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Determination of the frequency of extraintestinal manifestations in patients with inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a systemic disease whose etiology and pathogenesis are not fully understood and that affects organs and systems other than the gastrointestinal system. Many patients with IBD can develop extraintestinal manifestations (EIMs), affecting numerous organs and systems. The medical records of IBD patients followed in our gastroenterology clinic were retrospectively examined. While patients with Crohn's disease (CD) were grouped by anatomical site and clinical type, patients with ulcerative colitis (UC) were grouped by anatomical site of involvement.They examined the association between the presence of EIMs and demographic characteristics, diagnostic groups, sex, age groups, anatomical involvement, CD clinical types and fistula types. In addition, the patient groups and the relationship between EIM subgroups were evaluated. The study consisted of 393 patients with IBD, including 276 patients with UC and 117 with CD. The frequency of at least one EIM was 35.4% in 139 patients. When subgroups were examined,hepatosteatosis was the most common EIM, followed by hepatobiliary manifestations. EIM frequency was higher in CD than in UC when the two were compared. There was no significant relationship between EIM and diagnosis groups, anatomical location, clinical type of CD, or fistula types. Regarding the relationship between EIMs, there was no direct proportional relationship, but there was a significant decrease in the incidence of other EIMs in some EIMs. Determining the prevalence and risk factors associated with EIMs and raising awareness about this issue may aid in its early diagnosis and treatment. Thus, complications that may arise during the follow-up process can be avoided.

Keywords: Inflammatory bowel disease, extraintestinal manifestations, Crohn's disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is a chronic, inflammatory disease of the gastrointestinal tract. Its two most prevalent subtypes are ulcerative colitis (UC) and Crohn's disease (CD) Clinically indistinguishable cases of indeterminate colitis (IC) are also included in this definition. IBD pathogenesis includes an immune-mediated inflammatory response to an unknown environmental trigger that interacts with the intestinal flora in genetically susceptible individuals [1]. Although CD and UC can occur at any age, the peak age of onset for CD is typically between 20 and 30 years, and for UC, it is between 30 and 40 years [1]. Various studies have demonstrated a bimodal age distribution with a potential second peak between 50 and 80 years. Although the cause of IBD is mainly unknown, genetic, environmental, or microbial factors interact with immune responses in a complex manner. The environment, genetics, gut microbiota, and immune response have significantly contributed to Crohn's disease and ulcerative colitis (UC) in recent years. IBD is a group nof inflammatory bowel disease in which systemic inflammation affects organs and systems other than the digestive system [2]. EIMs associated with IBD are common in individuals with UC or CD. EIM can occur before onset, concurrently with the disease, or after its diagnosis. These discoveries may involve multiple organ systems. EIM rates in IBD have been reported to range from 6% to 47% [3]. Up to 50% of IBD patients, may experience at least one EIM prior to the diagnosis of IBD [4]. Multiple factors may contribute to extraintestinal organ involvement in IBD. Smoking, colon disease and perianal CD

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are risk factors strongly associated with the development of EIMs [5]. EIMs and extraintestinal complications are the two groups into which extraintestinal findings are divided. EIM frequently affects the musculoskeletal, skin, hepatobiliary, ocular and respiratory systems. Extraintestinal complications mainly arise from the disease and include malabsorption, osteoporosis, peripheral neuropathies, kidney stones, gallstones and IBD treatment-related side effects [3]. EIMs negatively affect the quality of life of patients. The pathogenesis of EIMs in IBD remains unclear. Many hypotheses have been proposed, including genetic predisposition and autoantibodies against organ-specific cellular antigens shared by the gastrointestinal tract and other organ systems. The diseased gastrointestinal mucosa may trigger an immune response because it shares common epitopes in extraintestinal areas [3]. The triggers of autoimmune responses in some organs are influenced by genetic factors. EIM is associated with significant histocompatibility complex loci in inflammatory bowel disease [3]. EIM is more likely to occur in patients with UC when the HLA-DR103 genotype is present, even though it is more common in patients with CD, HLA-A2, HLA-DR1 and HLA-DQ.

Regarding intestinal disease activity, EIMs can be divided into three groups. The first group is directly related to bowel disease and parallels the disease process in its progression. Episcleritis, erythema nodosum, oral aphthous ulcers and peripheral arthritis are all examples of EIMs in this group [6]. The second group of EIMs includes ankylosing spondylitis (AS) and uveitis and develops independently of intestinal disease activity [6]. This third group includes pyoderma gangrenosum (PG) and primary sclerosing cholangitis (PSC), both of which have an uncertain relationship with intestinal inflammation. The probability of developing EIM increases with disease duration and in patients who have previously had EIM [4].

EIMs contribute significantly to morbidity and mortality [7]. Knowledge of the prevalence, pathophysiology and clinical presentation of EIMs is important to tailor treatment options to cover all aspects of IBD [6]. A multidisciplinary approach is required to adequately address EIMs and improve patients' quality of life.

Material and Methods

The ICD codes of patients who were followed up for IBD at the gastroenterology outpatient clinic of gastroenterology between January 2014 and December 2016 were analyzed. Retrospective reviews were performed on the patients' files and computer records. Patients with missing clinical data or uncertain diagnosis were excluded from the study. The study included patients with extraintestinal findings at their initial admission. The patient's age, sex, date of diagnosis, involvement sites, presence of fistula and extraintestinal findings were recorded. All patients who participated in the study underwent endoscopic and pathological examinations.

Using the Montreal classification, UC patients were classified according to the anatomical sites of involvement [8]. The disease confined to the rectum was evaluated as proctitis, the involvement of the colorectal region distal to the splenic flexure was diagnosed as UC with left colon involvement and the disease extending to the proximal splenic flexure was classified as extensive UC. CD patient classification was based on anatomical and clinical behavior patterns. It was divided into subtypes as obstructive (stricture), fistulizing (penetrating) and inflammatory (nonstricture+structuring) based on clinical behavior. It was also classified as ileal, colonic, ileocolonic and upper GI involvement based on the location of involvement [8]. Fistula types were entero-enteric, enterovesical, enterovaginal, enterocutaneous and perianal. They examined additional imaging techniques for determining the prevalence of CD. The patients' surgical treatment was divided into palliative and total colectomy.

The extraintestinal manifestations were musculoskeletal, dermatological, ocular, hepatobiliary, urogenital, renal, pulmonary, thromboembolic and metabolic bone disease. Rheumatologists evaluated and diagnosed patients' musculoskeletal involvement cases as positive. Musculoskeletal system findings are divided into 2 different clinical subgroups: axial and peripheral. Peripheral joint involvement was grouped as type 1 and type 2 arthropathy, and axial involvement was grouped as sacroiliitis and AS. Cases that were evaluated and diagnosed by a dermatologist and ophthalmologist for ocular and dermatological involvement were deemed EIM. Common skin findings in patients were erythema nodosum, pyoderma gangrenosum, sweet syndrome and aphthous stomatitis. Episcleritis, scleritis and anterior uveitis are common ophthalmological EIMs. Cases imaged and diagnosed with pulmonary involvement by a pulmonologist were accepted. Bronchiectasis, interstitial lung disease, and organizing pneumonia are common lung findings. According to the type of pulmonary involvement, patients were grouped as bronchiectasis and interstitial lung disease. Liver and biliary tract disease involvement included PSC, hepatosteatosis, cholelithiasis, and cholangiocarcinoma. Patients with abdominal imaging for cholelithiasis and hepatosteatosis, patients with elevated ALP and GGT for PSC, and those with characteristic features on MRCP or ERCP were considered as hepatobiliary involvement. Patients diagnosed with liver biopsy in suspicious cases that could not be diagnosed were accepted as EIM. When evaluating patients who underwent bone mineral densitometry for metabolic bone disease, cases of thromboembolic manifestations that were clinically and imaging-proven were considered as EIMs. Thromboembolic events were grouped as DVT and other thromboses. Although it is seen in renal involvement, nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis and secondary (AA) amyloidosis are usually seen.

This study's data were evaluated using the SPSS 16.0 (SPSS Inc.,

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Chicago, Illinois, United States) software. The Shapiro–Wilk test was used to ensure the normality of continuous variables. Student's t test was used to compare the mean of two independent groups. The Mann–Whitney U test was used in comparisons made for diagnostic times. The descriptive statistics were expressed as the mean, standard deviation, median, minimum, and maximum values per the analysis technique. During the examination of the relationship between categorical variables, the chi-square test was utilized, and two ratio comparisons were made for variables with more than two categories and a relationship. Descriptive statistics were given as frequencies and percentages. The level of statistical significance was set at 0.05 for all employed methods.

Ethical approval (10.02.2017-02) was obtained from the Gazi University ethics commission and therefore the study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Results

While the study included 393 patients with IBD, 276 patients had UC, and 117 had CD. The demographic and clinical characteristics of the patients are summarized in Table 1. Patients had widely varying follow-up times. At least one EIM was observed in 139 of 393 patients in our study, and the frequency was 35.4%.

When UC and CD were compared in malignancy development, 7 UC patients and 1 CD patient were diagnosed with malignancy. More than one malignancy was detected in one patient.In the same patient, more than one malignancy was discovered. Particularly cholangiocellular carcinoma and colorectal carcinoma were observed in UC cases.

In 139 (35.4%) of the patients included in the study, at least one EIM was identified, while EIM was not detected in 254 (64.6%) patients. Table 2 summarizes clinical characteristics based on the presence of EIM.

Table 1. Baseline characteristics and comparisons of the patients

Parameter	Total (n=393)	UC (n=276)	CD (n=117)
Sex, n (%)			
Female	171 (43.5)	115 (41.7)	56 (47.9)
Male	222 (56.5)	161 (58.3)	61 (52.1)
Age, mean (±SD)	44.72±15.04	47.09±15.21	39.13±13.07
Mean follow-up time, months, median (min-max)	51 (1-431)	58 (3-431)	37 (1-427)
CD types according to anatomical involvement, n (%)			
Ileal	62 (53)	-	62 (53.0)
Colonic	6 (5.1)	-	6 (5.1)
Ileocolonic	49 (41.9)	-	49 (41.9)
Isolated upper gastrointestinal	0 (0.0)	-	0 (0.0)
CD clinical behavior types, n (%)			
Non-penetrating, non-stricturing	86 (73.5)	-	86 (73.5)
Stricturing (obstructive)	8 (6.8)	-	8 (6.8)
Penetrating (fistulizing)	20 (17.1)	-	20 (17.1)
Penetrating+stricturing	3 (2.6)	-	3 (2.6)
UC types according to anatomical involvement, n (%)			
Proctitis	49 (17.8)	49 (17.8)	-
Left-sided	129 (46.7)	129 (46.7)	-
Extensive colitis, pancolitis	98 (35.5)	98 (35.5)	-
Development of malignancy, n			
Colorectal cancer	2	2	0
Cholangiocellular carsinom	1	1	0
Others	8	7	1
Surgical treatment, n (%)	22 (5.6)	8 (2.9)	14 (12)
EIM frequency, n (%)	139 (35.4)	83 (30.1)	56 (47.9)

UC: ulcerative colitis, CD: Crohn disease, EIM: extraintestinal manifestations

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Table 2. Clinical features according to the presence of EIM

	EIM+ (n=139)	EIM- (n=254)	p
Age, mean (±SD)	47.68±14.69	43.10±15.01	0.004
Sex, n (%)			
Male, n (%)	71 (51.1)	151 (59.4)	0.110
Female, n (%)	68 (48.9)	103 (40.6)	
UC, n (%)	83 (30.1)	193 (69.9)	0.001
CD, n (%)	56 (47.9)	61 (52.1)	
UC anatomical site of involvement, n (%)			
Proctitis	14 (16.9)	35 (18.1)	0.304
Left-sided	34 (41)	95 (49.2)	
Extensive colitis	35 (42.2)	63 (32.6)	
CD types according to anatomical involvement, n (%)			
Ileal	31 (31)	31 (50.8)	0.483
Colonic	4 (7.1)	2 (3.3)	
Ileocolonic	21 (37.5)	28 (45.9)	
Isolated upper gastrointestinal	0 (0.0)	0 (0.0)	
CD clinical behavior types, n (%)			
Non-penetrating, non-stricturing	44 (78.6)	42 (68.9)	0.572
Stricturing (obstructive)	4 (7.1)	4 (6.6)	
Penetrating (fistulizing)	7 (12.5)	13 (21.3)	
Penetrating+stricturing	1 (1.8)	2 (3.3)	
Fistula distribution, n (%)			
Enteroenteric	4 (30.8)	5 (26.3)	0.407
Enterocutaneous	2 (15.4)	3 (15.8)	
Enterovaginal	0 (0.0)	1 (5.3)	
Perianal	5 (38.5)	10 (52.6)	
Enterovesical	2 (15.4)	0 (0,0)	
Follow-up <60 months, n (%)	70 (50.4)	153 (60.2)	0.059
Follow-up >60 months, n (%)	69 (49.6)	101 (39.8)	

UC: ulcerative colitis, CD: Crohn disease

EIM was found in 56 (47.9%) of 117 CD patients and 83 (30.1%) of 276 UC patients. EIM was 2.14 times more prevalent in CD patients than in UC patients. One EIM was detected in 65 (78.3%) of UC patients, and more than one EIM was detected in 18 (21.7%) patients. While 1 EIM (48.2%) was seen in 27 of those with CD, more than one EIM was observed in 29 (51.8%). Table 3 shows the distribution of EIM in UC and CD. Although hepatobiliary involvement was the most common EIM, the frequency of musculoskeletal and hepatobiliary involvement was higher in CD. Considering the subgroups, CD had a higher frequency of Type 1 peripheral arthropathy, sacroiliitis and hepatosteatosis, while UC had a higher frequency of PSC. PSC was only observed in UC patients. Regarding other EIMs, there was no statistically significant difference between CD and UC. All instances of eye involvement involved uveitis patients. We did not observe episcleritis or scleritis in our patients. Metabolic bone disease included osteoporosis and osteomalacia, other metabolic bone diseases were not seen.

The total frequency of EIM did not have a statistically significant relationship with gender. The frequency of musculoskeletal and skin involvement was found to be statistically significantly higher in females only (p=0.002 and p=0.001). When the frequency of EIM in the geriatric and adult populations was compared, 18 (42.9%) of 42 geriatric patients exhibited at least one EIM. The elderly age group had a higher incidence of thromboembolic events. Pulmonary involvement was only found in the elderly age group.

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Table 3. Distribution of EIM in patients

	Total n (%)	UC n (%)	CD n (%)	p
EIM overall frequency (patient with at least one EIM)	139 (35,4)	83 (30.1)	56 (47.9)	0.001
Musculoskeletal involvement, n (%)	**50 (36.0)**	**19 (6.9)**	**31 (26.5)**	**<0.001**
Type 1 peripheral arthropathy	16 (11.5)	5 (1.8)	11 (9.4)	**0.012**
Type 2 peripheral arthropathy	12 (8.6)	5 (1.8)	7 (6.0)	0.170
Ankylosing spondylitis	18 (12.9)	9 (3.3)	9 (7.7)	0.344
Sacroileitis	4 (2.9)	0 (0.0)	4 (3.4)	**0.013**
Skin sign, n (%)	**25 (18.0)**	**13 (4.7)**	**12 (10.3)**	**0.039**
Erythema nodosum	8 (5.8)	3 (3.8)	5 (4.3)	0.117
Sweet's syndrome	1 (0.7)	1(0.4)	0 (0.0)	0.414
Psoriasis	2 (1.4)	1 (0.4)	1 (0.9)	**0.026**
Aphthous stomatitis	14 (10.1)	8 (2.9)	6 (5.1)	0.057
Eye sign, n (%)	**7 (0.5)**	4 (1.4)	3 (2.6)	0.429
Uveitis	7 (0.5)	4 (1.4)	3 (2.6)	0.867
Hepatobiliary involvement, n (%)	**80 (57.6)**	**43 (15.6)**	**37 (31.6)**	**<0.001**
Hepatosteatosis	60 (43.2)	28 (10.1)	32 (27.4)	**<0.001**
Primary sclerosing cholangitis	10 (7.2)	10 (3.6)	0 (0.0)	**0.035**
Cholelithiasis	21 (15.1)	10 (3.6)	11 (9.4)	**0.024**
Thromboembolic event, n (%)	**6 (4.3)**	**4 (1.4)**	**2(1.7)**	0.848
Deep vein thrombosis	4 (2.9)	3 (1.1)	1 (0.9)	0.538
Other	2 (1.4)	1 (0.4)	1 (0.9)	0.768
Renal involvement, n (%)	**15 (10.8)**	**9 (3.3)**	**6 (5.1)**	0.377
Nephrolithiasis	13 (9.4)	8 (2.9)	5 (4.3)	0.768
Tubulointerstitial nephritis/glomerulonephritis	2 (1.4)	1 (0.4)	1 (0.9)	0.990
Pulmonary involvement, n (%)	**2 (1.4)**	**2 (0.7)**	**0 (0)**	1.00
Bronchiectasis	1 (0.7)	1 (0.35)	0 (0)	0.414
Interstitial lung disease	1 (0.7)	1 (0.35)	0 (0)	0.414
Metabolic bone disease, n (%)	**19 (13.7)**	**10 (3.6)**	**9 (7.7)**	0.086

EIM: extraintestinal manifestations

The frequency of sacroiliitis, erythema nodosum, and nephrolithiasis in patients with colonic involvement was higher ($p<0.05$ for each). In contrast, the frequency of aphthous stomatitis was found to be higher ($p<0.05$) in patients with ileocolonic involvement. When UC patients were evaluated in terms of EIMs according to their anatomical involvement, patients with hepatosteatosis proctitis and patients with extensive colitis were found to have a higher incidence of EIMs and evaluated the relationship between EIMs. Statistically significant relationships are shown in Table 4.

Table 4. The relationship between EIMs

	Metabolic bone disease + (n: 19)	**Metabolic bone disease – (n: 374)**	**p**
Musculoskeletal involvement	6 (31.6%)	44 (11.8%)	**0.023**
	Eye sign + (n: 25)	**Eye sign – (n: 386)**	**p**
Musculoskeletal involvement	3 (42.9%)	47 (12.2%)	**0.047**
	Thromboembolic event + (n: 6)	**Thromboembolic event – (n: 387)**	**p**
Skin sign	2 (33.3%)	23 (5.9%)	**0.045**
Renal involvement	2 (33.3%)	13 (3.4%)	**0.019**
Pulmonary involvement	1 (16.7%)	1 (0.3%)	**0.030**
	Pulmonary involvement + (n: 2)	**Pulmonary involvement – (n: 391)**	**p**
Thromboembolic event	1 (50.0%)	5 (1.3%)	**0.030**

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The dates of diagnosis for EIMs and IBD were evaluated. Before the diagnosis of IBD, simultaneously with the diagnosis of IBD, and after the diagnosis of IBD, the time of appearance of EIMs was grouped according to the diagnosis of IBD. 51 EIMs occurred before the diagnosis, 13 EIMs occurred concurrently with the diagnosis, and 137 EIMs occurred after the diagnosis. When the groups were compared, type 2 arthropathy and pulmonary involvement were not observed prior to the IBD diagnosis, and most EIMs were diagnosed after the IBD diagnosis.

The median emergence times of EIMs were determined. According to the diagnosis of IBD, the median onset time for patients with type 1 peripheral arthropathy is 28.5 months (-117/183), type 2 peripheral 13 months (0/103), AS -5 months (-121/180), sacroileitis 17 months (-3/72), osteoporosis 52 months (-73/141), skin involvement eight months (-24/148), eye involvement 40 months (-26/119), hepatosteatosis 23.5 months (-48/194), cholelithiasis 22 months (-218/409), PSK 42 months (-7/261), thromboembolism 11 months (-128/51), renal involvement 41 months (-287/336) pulmonary involvement 114 months (39/189).

Discussion

The literature has reported a frequency of EIM in IBD from 6% to 47% [3]. The frequency of EIM was found to be 35.4% in our study, which is consistent with the literature. Hepatobiliary manifestations were the most common EIM, and CD had a higher frequency of EIM than UC. There was no direct proportional relationship found when the relationship between EIM and itself was evaluated.

In a study involving 950 patients in Switzerland [9], the frequency of EIM was found to be 38.1%, while in a study conducted in Italy and published in 2014, the frequency of EIM was found to be 40.6% [10]. The cumulative prevalence of EIM was 17.6% in a prospective, population-based cohort study carried out in Europe and published in 2015 [11]. In a 2009 multicentric study conducted by N.Tozün et al. in which 12 centers participated, the frequency of EIM was 15% in UC and 31% in CD [12]. In this study, extraintestinal and local complications were more prevalent in patients with Crohn's disease. The frequency of EIM was found to be 19.2% in a retrospective study by A. Uyankolu et al. published in 2014, which included 494 patients [13]. Unlike other studies, the meta-analysis reporting the prevalence of at least 1 joint, ocular, or extracutaneous bowel manifestation in IBD was 24%, 27%, and 35% in IBD, UC, and CD, respectively [2].According to the study's findings, the incidence of EIM was similar between CD and UC, with seronegative arthritis being the most common form of EIM. In the study, which aimed to determine the risk factors by evaluating the characteristics of patients with EIM, it was recommended that patients who have been treated for IBD for more than 10 years or who use biologic drugs should be carefully monitored because they are at high risk for EIM [14].

In the study by Mendoza et al., joint manifestations were found to be the most common EIM, comparing the differences in extraintestinal findings between UC and CD [15]. Hepatobiliary involvement, venous thromboembolism, and arthralgia were more common in UC, whereas EN and peripheral arthritis were more common in CD [15].

While many studies reported an increased prevalence of EIM in women, in our study, when the presence of EIM was evaluated according to gender, the distribution of sexes in EIMs was similar. No difference between genders was observed in the studies conducted by Isene et al. [11] and Vavricka et al. [9]. Mucocutaneous manifestations and peripheral arthropathy are more common in women, according to studies. In our study, women were more likely to exhibit type 2 peripheral arthropathy, erythema nodosum, and aphthous stomatitis. PSK was found to be more common in men, but it was not found to be statistically significant.

The pathogenesis of colorectal cancer in IBD patients is unknown. Long disease duration, the prevalence of colitis, family history of colorectal cancer, association with PSC, and inflammation all increase the risk of colorectal cancer in IBD [16]. Lymphoma and non-melanoma skin cancer are risks for patients with inflammatory bowel disease [17]. Canavan et al. [18] reported in a meta-analysis of 12 publications that the cumulative risk for patients with CD was 2.9% at ten years, 5.6% at 20 years, and 8.3% after 30 years. These patients had extensive colitis consistent with the literature, even though the number of colorectal carcinoma and cholangiocellular carcinoma cases in our study who developed malignancy was insufficient for evaluation.

The epidemiology, clinical presentation, and management of IBD in elderly patients were reviewed in a review published in 2015 [19]. Similar to our findings in this review, UC was more prevalent than CD among the elderly. In this study, older patients with UC and CD had a lower incidence of EIM. No study comparing the frequency of EIM in the geriatric and adult age groups, or the frequency of EIM in the geriatric group, was found in the literature.

One thousand two hundred forty-nine patients were included in a 2015 study conducted in Switzerland that evaluated the chronological order of the appearance of EIMs relative to the time of IBD diagnosis. In 25.8% of cases, patients presented with their first EIM before IBD diagnosis, whereas in 74.2% of cases, EIMs were observed after IBD diagnosis [20]. Due to the nonspecific symptoms of joint pain, arthritis is more challenging to diagnose at the onset than IBD.

According to the literature, the prevalence of musculoskeletal involvement ranges from 6% to 46%. According to a 2017 systematic review and meta-analysis, spondyloarthropathies occur in IBD at a rate of up to 13%, with AS having the lowest incidence (3%), followed by sacroiliitis (10%) and peripheral arthritis (13%) [21]. The prevalence of musculoskeletal involvement was found to be more common in CD than in UC in this study. Similar to the literature, our study found that

musculoskeletal involvement occurs more frequently in CD than in UC. In a recently published study, arthropathy and arthritis were found to be the most common EIM in patients with both UC and CD [22].

The cutaneous manifestations of IBD are well-defined EIMs. Considering studies conducted in Turkey, a 2009 study involving 352 patients found the frequency of patients with at least one mucocutaneous manifestation to be 9.3%. [23]. In this study, EN was associated with active disease and peripheral arthritis, despite being more common in CD. In another study conducted in Türkiye in 2014, 92 patients participated, and the frequency of mucocutaneous manifestations was 53.6%, higher than in the literature [24]. In this study, mucocutaneous manifestations were observed more frequently in women.

Ocular EIMs are more common in patients with IBD than in the general population, while CD and UC have an inconsistent prevalence [25]. Ophthalmic findings can be seen in up to 13% of IBD patients [26]. In addition, a recently published review showed that the probability of uveitis is significantly increased in patients with CD compared to patients with UC [25].

Up to 30% of IBD patients have abnormal liver biochemical tests, so a diagnosis must be made [27]. In a 2014 systematic review comprising 146 articles, cholelithiasis was more prevalent in patients with CD than in the general population. In contrast, PSC was more prevalent in patients with UC than those with CD [28]. The high prevalence of hepatosteatosis in our study may be attributable to the rise in obesity, the shift in dietary habits, and increased imaging techniques.

The risk of arterial and venous thromboembolic complications is higher in patients with IBD. The relative risk for DVT and pulmonary embolism in IBD patients was 2.20 in a recent meta-analysis that included 11 case-control and cohort studies [29].

IBD patients have a higher risk of bone loss than the general population. Although numerous factors contribute to the etiology, age, steroid therapy, extensive small bowel disease, and resection are significant contributors. Osteoporosis has been reported in patients with IBD at a rate ranging from 5% to 37% [4]. Uncertainty exists regarding the relationship between UC, CD, and BMD. In Taiwan, a cohort of 3141 IBD patients revealed that CD patients had a higher risk of osteoporosis than UC patients [30]. In contrast to these studies, our study found similar rates of metabolic bone disease in UC and CD.

Studies demonstrating the relationships between EIMs and some EIMs have been demonstrated to be related in the literature. In our study, we did not find a significant relationship between EIMs when we individually examined the relationship between subgroups of EIMs. The small number of patients with ocular involvement and the absence of episcleritis, scleritis, and PG may have impacted the relationship between EIM and EIM.

Our research is limited because it is a retrospective prevalence study. Patients with insufficient data were excluded from the study when the medical records of the patients were examined. Patients who were found to have EIM at the time of their initial admission to our hospital were included in the study regardless of the length of their follow-up. EIM is more likely to develop the longer the disease has been present and if there have been previous EIMs. Because we included newly diagnosed cases in our study, the frequency of EIM may be lower than expected.

Conclusion

IBD is a complex disease with widespread systemic manifestations. Some EIMs do not respond to IBD treatment and therefore require close monitoring and additional treatment to prevent complications. Evaluation of patients with a multidisciplinary approach becomes important in managing extraintestinal symptoms. It may be possible to adequately evaluate EIMs in clinical practice and improve patients' quality of life with increased awareness.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This retrospective prevalence study was approved by the Gazi University ethics commission (10.02.2017-02).

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