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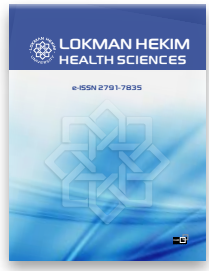

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ORIGINAL ARTICLE

Extra-Intestinal Manifestations in Patients with Inflammatory Bowel Disease

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Abstract

Introduction: Extra-intestinal manifestations (EIMs) significantly contribute to morbidity in patients with inflammatory bowel diseases (IBDs). This study aimed to determine the prevalence and distribution of EIMs in patients with ulcerative colitis (UC) and Crohn's disease (CD) and to evaluate associations between EIMs, disease activity, and demographic factors.

Methods: This single-center, descriptive observational study included 121 adult IBD patients (65 UC, 56 CD). EIMs were systematically assessed through specialist consultations (rheumatology, dermatology, ophthalmology) and review of laboratory, imaging, and clinical data. Disease activity was classified using standardized indices (CD Activity Index for CD; Truelove and Witts/Mayo Score for UC). Statistical analyses were performed to identify associations between variables.

Results: At least one EIM was identified in 57.0% (n=69) of patients. The most frequent EIMs were hepatobiliary (33.9%), bone-joint (28.9%), and skin-mucosal (24.8%). EIM prevalence was not associated with age or gender. However, differences were observed between disease types: Urinary involvement (29.2% in UC vs. 8.9% in CD; p=0.005) and cardiovascular involvement (16.9% in UC vs. 1.8% in CD; p=0.005) were both more common in UC. Oral cavity (p=0.018), cardiovascular (p=0.032), and urinary (p=0.046) manifestations were significantly associated with active disease. In contrast, hepatobiliary manifestations were more frequently observed in patients in remission.

Discussion and Conclusion: EIMs are highly prevalent in IBD, affecting over half of this patient cohort. The findings reveal that specific EIMs are associated with distinct disease phenotypes (e.g., urinary/cardiovascular in UC) and disease activity status (e.g., oral/cardiovascular in active disease vs. hepatobiliary in remission). This underscores the necessity of routine, multidisciplinary screening for EIMs, even in patients with asymptomatic or inactive intestinal disease, to ensure comprehensive management.

Keywords: Crohn's disease; Disease activity; Extraintestinal manifestations; Inflammatory bowel disease; Ulcerative colitis

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E-mail: serapbicr@gmail.com **Submitted:** 12.10.2025 **Revised:** 21.01.2026 **Accepted:** 05.02.2026 **Available Online:** 06.08.2026

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis, are chronic inflammatory disorders characterized by relapsing diarrhea, abdominal pain, gastrointestinal bleeding, and malabsorption.[1] UC primarily involves the mucosa and submucosa of the colon, and clinical severity correlates with the extent of inflammation.[2] CD is characterized by transmural inflammation that may affect any part of the gastrointestinal tract, most commonly the terminal ileum, resulting in a wide spectrum of symptoms ranging from abdominal pain and diarrhea to perianal complications and dyspeptic complaints.[3]

In addition to intestinal involvement, extra-intestinal manifestations (EIMs) frequently occur in IBD and may affect several organ systems, manifesting with varying degrees of severity.[4] EIMs commonly involve the musculoskeletal, dermatological, ocular, hepatobiliary, hematological, and genitourinary systems.[5] The underlying mechanisms remain incompletely understood; however, immune dysregulation, altered leukocyte, gut microbiota alterations, and genetic predisposition have been suggested.[5]

Since EIMs contribute substantially to morbidity and may adversely influence treatment outcomes, early recognition and appropriate management are essential for improving overall disease prognosis.[6] Standardized indices, including the CD Activity Index (CDAI) for CD and the Mayo Score for UC, are commonly used to assess disease activity and guide clinical decisions.[7,8] Considering the clinical significance of EIMs, the aim of this study was to determine the prevalence and systemic distribution of EIMs in patients with IBD and to evaluate their associations with disease activity and demographic factors such as age and gender.

Materials and Methods

Study Design, Setting, and Ethical Considerations

This descriptive observational study was conducted at a 1300-bed tertiary university hospital. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the Erciyes University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 2020/476; Date: September 23, 2020). All participants provided written informed consent before enrollment.

Study Population and Enrollment

The study included 121 adult patients with clinically, endoscopically, and/or histopathologically confirmed IBD. All consecutive patients who presented to or were followed at the gastroenterology outpatient clinic and inpatient ward between October 15, 2020, and October 15, 2021, were enrolled.

Data Collection

Data were recorded using a standardized follow-up form. The following parameters were collected:

Demographic and clinical characteristics, disease duration, number of comorbidities (including hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease), complications, treatments, laboratory findings, EIMs.

Assessment of Disease Activity

Disease activity was assessed using established indices.

- UC: Activity was assessed using the Truelove and Witts Index and the Mayo Score.[7,8] Mild UC and Mayo endoscopic scores of 0–2 were considered inactive disease
- CD: Activity was assessed using the CD Activity Index (CDAI).[9] A CDAI score <150 was considered inactive disease.

Assessment of EIMs

All patients underwent a multidisciplinary evaluation. Routine laboratory tests were performed in every patient at baseline, with additional advanced investigations completed as indicated for relevant organ systems.

- Rheumatologic Assessment: This included a physical examination of peripheral joints and the spine and radiographs in all patients. Sacroiliac magnetic resonance imaging was performed only in cases with suspected axial involvement. Ankylosing spondylitis and axial manifestations were classified according to the Assessment of Spondylo Arthritis International Society criteria.[10]
- Dermatologic Assessment: This consisted of a complete skin and oral cavity examination. Previously documented dermatologic manifestations (e.g., erythema nodosum, pyoderma gangrenosum) were confirmed through chart review.
- Ophthalmologic Assessment: A standardized evaluation, including slit-lamp and fundoscopic examination, was performed by the same ophthalmologist for all patients.
- Hematologic Assessment: Manifestations were evaluated using complete blood count and anemia parameters. A peripheral smear was performed when necessary.
- Hepatobiliary and Genitourinary Assessment: These manifestations were assessed using laboratory markers, abdominal and urinary ultrasonography, magnetic resonance cholangiopancreatography, and autoimmune serology.

Table 1. Demographic and clinical characteristics of patients with ulcerative colitis and Crohn's disease

Variables	Ulcerative colitis (n=65)	Crohn's disease (n=56)	p
Female sex, n (%)	26 (40.0)	31 (55.4)	0.092
Smoking, n (%)	20 (30.8)	25 (44.6)	0.083
Chronic comorbidity, n (%)	19 (29.2)	8 (14.3)	**0.049**
Age (years), mean±SD	47.92 ± 12.99	40.04 ± 13.73	0.002
Age at diagnosis (years), mean±SD	39.63±12.42	35.51 ± 12.53	0.073
Surgical history, n (%)	6 (9.2)*	24 (42.9)*	**<0.01**

*: Gastrointestinal or appendectomy operations. Surgical history includes previous gastrointestinal surgery and/or appendectomy. SD: Standard deviation.

Inclusion Criteria

Patients were included if they met all of the following conditions:

1. Age ≥18 and <90 years.
2. Presentation to or follow-up at the gastroenterology outpatient clinic or inpatient ward of the study center between October 15, 2020, and October 15, 2021.
3. A confirmed diagnosis of UC or CD based on clinical, endoscopic and/or histopathological findings.
4. Provision of written informed consent for participation in the study.

Exclusion Criteria

Patients were excluded if they met any of the following conditions:

1. Inability to determine disease activity due to prior total colectomy or permanent stoma.
2. Active severe infection, malignancy, or pregnancy during the study period.
3. End-stage liver disease or end-stage renal disease that could interfere with the evaluation of EIMs.
4. Missing or insufficient clinical data regarding primary study variables.
5. Refusal or inability to provide written informed consent.

Data Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequency, percentage, mean±standard deviation, and minimum–maximum values. The normality of the distribution of quantitative data was determined using the Kolmogorov–Smirnov test. Continuous variables were compared using the Independent Samples t-test or the Mann–Whitney U test, depending on the distribution. Categorical variables were evaluated using the Pearson Chi-square test, with Yates' continuity correction applied for 2×2 contingency tables, and Fisher's exact test was used when appropriate. A two-tailed $p<0.05$ was considered statistically significant.

Results

A total of 121 patients were included in the study, consisting of 57 females (47.1%) and 64 males (52.9%). The mean age was 44.27±13.86 years (range 18–75), and the mean age at diagnosis was 37.72±12.59 years (range 14–71). UC patients had a significantly higher age at diagnosis compared with CD patients ($p<0.05$). No differences were detected between UC and CD groups regarding gender, education level, family structure, or smoking status ($p>0.05$), although smoking was more frequent in CD. Chronic comorbidities were more common in UC (Table 1). There was no significant difference between groups in terms of flare frequency ($p>0.05$). However, surgical intervention was significantly more frequent in CD, with 42.9% having undergone gastrointestinal or appendectomy procedures ($p<0.01$).

Comparison of biochemical and nutritional parameters between the groups is shown in Table 2. Reference ranges used to define biochemical abnormalities were as follows: C-reactive protein (CRP) 0–49.2 nmol/L, erythrocyte sedimentation rate (ESR) 0–20 mm/h, hemoglobin 12–16 g/dL for females and 13–17 g/dL for males, transferrin saturation 20–45%, ferritin 15–150 ng/mL, vitamin B12 200–900 pg/mL, folate 3–17 ng/mL, serum albumin 3.5–5.0 g/dL, and total protein 6.0–8.3 g/dL. The analysis showed a significantly higher prevalence of inflammatory markers and nutritional deficiencies in the CD cohort. Specifically, elevated CRP was significantly more frequent in CD patients (69.6%) than in UC patients (38.5%; $p=0.001$). Anemia was also more common in the CD group (44.6%) compared to the UC group (26.2%; $p=0.033$). Nutritional deficiencies were higher in CD. This included significantly higher rates of Vitamin B12 deficiency (19.6% in CD vs. 4.6% in UC;

Table 2. Comparison of biochemical parameters in patients with ulcerative colitis and Crohn's disease

Biochemical parameter	Ulcerative colitis (n=65) n (%)	Crohn's disease (n=56) n (%)	p
Elevated CRP (>49.2 nmol/L)	25 (38.5)	39 (69.6)	**0.001***
Elevated ESR	20 (30.8)	25 (44.6)	0.115*
Anemia	17 (26.2)	25 (44.6)	**0.033***
Iron deficiency (TSAT<%20)	18 (27.7)	25 (44.6)	0.052*
Low ferritin	13 (20.0)	8 (14.3)	0.408**
Vitamin B12 deficiency	3 (4.6)	11 (19.6)	**0.022****
Folate deficiency	1 (1.5)	12 (21.4)	**0.001****
Hypoalbuminemia	2 (3.1)	7 (12.5)	**0.049*****

*: Pearson's Chi-square test; **: Continuity correction; ***: Fisher's exact test. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SD: Standard deviation; TSAT: Transferrin saturation.

Table 3. Association of extraintestinal manifestations with ulcerative colitis and Crohn's disease

Extraintestinal manifestation	Ulcerative colitis (n=65) n (%)	Crohn's disease (n=56) n (%)	p
Hepatobiliary Manifestation	22 (33.8)	19 (33.9)	0.992*
Bone-joint Manifestation	19 (29.2)	16 (28.6)	0.936*
Skin-mucosal Manifestation	16 (24.6)	14 (25.0)	0.961*
Urinary Manifestation	19 (29.2)	5 (8.9)	**0.005****
Ocular Manifestation	9 (13.8)	5 (8.9)	0.577**
Cardiovascular Manifestation	11 (16.9)	1 (1.8)	**0.006*****
≥1 EIM present	38 (58.5)	31 (55.4)	0.731*

*: Pearson's Chi-square Test; **: Continuity correction; ***: Fisher's exact test. EIM: Extraintestinal manifestations.

p=0.010) and folate deficiency (21.4% in CD vs. 1.5% in UC; p<0.001). Furthermore, hypoproteinemia (p=0.049) and hypoalbuminemia (p=0.049) were both significantly more prevalent in CD patients. Differences in elevated ESR, iron deficiency, and low ferritin levels were not statistically significant between the two groups.

EIMs were identified in 69 patients (57.0%). Their distribution was as follows: Hepatobiliary (33.9%), bone-joint (28.9%), skin-mucosal (24.8%), urinary (19.8%), ocular (11.6%), and cardiovascular system (9.9%) (Table 3). Hepatic steatosis represented the most common hepatobiliary manifestation (70.7%), followed by hepatomegaly (17%), cholelithiasis (9.8%), and primary sclerosing cholangitis (2.4%). Among musculoskeletal EIMs, isolated sacroiliitis and osteoporosis were the most frequent (each 28.6%), followed by peripheral spondylarthritis (25.7%) and ankylosing spondylitis (17.1%).

Skin-mucosal manifestations were observed in 30 patients, most commonly psoriasis (30.4%). Aphthous stomatitis was identified as the sole oral involvement in 8 patients (6.6%). Ophthalmic EIMs included uveitis (35.7%) and episcleritis (21.4%), with all episcleritis cases detected during active CD. Urinary tract involvement was mainly renal calculi (25%). Cardiovascular EIMs consisted of thromboembolic complications in five patients.

Table 4 presents a detailed analysis of EIMs by comparing four distinct patient subgroups: Active UC, Inactive UC, Active CD, and Inactive CD. Accordingly, oral cavity manifestations were significantly linked to disease activity (p=0.018), being most frequent in active states and absent in inactive CD. Both cardiovascular (p=0.032) and urinary (p=0.046) manifestations also showed significant differences, with their prevalence being notably higher in UC patients, compared to CD patients. No significant associations were found for hepatobiliary (p=0.749) or bone-joint (p=0.240) involvement across the four groups. While the overall prevalence of having at least one EIM was high in all subgroups, there was no significant difference between them (p=0.861) (Fig. 1).

Discussion

The European Crohn's and Colitis Organisation emphasizes that EIMs are an essential component of IBD and

Table 4. Association of extraintestinal manifestations with disease activity in ulcerative colitis and Crohn's disease

Extraintestinal manifestation	Active UC (n=34) n (%)	Inactive UC (n=31) n (%)	Active CD (n=28) n (%)	Inactive CD (n=28) n (%)	p
Ocular manifestation	6 (17.6)	3 (9.7)	3 (10.7)	2 (7.1)	0.653
Oral cavity manifestation	3 (8.8)	1 (3.2)	4 (14.3)	0 (0.0)	**0.018**
Skin–mucosal manifestation	8 (23.5)	5 (16.1)	3 (10.7)	7 (25.0)	0.469*
Urinary manifestation	10 (29.4)	9 (29.0)	2 (7.1)	3 (10.7)	**0.046***
Hepatobiliary manifestation	10 (29.4)	12 (38.7)	8 (28.6)	11 (39.3)	0.749*
Cardiovascular manifestation	6 (17.6)	5 (16.1)	1 (3.6)	0 (0.0)	**0.032***
Bone–joint manifestation	13 (38.2)	6 (19.4)	6 (21.4)	10 (35.7)	0.240**
≥1 EIM	20 (58.8)	18 (58.1)	15 (53.6)	16 (57.1)	0.861**

*: Fishers' exact Test; **: Pearson's Chi-square Test. UC: Ulcerative colitis; CD: Crohn's disease; EIM: Extraintestinal manifestations.

should be integrated into overall disease management through a multidisciplinary approach.[6] In line with these recommendations, our study systematically assessed not only intestinal disease activity but also the presence of EIMs. More than half of the patients exhibited at least one EIM, underscoring the clinical relevance of routine and structured EIM screening. No significant association was observed between age or gender and the occurrence of EIMs. Oral cavity involvement was strongly associated with active CD, whereas hepatobiliary manifestations were more frequently observed during remission in both UC and CD, supporting the concept that each IBD phenotype exhibits a distinct EIM profile.

Venous thromboembolism (VTE) remains one of the most clinically significant EIMs in IBD. A large meta-analysis including more than three million patients reported that individuals with IBD have approximately twice the risk of VTE compared with the general population.[11] Consistent with these findings, our study demonstrated an increased thrombotic risk, particularly among patients with UC

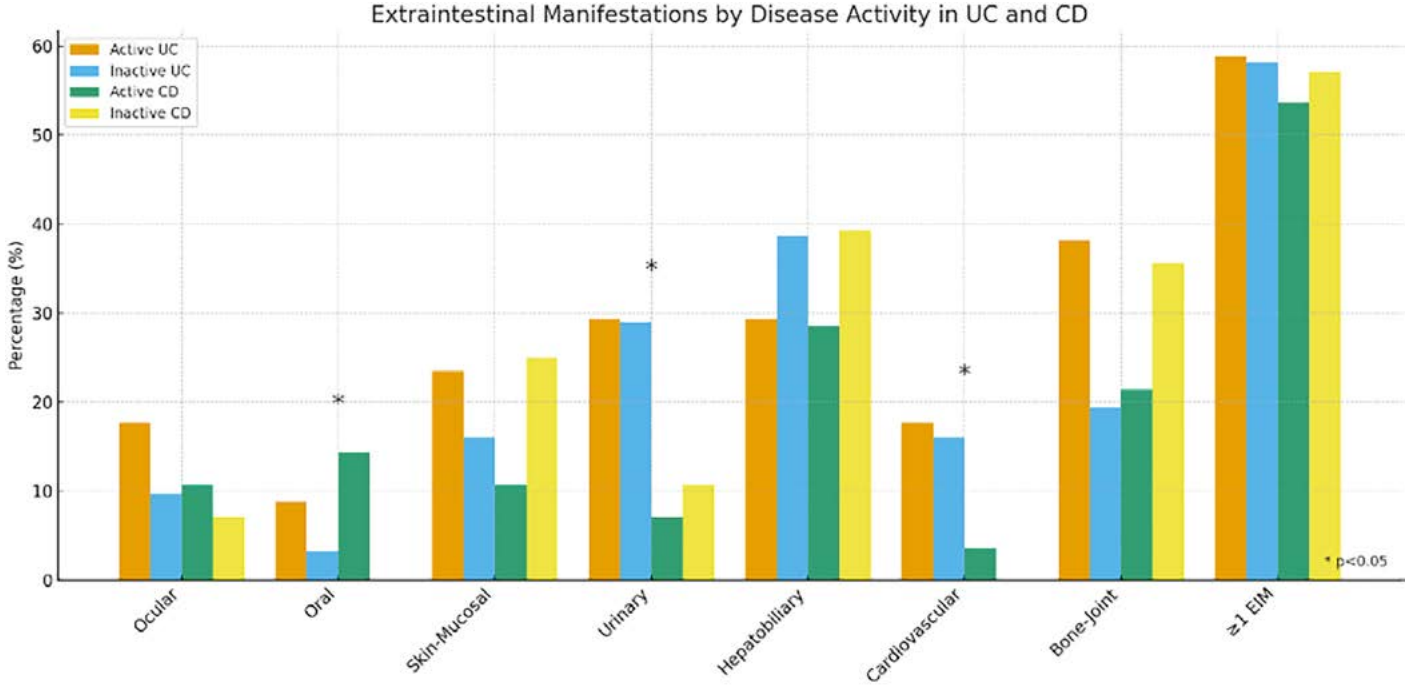

Figure 1. Distribution of extraintestinal manifestations according to disease activity in ulcerative colitis and Crohn's disease. Comparison of extraintestinal manifestations by disease activity in UC and CD. Percentages represent the proportion of patients within each subgroup exhibiting specific extraintestinal manifestations. Asterisks indicate statistically significant differences between active and inactive disease periods (*p<0.05). UC active/inactive and CD active/inactive groups are shown in different bar colors for visual clarity.

UC: Ulcerative colitis; CD: Crohn's disease; EIM: Extraintestinal manifestation.

during active disease. This highlights the importance of careful VTE risk assessment and appropriate prophylactic strategies during disease flares. A population-based Swedish study of 342 IBD patients revealed that the incidence and prevalence of anemia were significantly higher in CD (19.3/100 person-years; prevalence 28.7%) than in UC (12.9/100 person-years; prevalence 16.5%; odds ratio = 1.60; 95% confidence interval: 1.02–2.51).[12] In our cohort, we similarly observed a higher anemia rate in CD, while most UC patients were in remission, which may explain the difference in anemia frequency. Among hepatobiliary manifestations, hepatic steatosis was the most frequently observed, which is consistent with the reported increased prevalence of non-alcoholic fatty liver disease in patients with IBD.[13] This association has been attributed to chronic inflammation, metabolic alterations, and treatment-related hepatotoxicity.[14] However, the absence of a healthy control group in our study limits the ability to fully evaluate the contribution of these environmental and metabolic factors. Musculoskeletal involvement consisted of isolated sacroiliitis, osteoporosis, peripheral spondyloarthritis, and ankylosing spondylitis. In our cohort, peripheral spondyloarthritis was more common in UC, whereas axial manifestations were more prevalent in CD, indicating distinct musculoskeletal phenotypes according to disease subtype. This finding aligns with previous reports suggesting variability in the frequency and pattern of musculoskeletal EIMs in IBD.[15] The low HLA-B27 positivity observed supports current evidence that IBD-associated spondyloarthritis often develops in HLA-B27-negative patients and may present with a different clinical phenotype.[16,17]

Skin-mucosal manifestations were detected at rates similar to previous studies, although specific lesions such as erythema nodosum and pyoderma gangrenosum were rarely observed, likely due to the small sample size and predominance of remission in our cohort. Ocular involvement in the form of episcleritis was identified only in active CD, supporting the concept that ocular inflammation is closely related to intestinal inflammatory activity.[18,19] Among urinary manifestations, nephrolithiasis was the most common finding. Notably, urinary involvement was more frequent in UC, which contrasts with earlier studies. The lack of stone-type analysis may have contributed to this observation and highlights the need for careful metabolic evaluation in IBD patients.[20,21] Oral cavity manifestations were significantly associated with active CD, consistent with previous evidence. In a large retrospective study including 676 patients with CD, Cagir et al.[22] reported that specific oral lesions, including orofacial granulomatosis and cobblestone appearance, were significantly associated with higher disease activity. This finding aligns with our study, in which oral manifestations were more common in patients with active CD. Although pulmonary findings have occasionally been described in patients with IBD, they are rare, non-specific, and are not classified as true EIMs.[23] Since none of the patients in our cohort presented with respiratory symptoms, pulmonary involvement was not additionally evaluated in this study. Table 4 summarizes the relationship between each EIM and disease activity, demonstrating distinct clinical patterns between UC and CD.

Limitations

This study has several limitations that should be acknowledged. First, it was conducted at a single tertiary center with a relatively small sample size, which may limit the generalizability of the findings. Second, the predominance of patients in remission may have led to an underestimation of certain EIMs, particularly those known to fluctuate with disease activity. Third, the lack of detailed stone composition analysis and the absence of advanced diagnostic modalities for selected EIMs restricted more granular subgroup classification. In addition, the absence of a healthy control group limits the interpretation of hepatobiliary and metabolic abnormalities, as these findings cannot be compared with baseline rates in the general population. Furthermore, given the exploratory nature of the subgroup analyses and the large number of pairwise comparisons performed, the possibility of type I error cannot be excluded. Taken together, these limitations underscore the need for multicenter studies with larger and more diverse cohorts, supported by comprehensive diagnostic evaluations, to better elucidate the complex relationship between disease activity and EIM patterns.

Conclusion

This study demonstrates that EIMs are highly prevalent among patients with IBD, affecting more than half of the cohort. The patterns and systemic distribution of EIMs differed substantially between UC and CD, as well as between active and inactive disease states. Urinary and cardiovascular manifestations were more prominent in UC, whereas oral cavity, musculoskeletal, and ocular manifestations were predominantly associated with CD, especially during periods of active inflammation. These findings highlight that each IBD subtype exhibits a unique EIM profile, underlining the importance of phenotype-specific assessment and surveillance.

The results underscore the necessity of routine, structured, and multidisciplinary evaluation of EIMs as an integral part of IBD management. Incorporating musculoskeletal, hepatobiliary, dermatologic, ocular, and oral examinations into standard clinical follow-up may facilitate earlier detection of clinically meaningful but sometimes subtle manifestations. Early recognition and timely treatment of EIMs can reduce morbidity, improve overall quality of life, and potentially mitigate long-term complications.

Furthermore, the observed relationships between disease activity and certain EIMs – particularly oral cavity and cardiovascular manifestations – suggest that EIMs may serve as useful clinical indicators of systemic inflammatory burden. This relationship warrants closer attention in daily practice and may contribute to more comprehensive disease monitoring strategies.

Given the single-center nature of this study and the absence of a healthy control group, multicenter research involving larger and more diverse populations is needed to confirm these associations and to better delineate the biological mechanisms underlying EIM development in IBD. Future studies integrating advanced imaging, metabolic profiling, and longitudinal follow-up may provide deeper insight into the dynamic interplay between intestinal inflammation and extra-intestinal involvement.

Ethics Committee Approval: The Erciyes University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 23.09.2020, number: 2020/476).

Informed Consent: Written informed consent was obtained from participants.

Conflict of Interest: None declared.

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