority topics in UC-related research because they have the potential to support diagnosis, noninvasively monitor endoscopic and

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histological activity, determine disease activity, prognosis, and predict response to treatment.

Various evaluation systems based on symptoms, endoscopic findings, histological diagnosis and biomarkers are used to determine disease activity in IBD. Depending on the disease activity and the overall activity of the disease, treatment varies significantly, from locally effective treatment options to systemic immune suppression. Therefore, accurately assessing the level of active disease is vital in choosing the most appropriate treatment strategy for patients with this disease.

Starting with Truelove and Witts' study in 1955; various activity scores have been developed using various variables. The most popular and widely used of these scores in clinical practice are the Mayo Score and the Truelove and Witts score [5].

The most studied serological antibody markers in IBD are anti-Saccharomyces cerevisiae antibodies (ASCA), ANCA and, more recently, autoantibodies against glycoprotein-2 [6]. ANCA are autoantibodies formed against different enzymes such as proteinase 3 (PR3) and myeloperoxidase (MPO) in the cytoplasmic granules of neutrophils and are used in the diagnosis of systemic vasculitis. Recently, PR3-ANCA has been found to be positive in IBD patients, especially UC [7].

We hypothesise that fecal biomarker levels and ANCA positivity would be higher in patients with active UC than in patients with remission or mild UC. Thus, we aimed to compare FC and FL levels in UC patients with SEO, Mayo, TLW activity index results and to compare FC and FL levels between groups with different disease activity. We also aimed to investigate the relationship between patients' p-ANCA results and disease activity.

METHODS

Eighty patients diagnosed with UC who were adults and not pregnant were included in the study. These patients were selected among patients who applied to Ondokuz Mayıs University Gastroenterology department between May 2023 and September 2023. Among adult patients diagnosed with UC, those who complained of diarrhea and suspected infectious gastroenteritis or had a positive test for infectious gastroenteritis in the examinations requested by the clinician were not included in the study.

Patients were classified as mild, moderate or severe according to the daily frequency of defecation, fever, pulse and hemoglobin (Hb) parameters in the TLW index. In the SEO scoring criteria, after scoring the presence of bloody stool, defecation frequency; Hb, albumin and sedimentation levels, those with scores lower than 150 were classified as mild, those with scores higher than 200 were classified as active, and those with scores between 150-200 were classified as moderate. In the Mayo scoring system, there are additional parameters including endoscopic findings and there are criteria under 4 main headings. According to these parameters, the patient's findings are scored between 0 and 12, and patients with scores above 7 are classified as severe [5,8,9].

Calprotectin levels measurement was performed with the Calprotectin ELISA (Euroimmun, Germany) kit according to the test steps and photometric measurement of color intensity was made on the ChroMate reader at a wavelength of 450 nm. The concentrations of the samples were calculated by creating a calibration curve with the studied calprotectin standards. Lactoferrin measurements were conducted in a comparable manner using Lactoferrin Scan (TECHLAB, USA) kit.

ANCA examinations were performed using the IIFT: Granulocyte Mosaic 13 (Euroimmun, Germany) kit based on the indirect immunofluorescent antibody (IIFA) method by preparing preparations (BIOCHIPs) and evaluated under a fluorescence microscope in the dark. For each patient, there are 3 different antigen-fixed field placed on BIOCHIP. Ethanol fixed granulocytes are the standard substrate for perinuclear/ cytoplasmic ANCA determination. Formalin-fixed granulocyte substrate is for presence of formalin resistance and mixed substrate consisting of ethanol fixed granulocytes and HEp-2 cells field is helpful to determine pseudo-p-ANCA positivity caused by the presence of antinuclear antibody (ANA) positive. p-ANCA result was given as a result of the evaluation of these 3 parametres together. The design of BIOCHIPs and sample images of our patient outcomes are shown in Figure 1.

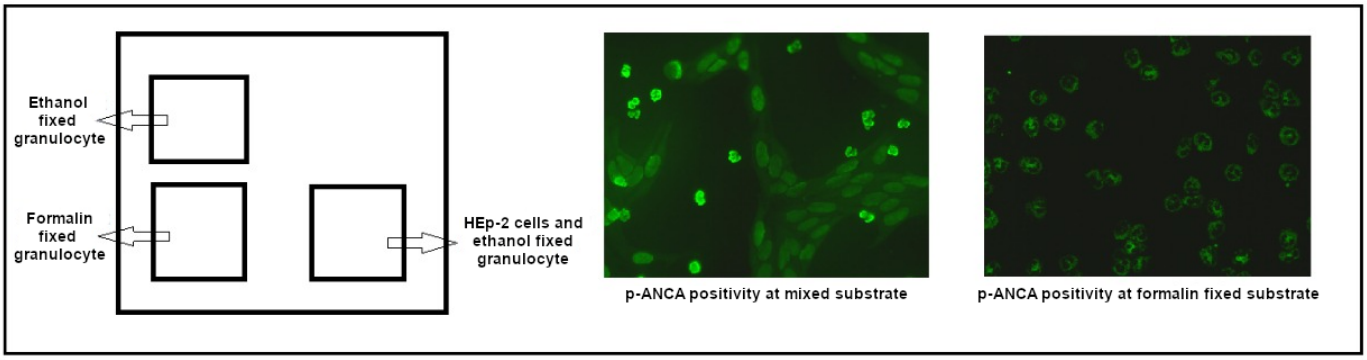

Figure 1. BIOCHIP design and sample images of patient outcomes

Approval for this study was granted by the Ondokuz Mayıs University Clinical Research Ethics Committee on 10/05/2023, with approval number 2023/155.

Sample characteristics

Following the provision of informed consent by the patients, stool and blood samples were collected for subsequent analysis. Stool samples were stored at -80 °C until all samples were collected. Patient blood samples were collected in yellow-capped gel tubes and centrifuged, then their serum was separated and frozen at -80°C and stored until the sample processing day.

Statistical analysis

The study data were computerized and analyzed using SPSS for Windows 22.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as mean (±) standard deviation, median (Quintile 1-Quintile 3), frequency distribution and percentage. The conformity of the variables to normal distribution was examined using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Student's T Test and Fisher's Exactness Test were used for the groups that fit the normal distribution; Mann-Whitney U Test was used for the groups that did not fit the normal distribution.

ROC analysis was performed to investigate the relationship between biochemical parameters and disease activity level. Area under the curve (AUC) values for ROC analysis were considered as: 0.90-1.00 (very good), 0.80-0.89 (good), 0.70-0.79 (moderate), 0.51-0.69 (poor), 0-0.59 (no significant test). The cut-off point was calculated according to the Youden Index (J = Sensitivity + Specificity- 1). Statistical significance level was accepted as $p<0.05$.

RESULTS

The demographic and laboratory data of the 80 patients included in the study are presented in Table 1. Disease activity was calculated for the patients using 3 different clinical activity indices (MAYO, Truelove Witts, SEO). MAYO scoring could be calculated in 44 patients who underwent endoscopy, while the other two classification methods were applied to the entire patient group. The disease activity groups of the patients are shown in Table 2. Fecal biomarker levels in the whole patient group were 241.5 µg/g (Q1:13.7−Q3:1092.0) for FC and 153.7 µg/g (Q1:41.7−Q3:213.0) for FL.

Evaluation according to MAYO clinical activity index

According to MAYO, patients were divided into two groups as severe (n=22) and inactive-mild-moderate (n=22) and FC, FL, CRP, and sedimentation levels were compared. Statistically significant differences were found between the groups in FL (z=2,488; p=0.013), FC (z=4,580; p=0.001), and sedimentation levels (z=3,405; p=0.001). The comparison of FC, FL levels and the median level in each patient is shown in Figure 2A.

As a result of the ROC analysis performed to calculate the highest sensitivity and specificity levels of biomarkers between the two patient groups, FC (AUC=0.901, p=0.001) showed the highest performance. The cut-off value for FC was 384.810 µg/g (sensitivity 95.5%, specificity 76.4%) and for FL 134.268 µg/g (sensitivity 90.9%, specificity 59.1%). The results of the ROC analysis of FC and FL levels according to the MAYO classification are presented in Table 3, while the ROC curve is illustrated in Figure 2B.

Evaluation according to TLW activity index

According to TLW activity index, the patient group was divided into two groups as severe (n=17) and mild-moderate (n=63); then, FC and FL levels were compared. Statistically significant differences were found between the groups for both FL (z=2,758; p=0.006) and FC (z=2,941; p=0.003). The comparison of FC and FL levels and the median level for each case is shown in Figure 2C.

As a result of the ROC analysis performed to demonstrate the discriminative power of the biomarkers, it was

Table 1. Patient characteristics

Parameter		Median [Q1-Q3] / Mean±SD / n (%)
Age		51 [33-60]
Sex	Male	48 (60.0%)
	Female	32 (40.0%)
HGB (g/dL)		13.1±2.0
Alb (g/dL)		4.1±0.6
CRP (mg/L)		5.3 [0-14.0]
ESR (mm/h)		36.5 [24.0-54.5]
Fecal occult blood	Positive	54 (67.5%)
	Negative	26 (32.5%)
Sigmoidoscopy	Present	44 (55.0%)
	None	36 (45.0%)
Daily feces	0	38 (47.5%)
	1	24 (30.0%)
	2	18 (22.5%)
Presence of blood in feces	0	47 (58.8%)
	1	11 (13.8%)
	2	9 (11.3%)
	3	13 (16.3%)

Abbreviations: Alb- albumin, CRP- C-reactive protein, ESR- erythrocyte sedimentation rate, HGB- hemoglobin, SD- standard deviation, Q- quartile.

Table 2. Disease activity according to MAYO, TLW, and SEO classifications

Disease activity	MAYO (n=44)	TLW (n=80)	SEO (n=80)
Inactive	5.0% (n=4)	-	-
Mild	11.3% (n=9)	16.3% (n=13)	48.8% (n=39)
Moderate	11.3% (n=9)	62.5% (n=50)	23.8% (n=19)
Severe	27.5% (n=22)	21.3% (n=17)	27.5% (n=22)

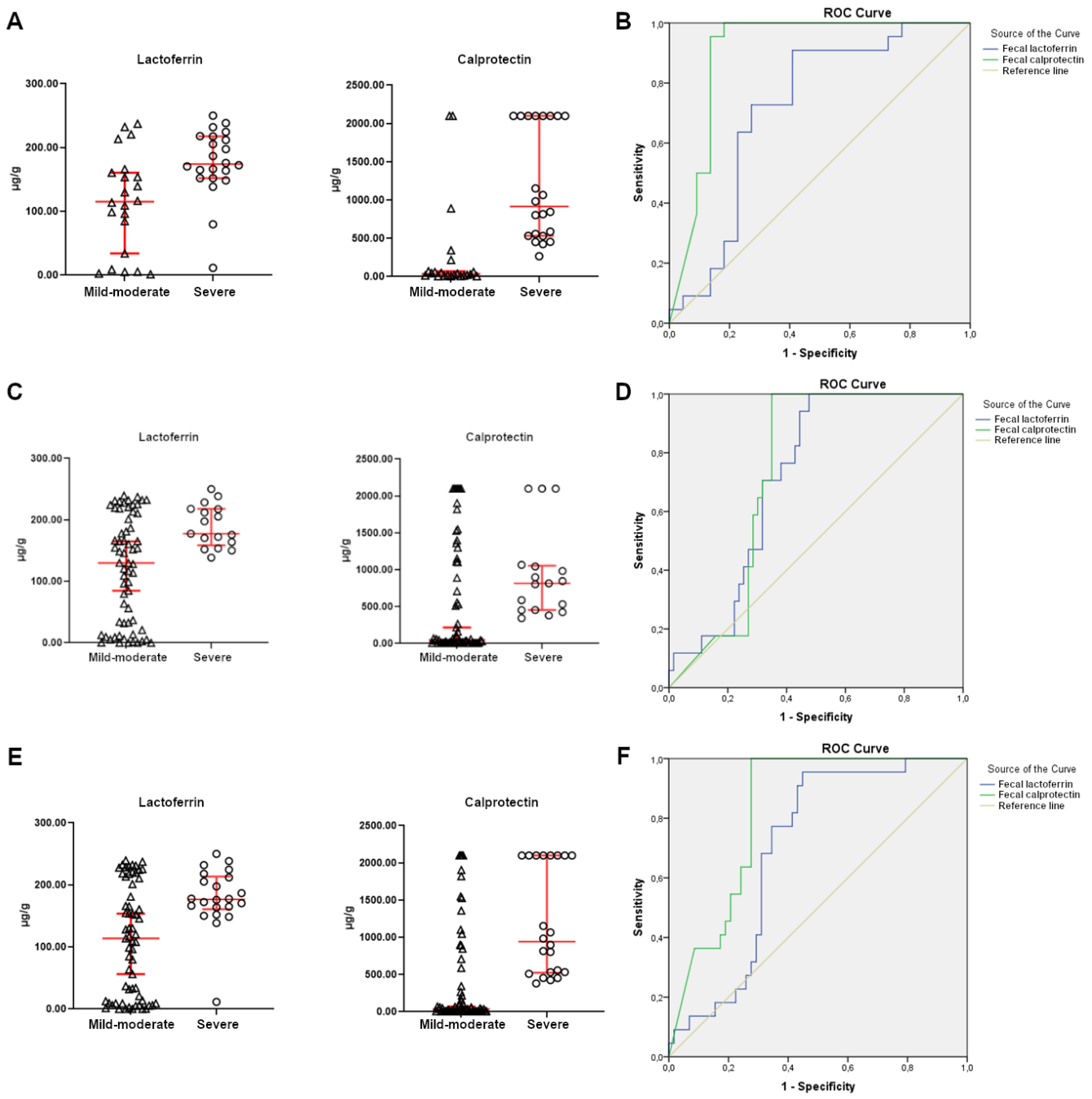

Figure 2. Fecal lactoferrin and calprotectin - comparison across desease severity groups and ROC curves. A and B - MAYO classification; C and D - TLW index classification; E and F - SEO classification.

found that FC (AUC=0.733, *p*=0.003) and FL (AUC=0.719, *p*=0.006) levels were statistically significant in indicating disease activation. The cut-off value for FC was established at 305.38 µg/g, while FL was set at 134.37 µg/g. The results of the ROC analysis of FC and FL levels according to the TLW classification are presented in Table 3, while the ROC curve is illustrated in Figure 2D.

Evaluation according to SEO scoring index

Using SEO classification, patients were divided into two groups as Active (n=22) and Mild-Moderate (n=58); then, FC and FL levels were compared. Statistically significant differences were found between the groups for both FL (z=2,715; *p*=0.007) and FC (z:4,503; *p*=0.001). The comparison of FC and FL levels and median level for each case is shown in Figure 2E.

As a result of ROC analysis, it was observed that FC (AUC=0.827, *p*=0.001) and FL (AUC=0.697, *p*=0.007) levels were statistically significantly differentiated at the disease level. The cut-off value for FC was 362.22 µg/g (sensitivity 100%, specificity 72.4%) and for FL it was 147.38 µg/g (sensitivity 90.9%, specificity 56.9%). The results of the ROC analysis of FC and FL levels according to the SEO classification are presented in Table 3, while the ROC curve is illustrated in Figure 2F.

Table 3. ROC analysis results according to MAYO, TLW, and SEO classification

	Parameters	AUC	SD	*p* value	95% CI
MAYO	FL	0.719	0.082	0.013	0.559–0.879
	FC	0.901	0.055	0.000	0.793–1.000
TLW	FL	0.719	0.056	0.006	0.609–0.829
	FC	0.733	0.054	0.003	0.627–0.839
SEO	FL	0.697	0.059	0.007	0.582–0.813
	FC	0.827	0.045	0.001	0.739–0.915

Evaluation of ANCA test results by IIFA method

The ANCA results for 69% (n=55) of the patients in the study were positive, with 52% (n=29) of these patients exhibiting formalin resistance. In addition, the titer distribution of ANCA positive patients was evaluated as +1, +2 and +3 in 26, 18, and 11 patients, respectively.

When ANCA positivity was compared with patient groups according to clinical scoring systems, it was observed that ANCA positivity was statistically higher in the active/severe patient group in the MAYO and SEO classification compared to the mild patient group (p=0.021, p=0.008). Table 4 presents a comparison of disease levels and ANCA positivity in the MAYO, TLW, and SEO classification systems. When the relationship between formalin resistance and disease activity was investigated, it was observed that formalin-resistant ANCA positivity was statistically higher in the active/severe patient group in MAYO and SEO classification compared to the mild patient group (p=0.036, p=0.021). There was no statistically significant difference between disease activity levels and titers of ANCA positive patients (p>0.05).

DISCUSSION

Colonoscopic evaluation and histopathological examination, which are invasive methods, are frequently used as the gold standard method in the diagnosis and follow-up of IBD, but this method has difficulties such as patient preparation, difficulty in tolerance, and the need for specialist competence. Thus, scoring systems that combine various clinical and laboratory results and some even include endoscopic findings are used in the follow-up of the activation periods of UC patients. In recent years, studies on biomarkers, which focused especially FC and FL, that are easy to use, non-invasive and have adequate sensitivity and specificity have increased. Studies have been conducted in terms of diagnosis of IBD with FC, differentiation from Irritable Bowel Syndrome (IBS), endoscopic activity scoring or histological evaluation of the disease, recurrence of the disease, and response to treatment.

In 2008, Xiang et al. divided 66 UC patients into two groups as active and inactive with Shutterland activity index and investigated the concordance with FC. They showed that FC (402.16–35.93 µg/g), sedimentation (21.44–9.84 mm/h) and CRP (16.45–4.39mg/L) values were statistically significantly higher in active UC patients (p<0.001 for FC, p<0.005 for sedimentation and CRP). In ROC analysis of these biomarkers, the AUC for FC, CRP and sedimentation were 0.975, 0.740, 0.692 and p<0.05 for all three, respectively [10]. In 2022, in another study by Grgıc et al. investigating the relationship between MAYO score and FC in 126 UC patients, the FC level was 382.5 µg/g (197.5–1191.5 µg/g) in 56 (44.4%) active patients and 44 µg/g (18–90 µg/g) in 70 (55.6%) remission patients. In the ROC analysis for FC, the AUC was 0.912 with a specificity value of 76.8% and a sensitivity value of 92.9%. [11]. In a recent study in 2023, Acharya et al. investigated the correlation between FC level and MAYO scoring and reported that there was a correlation between sedimentation and FC level and disease activity score [12]. When we classified the UC patients according to the MAYO score, we found a statistically significant higher FC level of 916.0 µg/g (532.2–2100.0 µg/g) in the severe patient group compared to 34.6 µg/g (11.7–106.4 µg/g) in the mild-moderate patient group (p=0.001). In addition, 56.5 mm/hour to 28 mm/hour values for sedimentation, 9 mg/L to 4.5 mg/L values for CRP were

Table 4. Comparative analysis of ANCA results across patient groups

Index	Activity Level	ANCA		*p* value
		Negative	Positive	
MAYO	Inactive-Mild-Moderate	45.5%	54.5%	0.021*
	Severe	13.6%	84.4%	
TLW	Mild-Moderate	36.5%	63.5%	0.051
	Severe	11.8%	88.2%	
SEO	Mild-Moderate	39.7%	60.3%	0.008*
	Severe	9.1%	90.9%	

* Statistically significant results.

observed and statistically significant difference was obtained between the groups for sedimentation (p=0.001). According to ROC analysis, the highest performance was obtained in FC (AUC=0.901) and the sensitivity and specificity values obtained for FC were 95.5% and 76.4%. In our study, FC and sedimentation values were found to be higher and significant in the active UC patient group; however, unlike other studies, no statistically significant difference was found in CRP levels. When analyzed according to the MAYO scoring, the lack of statistical significance in the CRP value may be due to the decrease in the sample group. As evidence of this, when our patients were grouped according to the SEO and TLW indices, a statistically significant difference in CRP levels was found between the groups for both indices.

FL is another non-invasive, easily applicable fecal marker with promising potential in the evaluation of IBD activity and has been shown in many studies to be compatible with endoscopic and histological activity by increasing mucosal inflammatory activity at a level that does not cause an increase in sedimentation and CRP values. [13-15]. In a large-scale study by Langhorst et al. in 2020 investigating the correlation of FL with disease activity status according to histological activity indices in 226 UC patients, FL concentrations were found to be significantly higher in patients with high histological disease activity 18.59 µg/g (Q1 6.06 to Q3 44.42) compared to those with low disease activity 3.14 µg/g (Q1 0.75 to Q3 11.05) (p<0.001). In the ROC analysis, FL AUC value was found to be 0.730. When a threshold value of 7.25 µg/g was taken as the manufacturer's recommendation for FL, sensitivity and specificity values were reported as 71.3% and 65.1% respectively [16]. In a meta-analysis study including 10 studies investigating the correlation of FL and FC with disease activity in IBD in 2020, Dai et al. found that the level of FL was discriminatory in disease activity with an AUC value of 0.880 in ROC analysis, and sensitivity and specificity values were calculated as 81% and 82%, respectively [17]. In our study, FL levels were found to be statistically significantly higher in the high disease activity group according to the Mayo, TLW, and SEO indices than in the low disease activity group according to all 3 scoring systems. The cut-off values for FL according to the Youden index were calculated to be 134 µg/g, 134 µg/g, and 147µg/g in the scoring systems, respectively. The sensitivity of these values was found to be between 90% and 100%. This variation in the sensitivity percentages calculated for FL in the studies, including our study, was thought to be due to the cut-off values.

According to the results obtained in our study, the power of FC to discriminate disease activity according to all scoring criteria was higher than FL according to ROC analysis results.

Studies on the association of p-ANCA with disease activity, response to treatment or risk of relapse are scarce in the literature [3]. The prevalence of p-ANCA-positive UC was reported to be 41%-73% in the 2020 international consensus on ANCA testing [18]. In our study, the prevalence of p-ANCA positive UC was found to be 69% with 55 patients. When the prevalence studies in the literature were analysed, it was observed that there was a wide range of varying rates and it was thought that this may be related to the study method. As the p-ANCA staining pattern in the IIFA method forms perinuclear staining, it may be affected by nuclear staining in ANA positive patients and may be interpreted as a false positive. Therefore, to exclude this situation, evaluation of ANA positivity with an additional substrate on the specimen, as in our study, suggested that false-positive p-ANCA appearances due to this effect could be eliminated.

A multicentre retrospective study involving 406 children with UC reported that severe disease was more common in p-ANCA-positive patients than in p-ANCA-negative patients [19]. Another study involving 432 UC patients found that p-ANCA positivity was associated with the number of UC relapses [20]. In our study, according to the SEO and Mayo indices, p-ANCA positivity was significantly higher in the severe/active patient group than in the mild disease group. High p-ANCA titres are observed in patients with active UC. However, many studies have found no statistical relationship between p-ANCA titres and UC activity [19,21]. In our study, the correlation between the increase in ANCA titres and the activity of the disease was investigated, but no statistically significant difference was found.

The primary limitation of our study was the relatively small number of patients included in the analysis. Additionally, the MAYO score comparisons were conducted with 44 patients, as colonoscopy could not be performed in all participants. However, the strength of our study should be acknowledged, as it contributes to the existing literature by evaluating fecal markers together with ANCA results.

CONCLUSIONS

Our study suggests that FC and FL are potentially useful surveillance markers that may be helpful in prioritising patients with UC for endoscopic evaluation when they present with symptoms of active disease or when the patient has not been prepared for endoscopy. Besides this, the data indicate that both biomarkers can be employed effectively in the differentiation of severe disease.

Moreover, an evaluation of the relationship between ANCA positivity and severe UC as a serological marker is recommended, given the lack of clarity in the existing literature and the relatively limited number of studies on this topic.

ABBREVIATIONS

ANA- antinucleer antibody

AUC- area under curve

CRP- C-reactive protein

ELISA- enzyme-linked immunosorbent assay

FC- fecal calprotectin

FL- fecal lactoferrin

Hb- hemoglobin

IBD- inflammatory bowel disease

IIFA- indirect immunfloresant antibody

p-ANCA- perinucleer antineutrophil cytoplasmic antibody

ROC- receiver operating characteristics

TLW- Truelove Witts

UC- ulcerative colitis

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AUTHORS' CONTRIBUTION

BU – analysis, investigation, data visualization, data management, supervision, project administration, writing draft

DGV – analysis, supervision, project administration, writing draft

AB, MUD – writing draft, review & editing

CONFLICT OF INTEREST

None to declare.

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