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Fecal Calprotectin at the Time of Diagnosis May Indicate the Presence of Complications In Inflammatory Bowel Disease

İnflamatuvar Bağırsak Hastalığında Tanı Anındaki Fekal Kalprotektin Komplikasyon Varlığını Gösterebilir

Murat Erkut[1], Esra Ozkaya[2], Sami Fidan[1], Arif Mansur Cosar[1]

[1]Karadeniz Technical University, Faculty of Medicine, Department of Gastroenterology, Trabzon, Turkey
[2]Karadeniz Technical University, Faculty of Medicine, Department of Clinical Microbiology, Trabzon, Turkey

Abstract

Aim: Our objective was to explore the correlation between the occurrence of complications at the time of diagnosis or during follow-up and fecal calprotectin levels in patients diagnosed with inflammatory bowel disease.

Material and Method: The fecal calprotectin level was examined utilizing the chromatographic lateral flow immunoassay method.

Results: A total of 76 patients were enrolled in the study, comprising 26 (34%) individuals with Crohn's disease and 50 (66%) with ulcerative colitis. Complications were observed in 17 (22%) patients at the time of diagnosis and in 20 (26%) patients during follow-up. Upon diagnosis, fecal calprotectin levels were categorized as low (<50 mg/kg) in 26 (34%) patients, borderline (50-100 mg/kg) in 16 (21%) patients, and high (>100 mg/kg) in 34 (45%) patients. Patients with high fecal calprotectin levels exhibited lower hemoglobin and albumin levels (p=0.013, p=0.012, respectively), and higher platelet count, erythrocyte sedimentation rate, and C-reactive protein levels (p<0.001, p=0.004, p<0.001, respectively) compared to those with low fecal calprotectin levels. Complications were more prevalent in patients with high fecal calprotectin levels than in those with low and borderline levels both at the time of diagnosis and during follow-up (p=0.001). The risk of developing complications was found to be 26 times higher at the time of diagnosis in patients with fecal calprotectin levels >100 µg/g compared to those with levels below this threshold. Similarly, the risk was 8 times higher during follow-up (p=0.006, p=0.015, respectively).

Conclusion: The utilization of fecal calprotectin levels in conjunction with tests indicating acute inflammation in inflammatory bowel disease may serve as a predictive factor for the onset of complications.

Keywords: Fecal calprotectin, inflammatory bowel disease, complications, acute phase reactants

Öz

Amaç: İnflamatuvar bağırsak hastalığı olan hastalarda tanı anında ya da takip esnasındaki komplikasyon varlığı ile fekal kalprotektin arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Fekal kalprotektin düzeyi, kromatografik lateral akım immünoassay metodu ile çalışıldı

Bulgular: Çalışmaya 26'sı (%34) Crohn's hastalığı ve 50'si (%66) ülseratif kolit olan toplam 76 hasta alındı. Tanı anı ve takip sırasında hastaların sırasıyla 17 (%22) ve 20'sinde (%26) komplikasyon gözlendi. Tanı anında fekal kalprotektin düzeyi 26 (%34) hastada düşük (<50 mg/kg), 16 (%21) hastada sınırda (50-100 mg/kg) ve 34 (%45) hastada yüksek (>100 mg/kg) idi. Fekal kalprotektin düzeyi yüksek olan hastalarda düşük olan hastalara göre hemoglobin ve albümin düzeyleri daha düşük (sırasıyla, p=0.013, p=0.012), trombosit, eritrosit sedimentasyon hızı ve C-reaktif protein düzeyleri daha yüksekti (sırasıyla, p<0.001, p=0.004, p<0.001). Hastaların tanı anı ve takipleri sırasında komplikasyon varlığı fekal kalprotektin düzeyi yüksek olanlarda, düşük ve sınırda olanlara göre daha yüksek oranda olduğu gözlendi (p=0.001). Fekal kalprotektin düzeyi >100 mg/kg olan hastalarda bu değerin altında olan hastalara göre tanı anında komplikasyon gelişme riskinin 26 kat, takip esnasında ise 8 kat daha yüksek olduğu tespit edildi (sırasıyla, p=0.006, p=0.015).

Sonuç: İnflamatuvar bağırsak hastalığında akut inflamasyonu gösteren tetkiklerle birlikte fekal kalprotektin düzeyinin kullanılması komplikasyon gelişimini öngörebilir.

Anahtar Kelimeler: Fekal kalprotektin, inflamatuvar bağırsak hastalığı, komplikasyonlar, akut faz reaktanları

Corresponding *(İletişim)*: Murat ERKUT, Karadeniz Technical University, Faculty of Medicine, Department of Gastroenterology, Trabzon, Turkey
E-mail *(E-posta)*: drmerkut@gmail.com
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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal system (GIS), presenting in two distinct types: Crohn's disease (CD) and ulcerative colitis (UC), each exhibiting diverse clinical symptoms and outcomes. CD manifests as transmural inflammation affecting any segment of the GIS, while UC is confined to the mucosal layer of the colon.[1] Complications such as toxic megacolon, perforation, abscess, stricture, obstruction, bleeding, and fistula may arise in these patients, significantly compromising quality of life, necessitating hospitalization, surgical interventions, and potentially posing life-threatening risks.[2] Although more assertive treatment approaches mitigate intestinal damage and reduce the likelihood of complications, hospitalization, and the need for surgery, the associated side effects and increased treatment costs may yield unfavorable outcomes.

Calprotectin is a 36-kDa protein, a member of the S100 calcium-binding family. Primarily originating from neutrophils, it is also found to a lesser extent in monocytes and macrophages. Fecal calprotectin (FC) exhibits a concentration approximately six times higher in stool compared to healthy individuals' blood. This parameter serves as a valuable tool in distinguishing between non-inflammatory gastrointestinal diseases and IBD, offering insights into IBD response status and the presence of relapse.[3] For a recently diagnosed patient, the ability to predict the future course of the disease holds significance in shaping patient expectations and guiding treatment decisions. Consequently, there arises a necessity for the utilization of tests that are facile, non-invasive, expeditious, reliable, and cost-effective to assess the risk of complications. In our study, we specifically explored the correlation between the presence of complications at the time of diagnosis or during follow-up and FC levels in patients with IBD.

MATERIAL AND METHOD

This study represents a single-center, retrospective, observational investigation assessing patients diagnosed with IBD within the timeframe spanning January 2017 to December 2020 at Gastroenterology Clinic of Karadeniz Technical University Faculty of Medicine. Patient data were acquired through the electronic data recording system of the hospital, utilizing specific codes corresponding to IBD, CD, and UC. The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 03.02.2022, Decision No: 24237859-70).

Inclusion and Exclusion Criteria

This study enrolled patients who had received a diagnosis of IBD. Clinical, endoscopic, radiological, and histological findings were systematically evaluated to facilitate the diagnosis and differentiation of distinct IBD types. The inclusion criteria comprised patients aged 18 years and above. Conversely, patients with diagnoses of infectious gastroenteritis, Celiac disease, diverticulitis, microscopic colitis, autoimmune enteropathy, food allergy, cystic fibrosis, liver cirrhosis, infection, cancer, and those employing specific medications (proton pump inhibitor, non-steroidal anti-inflammatory drug) were excluded from the study. The patient inclusion and exclusion criteria are visually represented in **Figure 1**.

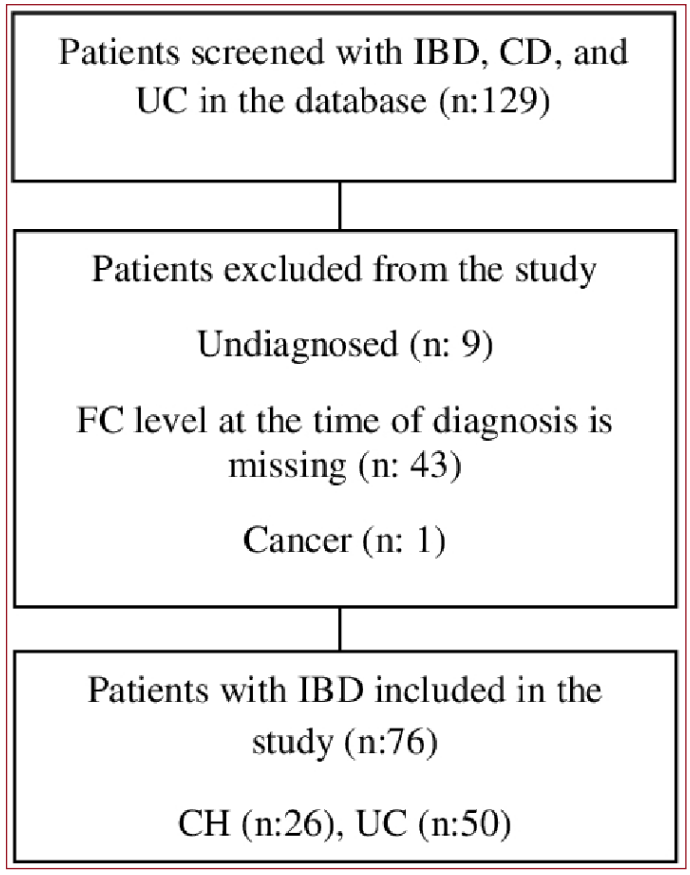

Figure 1: Flow chart of patients

Study Design

Patients diagnosed with IBD were stratified into three groups based on FC levels: FC level <50 µg/g (low), FC level 50-100 µg/g (borderline), and FC level >100 µg/g (high). Comparative analyses were conducted among these groups concerning the presence of complications at the time of diagnosis and during treatment. Complications, as defined, included toxic megacolon, bleeding, obstruction, perforation, stricture, abscess, and fistula.[2,4] Additionally, the groups were scrutinized with respect to age, gender, hemoglobin (Hb) level, leukocyte and platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin levels. Further considerations encompassed the location of involvement, extraintestinal manifestations, treatment modalities, anemia, infection at diagnosis, and the occurrence of surgical interventions. Following this comprehensive analysis, the same assessments were subsequently applied within the subgroups of CD and UC.

Fecal Calprotectin

For spot stool samples obtained from the patients, the FC antigen level was determined within 2 hours of their admission to the medical microbiology laboratory. The analysis involved the use of the Calprotectin Rapid Test Cassette kit (Feces) from ACRO Biotech Inc, Rancho Cucamonga, USA. Stool samples were subjected to examination through the chromatographic lateral flow immunoassay method, following the manufacturer's guidelines. The resulting bands were quantitatively measured utilizing the ACROLF Reader, also from ACRO Biotech Inc, Rancho Cucamonga, USA. Values below 50 µg/g were considered within the normal range.

Statistical Analysis

The statistical analysis was conducted using SPSS version 23. Descriptive statistics were reported as mean and standard deviation (SD) or median, minimum, and maximum based on the distribution of results. The Kolmogorov-Smirnov test was employed to assess the distribution of variables. For the comparison of data across three independent groups, the Chi-square test was applied for categorical variables, the ANOVA test for numerical variables with a normal distribution, and the Kruskal-Wallis test for numerical variables without a normal distribution. Logistic regression analysis was performed to investigate the association between the presence of complications at the time of diagnosis and during follow-up, and several factors including age, gender, extraintestinal manifestation, Hb and CRP, platelet count, and FC group at the time of diagnosis. In the logistic regression analysis, the FC group was dichotomized as <100 µg/g and ≥100 µg/g. The statistical significance level was set at $p<0.05$.

RESULTS

Patients

The study comprised a total of 76 patients, with 26 (34%) diagnosed with CD and 50 (66%) with UC. Among the participants, 43 (57%) were male, and 33 (43%) were female, with a mean age of 36±14 years. Extraintestinal manifestations were present in 13 (17%) patients. A majority of the patients, 73 (95%), received 5-aminosalicylic acid (5-ASA), while 23 (30%) received corticosteroids, 26 (34%) received thiopurines, and 8 (10%) received biologic agents. Anemia was present in 30 (40%) patients at the time of diagnosis. At the initial diagnosis, amebiasis was detected in 8 (11%) patients, Clostridium difficile infection (CDI) in 2 (3%) patients, and cytomegalovirus (CMV) infection in 4 (5%) patients. Thromboembolism was present in 2 (3%) patients.

Complications were observed in 17 (22%) patients at the time of diagnosis, with no complications observed in 59 (78%) patients. During follow-up, complications were noted in 20 (26%) patients, while 56 (74%) patients remained complication-free. Specifically, complications were observed in 15 (58%) patients with CD at the time of diagnosis and 17 (65%) during follow-up, while complications were observed in 2 (4%) patients with UC at the time of diagnosis and 3 (6%) during follow-up. Surgical intervention was performed in 7 (9%) patients. The detailed characteristics of the patients are presented in **Table 1**.

Table 1. Patient Characteristics

Characteristics	Total (n=76)	CD (n=26)	UC (n=50)
Age years, mean (±SD)	36 (±14)	32 (±13)	38 (±14)
Gender, n (%)			
Female	33 (43)	10 (39)	23 (46)
Male	43 (57)	16 (61)	27 (54)
Hb g/dl, mean (±SD)	12.8 (±2.1)	12.5 (±1.9)	13 (±2.2)
Leukocyte $\times10^9$/l, median (range)	7.9 (3.3-22)	7.8 (4.4-20)	8.3 (3.3-22)
Platelet $\times10^9$/l, median (range)	304 (172-638)	355 (199-638)	267 (172-541)
ESR mm/h, median (range)	14 (2-66)	23 (2-56)	10 (2-66)
CRP mg/l, median (range)	0.6 (0.1-116)	2.2 (0.1-116)	0.2 (0.1-29)
Albumin mg/dl, median (range)	4.1 (2.2-4.9)	3.9 (2.2-4.8)	4.2 (2.3-4.9)
Extraintestinal manifestation, n (%)	13 (17)	8 (31)	5 (10)
Treatment, n (%)			
5-ASA	73 (95)	24 (91)	50 (100)
Corticosteroids	23 (30)	15 (57)	8 (16)
Thiopurines	26 (34)	17 (65)	9 (18)
Biologic agents	8 (10)	6 (23)	2 (4)
Infection at the time of diagnosis, n (%)			
Amebiasis	8 (11)	2 (8)	6 (12)
CDI	2 (3)	2 (8)	0 (0)
CMV infection	4 (5)	0 (0)	4 (8)
Anemia at the time of diagnosis, n (%)	30 (40)	13 (50)	17 (34)
Thromboembolism, n (%)	2 (3)	0 (0)	2 (4)
Complications at the time of diagnosis, n (%)	17 (22)	15 (58)	2 (4)
Stricture	3 (4)	3 (12)	0 (0)
Obstruction	1 (1)	1 (4)	0 (0)
Bleeding	1 (1)	0 (0)	1 (2)
Fistula	3 (4)	3 (12)	0 (0)
Stricture+perforation	1 (1)	1 (4)	0 (0)
Abscess+fistula	4 (5)	4 (15)	0 (0)
Stricture+fistula	1 (1)	1 (4)	0 (0)
Obstruction+fistula	1 (1)	1 (4)	0 (0)
Bleeding+toxic megacolon	1 (1)	0 (0)	1 (2)
Stricture+abscess+fistula	1 (1)	1 (4)	0 (0)
Complications during the follow-up, n (%)	20 (26)	17 (65)	3 (6)
Stricture	3 (4)	3 (12)	0 (0)
Obstruction	1 (1)	1 (4)	0 (0)
Bleeding	1 (1)	0 (0)	1 (2)
Fistula	4 (5)	3 (12)	1 (2)
Stricture+perforation	1 (1)	1 (4)	0 (0)
Abscess+fistula	5 (7)	5 (19)	0 (0)
Stricture+fistula	1 (1)	1 (4)	0 (0)
Obstruction+fistula	1 (1)	1 (4)	0 (0)
Bleeding+toxic megacolon	1 (1)	0 (0)	1 (2)
Perforation+abscess+fistula	2 (3)	2 (8)	0 (0)
Surgical intervention, n (%)	7 (9)	7 (27)	0 (0)
Abscess	3 (4)	3 (12)	0 (0)
Stricture	1 (1)	1 (4)	0 (0)
Fistula	2 (3)	2 (10)	0 (0)
Stricture+ perforation	1 (1)	1 (4)	0 (0)

CD: Crohn's disease; UC: Ulcerative colitis; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs.

Comparison According to Fecal Calprotectin Group of Patients with Inflammatory Bowel Disease

At the time of diagnosis, FC) levels were categorized as follows: low (<50 µg/g) in 26 (34%) patients, borderline (50-100 µg/g) in 16 (21%) patients, and high (>100 µg/g) in 34 (45%) patients. Patients with borderline FC levels exhibited a higher age compared to those with low and high FC levels (p=0.009, p=0.020, respectively). No significant difference was observed between FC levels and gender. Patients with high FC levels had lower Hb and albumin levels (p=0.016, p=0.012, respectively). Additionally, platelet count, ESR, and CRP levels were higher in patients with high FC levels compared to those with low FC levels (p<0.001, p=0.004, p<0.001, respectively).

Extraintestinal involvement was more common in patients with high FC levels compared to those with low and borderline FC levels (p=0.002). The utilization of corticosteroids, thiopurines, and biological agents was higher in patients with high FC levels than in those with low and borderline levels, although this trend was observed to be statistically borderline (p=0.053). Amebiasis was observed in 3 (19%) patients, CDI in 1 (6%) patient, and CMV infection in 2 (13%) patients with borderline FC levels. In contrast, amebiasis was detected in 5 (15%) patients, CDI in 1 (3%) patient, and CMV infection in 2 (6%) patients with high FC levels. No infection was observed in patients with low FC levels.

Complications at the time of diagnosis and during follow-up were more frequent in patients with high FC levels compared to those with low and borderline levels (p<0.001, p<0.001, respectively). The rate of surgical intervention was higher in patients with high FC levels compared to those with low and borderline FC levels (p=0.038) (**Table 2**).

In the logistic regression analysis, it was observed that the risk of complications at the time of diagnosis and during follow-up was 26 and 8 times higher, respectively, in patients with fecal calprotectin (FC) levels >100 µg/g compared to those with FC levels below this threshold (p=0.006, p=0.015, respectively). The logistic regression model is presented in **Table 3**.

Table 2. Comparison According to Fecal Calprotectin Group of Patients with Inflammatory Bowel Disease

Characteristics	FC level (<50 µg/g) (n=26)	FC level (50-100 µg/g) (n=16)	FC level (>100 µg/g) (n=34)	p
Age years, mean (±SD)	32±13	45±15	34±13	0.007*
Gender, n (%)				
Female	8 (31)	10 (63)	15 (44)	0.131
Male	18 (69)	6 (37)	19 (56)	
Hb g/dl, mean (±SD)	13.7±1.7	12.9±2.4	12.1±2	0.016*
Leukocyte $\times 10^9$/l, median (range)	8 (5.1-12)	7.5 (4.5-11.3)	7.3 (3.3-22)	0.808
Platelet $\times 10^9$/l, median (range)	254 (172-374)	279 (185-509)	360 (196-638)	<0.001*
ESR mm/h, median (range)	6 (2-36)	12 (3-66)	23 (2-63)	0.004*
CRP mg/l, median (range)	0.2 (0.1-9.8)	0.4 (0.1-29)	2.3 (0.1-116)	<0.001*
Albumin mg/dl, median (range)	4.3 (2.8-4.9)	4.1 (2.3-4.7)	3.9 (2.2-4.8)	0.012*
Extraintestinal manifestation, n (%)				
Yes	2 (8)	0 (0)	11 (32)	0.004*
No	24 (92)	16 (100)	23 (68)	
Treatment, n (%)				
5-ASA	26 (100)	16 (100)	31 (90)	0.053
Corticosteroids	3 (11)	5 (32)	15 (44)	
Thiopurines	4 (15)	5 (32)	17 (49)	
Biologic agents	0 (0)	1 (6)	7 (20)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	3 (19)	5 (15)	0.087
CDI	0 (0)	1 (6)	1 (3)	0.069
CMV infection	0 (0)	2 (13)	2 (6)	0.260
Anemia at the time of diagnosis, n (%)				
Yes	6 (23)	5 (31)	19 (56)	0.027*
No	20 (77)	11 (69)	15 (44)	
Complications at the time of diagnosis, n (%)				
Yes	1 (4)	0 (0)	16 (47)	<0.001*
No	25 (96)	16 (100)	18 (53)	
Complications during the follow-up, n (%)				
Yes	3 (12)	0 (0)	17 (50)	<0.001*
No	23 (88)	16 (100)	17 (50)	
Surgical intervention, n (%)				
Yes	1 (4)	0 (0)	6 (18)	0.074
No	25 (96)	16 (100)	28 (82)	

FC: Fecal calprotectin; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs. * Statistically significant.

Table 3. Logistic Regression Model Associated with the Presence of Complications

Complications at the time of diagnosis	p	Exp (B)	Exp (B) for 95% confidence interval	
			Düşük	Yüksek
Age	0.147	0.949	0.884	1.019
Gender	0.394	0.432	0.063	2.972
Extraintestinal manifestation	0.359	0.438	0.075	2.557
Hb level at the time of diagnosis	0.403	0.824	0.523	1.298
Platelet count at the time of diagnosis	0.174	1.000	1.000	1.000
CRP level at the time of diagnosis	0.896	0.996	0.934	1.062
Calprotectin group	0.006*	25.967	2.502	269.482
Complications during the follow-up				
Age	0.094	0.950	0.894	1.009
Gender	0.316	0.424	0.079	2.270
Extraintestinal manifestation	0.698	0.720	0.137	3.785
Hb level at the time of diagnosis	0.360	0.834	0.566	1.230
Platelet count at the time of diagnosis	0.175	1.000	1.000	1.000
CRP level at the time of diagnosis	0.960	1.002	0.927	1.083
Calprotectin group	0.015*	7.885	1.497	41.544

Hb: Hemoglobin; CRP: C-reactive protein. The time of diagnosis: Nagelkerke R2=0.581; Omnibus chi-square=36.338, df=7, p=<0.001; Hosmer and Lemeshow=0.586. During the follow-up: Nagelkerke R2=0.499; Omnibus chi-square=31.741, df=3, p=<0.001; Hosmer and Lemeshow=0.677. * Statistically significant.

Comparison According to Fecal Calprotectin Group of Patients with Crohn's Disease and Ulcerative Colitis

Due to the limited number of patients with CD and UC, statistical comparisons could not be conducted for some values, and the patient data were presented in ratios.

In CD patients, lower Hb and albumin levels were observed in individuals with high FC levels, while platelet count and CRP levels were higher (p=0.035, p=0.028, p=0.011, p=0.004, respectively). The rate of extraintestinal manifestations was 0% (0/6) in patients with low FC levels, 0% (0/2) in patients with borderline FC levels, and 44% (8/18) in patients with high FC levels (p=0.025). The use of corticosteroids, thiopurines, and biologic agents was reported as 33% (2/6), 33% (2/6), 0% (0/6) in patients with low FC levels, 100% (2/2), 100% (2/2), 0% (0/2) in patients with borderline FC levels, and 62% (11/18), 73% (13/18), 34% (6/18) in patients with high FC levels, respectively. Amebiasis and CDI were not observed in patients with low FC levels, while they were present in 50% (1/2) of patients with borderline FC levels and 6% (1/18) of patients with high FC levels.

The rate of complications at the time of diagnosis was 17% (1/6) in patients with low FC levels and 0% (0/2) in patients with borderline FC levels, whereas it was 78% (14/18) in patients with high FC levels (p=0.004). Similarly, the rate of complications during follow-up was 33% (2/6) in patients with low FC levels and 0% (0/2) in patients with borderline FC levels, while it was 83% (15/18) in patients with high FC levels (p=0.008). The rate of surgical intervention was 17% (1/6) in patients with low FC levels, 0% (0/2) in patients with borderline FC levels, and 33% (6/18) in patients with high FC levels (**Table 4**).

UC patients, higher platelet count, ESR, and CRP levels were observed in individuals with high FC levels compared to those with low FC levels (p=0.029, p=0.034, p=0.039, respectively). The rate of extraintestinal involvement was 10% (2/20) in patients with low FC levels, 0% (0/14) in patients with borderline FC levels, and 19% (3/16) in patients with high FC levels. The utilization rates of corticosteroids, thiopurines, and biologic agents were reported as 5% (1/20), 10% (2/20), 0% (0/20) in patients with low FC levels, 21% (3/14), 21% (3/14), 7% (1/14) in patients with borderline FC levels, and 32% (5/16), 25% (4/16), and 6% (1/16) in patients with high FC levels, respectively. Amebiasis and CMV infections were not observed in patients with low FC levels, while they were detected in 14% (2/14) of patients with borderline FC levels. Amebiasis was observed in 2% (4/16) and CMV infection in 13% (2/16) of patients with high FC levels.

No complications were observed in patients with low and borderline FC levels at the time of diagnosis. However, complications were detected in 13% (2/16) of patients with high FC levels. During the follow-up period, the rate of complications was 5% (1/20) in patients with low FC levels, 0% (0/14) in patients with borderline FC levels, and 13% (2/16) in patients with high FC levels (**Table 4**).

DISCUSSION

FC is employed for the assessment of intestinal inflammation in patients with IBD.[5] A crucial application of FC is its utility in distinguishing between IBD and irritable bowel syndrome (IBS) without necessitating invasive procedures or endoscopy.[6] In the context of differential diagnosis, it has been observed that in patients with an FC level <50 µg/g, FC exhibits a sensitivity of 100% and a specificity ranging from 51% to 100%.[7] Furthermore, FC serves as an indicator of treatment response and relapse status in individuals with IBD.[6] Additionally, studies have demonstrated a correlation between FC levels and both endoscopic and histological findings.[8]

In IBD, serious and life-threatening complications can arise. To assess the progression of these patients, various factors are considered, including patient characteristics (such as symptoms, quality of life, daily activity, and previous treatments), inflammation status (disease prevalence, findings from endoscopy and imaging methods, and biological markers), and the presence of complications (intestinal injury, history of surgery). Different scoring systems are utilized to gauge disease activity, incorporating these diverse criteria.[9]

For CD, the CD activity index (CDAI) includes extraintestinal complications and hematocrit among its criteria.[10] In the case of UC, the Truelove-Witts severity index criteria involve Hb and ESR.[11] Moreover, various scoring systems assessing disease activity in IBD incorporate criteria such as CRP and albumin levels, anemia, and the use of corticosteroids and biological agents. The UC activity index in the American College of Gastroenterology (ACG) guide specifically includes Hb, ESR, CRP, and FC levels.[12] These criteria collectively contribute to a comprehensive evaluation of disease activity in individuals with IBD.

Table 4. Comparison According to Fecal Calprotectin Group of Patients with Crohn's Disease and Ulcerative Colitis

CD characteristics	FC level (<50 µg/g) (n=6)	FC level (50-100 µg/g) (n=2)	FC level (>100 µg/g) (n=18)	p
Age years, mean (±SD)	25±9	60±2	31±11	0.002*
Gender, n (%)				
Female	2 (33)	1 (50)	7 (39)	1.000
Male	4 (67)	1 (50)	11 (61)	
Hb g/dl, mean (±SD)	13.9±2.1	14.2±1.8	11.9±1.6	0.035*
Leukocyte $\times10^9$/l, median (range)	8.7 (7.7-10)	5.3 (5-5.6)	7.2 (4.4-20)	0.071
Platelet $\times10^9$/l, median (range)	307 (236-370)	238 (199-278)	414 (250-638)	0.011*
ESR mm/h, median (range)	10 (2-36)	25 (5-45)	23 (2-56)	0.366
CRP mg/l, median (range)	0.6 (0.1-1.5)	1.2 (0.1-2.4)	3.8 (0.1-116)	0.004*
Albumin mg/dl, median (range)	4.2 (4-4.7)	4.1 (3.9-4.4)	3.7 (2.2-4.8)	0.028*
Location of involvement, n (%)				
İleum	4 (67)	1 (50)	10 (56)	0.753
Colon	2 (33)	1 (50)	2 (11)	
İleocolon	0 (0)	0 (0)	4 (22)	
Upper GIS+ileum	0 (0)	0 (0)	1 (6)	
Upper GIS+colon	0 (0)	0 (0)	1 (6)	
Extraintestinal manifestation, n (%)				
Yes	0 (0)	0 (0)	8 (44)	0.164
No	6 (100)	2 (100)	10 (56)	
Treatment, n (%)				
5-ASA	6 (100)	2 (100)	16 (90)	0.630
Corticosteroids	2 (33)	2 (100)	11 (62)	
Thiopurines	2 (33)	2 (100)	13 (73)	
Biologic agents	0 (0)	0 (0)	6 (34)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	1 (50)	1 (6)	0.197
CDI	0 (0)	1 (50)	1 (6)	0.197
CMV infection	0 (0)	0 (0)	0 (0)	
Anemia at the time of diagnosis, n (%)				
Yes	2 (33)	0 (0)	11 (61)	0.252
No	4 (67)	2 (100)	7 (39)	
Complications at the time of diagnosis, n (%)				
Yes	1 (17)	0 (0)	14 (78)	0.004*
No	5 (83)	2 (100)	4 (22)	
Complications during the follow-up, n (%)				
Yes	2 (33)	0 (0)	15 (83)	0.008*
No	4 (67)	2 (100)	3 (17)	
Surgical intervention, n (%)				
Yes	1 (17)	0 (0)	6 (33)	0.509
No	5 (83)	2 (100)	12 (67)	
UC characteristics	**FC level (<50 µg/g) (n=20)**	**FC level (50-100 µg/g) (n=14)**	**FC level (>100 µg/g) (n=16)**	**p**
Age years, mean (±SD)	34±13	43±15	37±14	0.213
Gender, n (%)				
Female	6 (30)	9 (64)	8 (50)	1.000
Male	14 (70)	5 (36)	8 (50)	
Hb g/dl, mean (±SD)	13.6±1.7	12.7±2.5	12.3±2.4	0.204
Leukocyte $\times10^9$/l, median (range)	7.8 (5.1-12)	8.4 (4.5-11.3)	7.9 (3.3-22)	0.743
Platelet $\times10^9$/l, median (range)	241 (172-374)	290 (185-509)	312 (196-541)	0.029*
ESR mm/h, median (range)	5 (2-30)	12 (3-66)	20 (2-63)	0.034*
CRP mg/l, median (range)	0.1 (0.1-9.8)	0.3 (0.1-29)	0.6 (0.1-14)	0.039*
Albumin mg/dl, median (range)	4.3 (2.8-4.9)	4.1 (2.3-4.7)	4.1 (2.6-4.8)	0.299
Extraintestinal manifestation, n (%)				
Yes	2 (10)	0 (0)	3 (19)	0.164
No	18 (90)	14 (100)	13 (81)	
Treatment, n (%)				
5-ASA	20 (100)	14 (100)	16 (100)	0.469
Corticosteroids	1 (5)	3 (21)	5 (32)	
Thiopurines	2 (10)	3 (21)	4 (25)	
Biologic agents	0 (0)	1 (7)	1 (6)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	2 (14)	4 (25)	0.076
CDI	0 (0)	0 (0)	0 (0)	
CMV infection	0 (0)	2 (14)	2 (13)	0.220
Anemia at the time of diagnosis, n (%)				
Yes	4 (20)	5 (36)	8 (50)	0.252
No	16 (80)	9 (64)	8 (50)	
Complications at the time of diagnosis, n (%)				
Yes	0 (0)	0 (0)	2 (13)	0.172
No	20 (100)	14 (100)	14 (87)	
Complications during the follow-up, n (%)				
Yes	1 (5)	0 (0)	2 (13)	0.481
No	19 (95)	14 (100)	14 (87)	
Surgical intervention, n (%)				
Yes	0 (0)	0 (0)	0 (0)	
No	20 (100)	14 (100)	16 (100)	

CD: Crohn's disease; FC: Fecal calprotectin; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs, UC: Ulcerative colitis. * Statistically significant.

As FC is a protein associated with mucosal inflammation, it is hypothesized that its elevation may specifically indicate the presence of complications. In our study, we observed a higher incidence of complications at the time of diagnosis and during follow-up in patients with IBD who exhibited elevated FC levels. Furthermore, it was determined that the presence of complications at the time of diagnosis was 26 times higher, and the presence of complications during follow-up was 8 times higher in patients with FC levels exceeding 100 µg/g. Studies evaluating disease activity with FC are presented in the literature. In one study, it was determined that FC levels were higher in patients with active disease than in patients who were clinically and endoscopically in remission and had received anti-tumor necrotizing factor-α (anti-TNF-α) treatment.[13] Nevertheless, there is limited availability of studies demonstrating the relationship between the presence of complications and FC levels in patients with IBD. A study by Fabian et al. found that tissue calprotectin was not effective in revealing the development of complications in pediatric UC patients. However, FC was shown to be associated with chronic inflammation in the colonic mucosa. The study concluded that elevated FC levels in UC patients were linked to unfavorable clinical outcomes.[14] Similarly, in our study, we suggest that a high FC level in IBD patients is associated with negative outcomes.

In clinical practice, markers indicating acute inflammation, such as ESR, CRP, leukocyte and platelet counts, are commonly employed to assess disease activity in patients with IBD. Bodelier et al. demonstrated a higher rate of CRP falling below the normal level in patients in remission compared to those with active disease in IBD.[15] However, these markers are nonspecific and may elevate due to various factors such as obesity, smoking, and drug use.[1] CRP levels can be within the normal range in 30% of patients with active disease and elevated in 30% of patients without active disease, indicating that CRP alone may not be sufficient to evaluate disease progression.[16-18] In our study, we observed that ESR and CRP levels were higher in IBD patients with elevated FC levels compared to those with low FC levels. Ricanek et al. demonstrated that platelet count was higher in patients with a high IBD activity index.[19] Similarly, in our study, the platelet count, which tends to increase reactively in the presence of inflammation, was higher in patients with high FC levels compared to those with low FC levels. Albumin, a negative acute-phase reactant, was lower in patients with high FC levels than in those with low FC levels. Consequently, our study aligned with tests indicating acute inflammation in the group with high FC levels in IBD patients. In line with our findings, Abej et al. reported higher CRP levels and lower albumin levels in patients with positive FC compared to those with negative FC.[20]

Anemia is a common occurrence in 6-74% of patients with IBD, stemming from causes such as iron deficiency anemia, B12 and folic acid deficiency anemia, anemia of chronic disease, and malnutrition.[21] A study involving patients diagnosed with IBD demonstrated that Hb levels were lower in individuals with positive FC compared to those with negative FC.[20] Consistent with these findings, our study revealed lower Hb levels in patients with high FC levels than in those with low FC levels. In the subgroup analysis, Hb levels were lower in patients with high FC levels compared to those with low FC levels in patients with CD, but no significant difference was observed in patients with UC. Anemia in IBD can arise from deficiencies in iron, B12, and folate, as CD can involve the entire GIS. Furthermore, complications such as fistulas and abscesses that develop in CD may contribute to anemia of chronic disease.

In our study, we observed a higher utilization of corticosteroids, thiopurines, and biological agents in patients with high FC levels compared to those with low FC levels. This suggests that as disease activity and complications increase, there is a greater need for these treatments. The elevated usage of these therapeutic interventions in patients with higher FC levels may indicate a more pronounced disease severity, prompting the need for more frequent and potent medical interventions to control inflammation and address complications.

CONCLUSION

The statement highlights the substantive findings of the study, underscoring the ability of FC levels to predict the presence of complications during both the diagnosis and follow-up phases in individuals with IBD. The incorporation of FC alongside markers of acute inflammation is posited as a significant contributor to predicting disease trajectory and facilitating the development of risk models.

Firstly, it's important to note that this study is retrospective in nature, and furthermore, the number of patients is limited. Due to its retrospective design, the accurate scoring of the risk for IBD was challenging. Despite these limitations, we believe that this study can provide valuable insights for future research, offering a foundation to explore the relationship between FC and complications in patients with IBD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 03.02.2022, Decision No: 24237859-70).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Flynn S, Eisenstein S. Inflammatory bowel disease presentation and diagnosis. Surg Clin North Am 2019;99:1051-62.
2. Goldstone RN , Steinhagen RM. Abdominal emergencies in inflammatory bowel disease. Surg Clin North Am 2019;99:1141-50.
3. Ricciuto A, Griffiths AM. Clinical value of fecal calprotectin. Crit Rev Clin Lab Sci 2019;56:307-20.
4. Romberg-Camps MJL, Dagnelie PC, Kester ADM, et al. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol 2009;104:371-83.
5. Sipponen T, Kolho KL. Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease. Scand J Gastroenterol 2015;50:74-80.
6. Manceau H, Chicha-Cattoir V, Puy H, Peoc'h K. Fecal calprotectin in inflammatory bowel diseases: update and perspectives. Clin Chem Lab Med 2017;55:474-83.
7. Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess 2013;17:1-211.
8. Theede K, Holck S, Ibsen P, Ladelund S, Nordgaard-Lassen I, Nielsen AM. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. Clin Gastroenterol Hepatol 2015;13:1929-36.
9. Siegel CA, Bernstein CN. Identifying patients with inflammatory bowel diseases at high vs low risk of complications. Clin Gastroenterol Hepatol 2020;18:1261-7.
10. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon 2018;64:20-57.
11. Sehgal R, Koltun WA. Scoring system in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol 2010;4:513-21.
12. Pabla BS, Schwartz DA. Assessing severity of disease in patients with ulcerative colitis. Gastroenterol Clin North Am 2020;49:671-88.
13. Molander P, Sipponen T, Kemppainen H, et al. Achievement of deep remission during scheduled maintenance therapy with TNFα-blocking agents in IBD. J Crohns Colitis 2013;7:730-5.
14. Fabian O, Hradsky O, Lerchova T, Mikus F, Zamecnik J, Bronsky J. Limited clinical significance of tissue calprotectin levels in bowel mucosa for the prediction of complicated course of the disease in children with ulcerative colitis. Pathol Res Pract 2019;215:152689.
15. Bodelier AGL, Jonkers D, van den Heuvel TV, et al. High percentage of IBD patients with indefinite fecal calprotectin levels: Additional value of a combination score. Dig Dis Sci 2017;62:465-72.
16. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006;55:426-31.
17. Solem CA, Loftus Jr EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707-12.
18. Kwon JH, Im JP, Ye BD, et al. Disease phenotype, activity and clinical course prediction based on C-reactive protein levels at diagnosis in patients with Crohn's disease:results from the CONNECT study. Gut Liver 2016;10:595-603.
19. Ricanek P, Brackmann S, Perminow G, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. Scand J Gastroenterol 2011;46:1081-91.
20. Abej E, El-Matary W, Singh H, Bernstein CN. The utility of fecal calprotectin in the real-world clinical care of patients with inflammatory bowel disease. Can J Gastroenterol Hepatol 2016;2016:2483261.
21. Bergamaschi G, Sabatino AD, Corazza GR. Pathogenesis, diagnosis and treatment of anaemia in immune-mediated gastrointestinal disorders. Br JHaematol 2018;182:319-29.