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Frequency and Pattern of Extraintestinal Manifestations and Their Association with Disease Duration and Severity in Patients with Inflammatory Bowel Disease (IBD).

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Abstract

Background: Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are frequent systemic complications that represent a significant burden of disease and impact patients' quality of life. Information on their occurrence and risk factors in the local population is scarce. ***Objective:*** To determine the frequency and pattern of extraintestinal manifestations and their association with disease duration and disease severity among patients with inflammatory bowel disease. ***Methods:*** This is an analytical cross-sectional study that took place in the Department of Gastroenterology, Shalamar Medical and Dental College, Shalamar Hospital, Lahore, over six months from 1st October 2025 to 31st March 2026. All adult patients with a confirmed diagnosis of IBD were sampled consecutively for a total of 110 patients. A structured proforma was used to gather the demographic and clinical data. The Mayo Score for ulcerative colitis and the Crohn's Disease Activity Index (CDAI) for Crohn's disease were used to measure disease severity. Data were analyzed by SPSS version 26.0. ***Results:*** 37 (33.6%) patients had extraintestinal complications. The most common musculoskeletal involvement was followed by dermatological, ocular, and hepatobiliary involvement. Extraintestinal manifestations were significantly related to duration of the disease (>5 years) and high disease activity ($p<0.05$). Previous intestinal surgery and smoking were also independent factors in the multivariable logistic regression. ***Conclusion:*** Extraintestinal manifestations are frequent among patients with IBD and are significantly associated with prolonged disease duration and increased disease severity. Multidisciplinary management along with early recognition may yield better clinical outcomes and quality of life for these patients.

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

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated chronic inflammatory disease of the gastrointestinal tract, consisting mainly of Crohn's disease (CD) and ulcerative colitis (UC).[1] These conditions cause the intestine to flare up and then go into remission, with symptoms of pain in the abdomen, diarrhea, bleeding from the rectum, weight loss, and fatigue.[2] Although IBD mainly affects the gastrointestinal tract, it is increasingly recognized as a systemic disease with manifestations beyond the intestine.[3]

Extraintestinal manifestations (EIMs) can affect the musculoskeletal, dermatological, ocular, hepatobiliary, and other organ systems and often represent a significant portion of disease burden, impact on quality of life, and burden on health services.[4]

The prevalence of IBD has increased dramatically in the last few decades, and it is estimated that over 7 million people are living worldwide with the disease.[5] IBD is more common in North America and Europe and is becoming more common in newly industrialized areas such as South Asia as communities become more urbanized, their environments shift, and their diets change.[6] Extraintestinal manifestations of IBD are seen in around 20–40% of cases and have been reported at up to 50% throughout the course of the disease.[7]

The most prevalent are musculoskeletal, such as peripheral arthritis and axial spondyloarthritis, followed by dermatological, ocular, and hepatobiliary manifestations.[8] In some patients, EIMs may occur before the appearance of

gastrointestinal symptoms, while in others, EIMs may appear at the same time as the gastrointestinal symptoms or in chronic disease.[9]

Extraintestinal manifestations have been linked to increased disease activity, longer time to clinical remission, more extensive involvement of the intestine, and more frequent disease relapses.[10] The incidence and distribution of EIMs differ significantly, depending on genetic, environmental, and ethnic factors.[11]

These are important to identify early since they can necessitate a multidisciplinary approach to management and may markedly affect treatment, prognosis, and patient outcomes.[12] Recognizing patients who are more likely to develop EIMs can help identify patients for earlier intervention and better disease management over time.[13]

Although the incidence of IBD continues to be on the rise, information about the prevalence and the spectrum of extraintestinal manifestations in the local population is limited. Moreover, whether these phenomena have been sufficiently investigated concerning disease duration and disease severity in the regional clinical context has not been well studied. The production of locally generated evidence will advance knowledge of the clinical profile of patients with IBD and aid in comprehensive patient management. Hence, this study aimed to identify the incidence and characteristics of extraintestinal complications and their relationship with disease activity and duration in patients with inflammatory bowel diseases.

METHODOLOGY

This is an analytical cross-sectional study that took place in the Department office Gastroenterology, Shalamar Medical and Dental College, Shalamar Hospital, Lahore, over six months from 1st October 2025 to 31st March 2026.

Sample size was determined by using the OpenEpi version 3.01 with the following criteria: an anticipated frequency of 24% for extra intestinal manifestation in patients with inflammatory bowel disease, a 95% confidence level, 8% absolute precision (margin of error), design effect of 1.0.[7] These parameters were used to determine the minimum sample size of 110 participants, who were subsequently recruited to participate in the study.

Participant recruitment was done by using the non-probability consecutive sampling technique. Patients older than 18 years and with a confirmed diagnosis of inflammatory bowel disease, including Crohn's disease or ulcerative colitis, based on clinical, endoscopic, histopathological, and radiological findings, based on the standard diagnostic criteria, were included in the study. Participants were patients with a disease duration of at least three months and who had signed written informed consent to enter the study.

Patients with indeterminate colitis or other causes of chronic colitis, such as infectious, ischemic, radiation-induced, or microscopic colitis, were not included in the study. Patients with any other autoimmune or rheumatological condition, chronic liver disease not associated with inflammatory bowel disease, or dermatological or ophthalmological diseases before the diagnosis of inflammatory bowel disease were also excluded to avoid confounding. Pregnant women, patients with actively treated malignancy, critically ill patients, and those who could not be clinically evaluated or for whom there were incomplete medical records were excluded from the study.

The institutional ethics review committee of the respective hospital approved the initiation of the study. All eligible participants gave informed written consent before participation. All patients who attended the gastroenterology OPD or who were admitted to inpatient wards during the study period were screened for eligibility based on the inclusion and exclusion criteria. Those who met the eligibility criteria were recruited consecutively until the required sample size was reached.

The principal investigator used a structured and predesigned proforma to gather data. Demographic data such as age, gender, BMI, smoking history, and co-morbidities were taken. Patient interviews and medical records were used to gather clinical information such as type of inflammatory bowel disease, including Crohn's disease or ulcerative colitis, age at IBD diagnosis, disease duration, and current treatment, history of disease flares, previous intestinal surgery, and laboratory findings.

A thorough clinical examination was performed to check for extraintestinal manifestations in all participants. The presence of musculoskeletal manifestations, dermatological manifestations, and hepatobiliary manifestations was evaluated by clinical examination and/or specialist consultation, as appropriate, or medical records. Patients were classified based on the presence of extraintestinal manifestations.

Diseases were scored using disease-specific scoring systems that were validated. Patients with ulcerative colitis were assessed with the Mayo Score, and those with Crohn's disease were assessed with the Crohn's Disease Activity Index

(CDAI).[14, 15] The length of illness was measured from the date of diagnosis through enrollment and was expressed in years. Before entering the study database for statistical analysis, all data collected were checked for completeness and accuracy.

All the collected data were entered and analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0.

The Shapiro-Wilk test was applied to continuous variables to test for normality. Continuous variables were expressed as mean ± SD and non-normally distributed variables as median (IQR). Categorical variables were summarized in terms of frequencies and percentages. The frequency and pattern of extraintestinal manifestations were described using descriptive statistics.

The categorical variables, including gender, type of inflammatory bowel disease, disease severity categories, smoking status, and other clinical variables, were evaluated by the Chi-square test and Fisher's exact test. An independent samples t-test was used for continuous variables normally distributed between patients with EIM and without EIM, and a Mann–Whitney U test was used for non-normally distributed continuous variables.

Independent factors associated with the presence of extraintestinal manifestations were identified by binary logistic regression analysis. The univariable p-value <0.20 and those deemed clinically relevant were included in the multivariable logistic regression model. Adjusted odds ratios (AORs) with 95% confidence intervals (95% CIs) were reported as the strength of association. A two-tailed p-value of <0.05 was considered statistically significant throughout the analysis.

RESULTS

A total of 110 patients with inflammatory bowel disease were included in the study. The participants' mean age was 38.6±12.4 years, and the median disease duration was 5.0 years (2.0-8.0).

The majority of participants were men (56.4%), and the majority had ulcerative colitis (64.5%). About one-quarter smoked, and 28.2% were taking biologic therapy.

According to disease activity assessment, 27.3% of them had mild disease, 44.5% had moderate disease, and 28.2% had severe disease. In all patients, 33.6% had one or more extraintestinal manifestations. (Table 1)

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants (n = 110)

Variable	Summary
Age (years)	38.6 ± 12.4
BMI (kg/m²)	24.8 ± 4.1
Disease duration (years)	5.0 (2.0–8.0)
Age at diagnosis (years)	33.4 ± 11.7
Gender	
Male	62 (56.4%)
Female	48 (43.6%)
Ulcerative colitis	71 (64.5%)
Crohn's disease	39 (35.5%)
Current smoker	28 (25.5%)
Non-smoker	82 (74.5%)
Previous intestinal surgery	19 (17.3%)
No previous surgery	91 (82.7%)
Current biologic therapy	31 (28.2%)
Conventional therapy only	79 (71.8%)
Disease Severity	
Mild disease	30 (27.3%)
Moderate disease	49 (44.5%)
Severe disease	31 (28.2%)
Presence of ≥1 Extraintestinal manifestation	37 (33.6%)

Extraintestinal manifestations were detected in 37 (33.6%) patients. The most common symptoms were musculoskeletal, dermatological, ocular, and hepatobiliary symptoms. Peripheral arthritis was the most frequent single symptom, and almost one-tenth of patients had involvement of more than one extraintestinal system. (Table 2)

Table 2. Frequency and Pattern of Extraintestinal Manifestations among Patients with Inflammatory Bowel Disease (n = 110)

Extraintestinal manifestation	**n (%)**
Any extraintestinal manifestation	37 (33.6%)
Musculoskeletal manifestations	22 (20.0%)
Peripheral arthritis	15 (13.6%)
Axial arthropathy	7 (6.4%)
Dermatological manifestations	9 (8.2%)
Erythema nodosum	6 (5.5%)
Pyoderma gangrenosum	3 (2.7%)
Ocular manifestations	8 (7.3%)
Episcleritis	5 (4.5%)
Uveitis	3 (2.7%)
Hepatobiliary manifestations	6 (5.5%)
Primary sclerosing cholangitis	3 (2.7%)
Fatty liver/other hepatobiliary disorders	3 (2.7%)
More than one manifestation	10 (9.1%

A comparison between those who did and did not have extraintestinal manifestations showed that those with extraintestinal manifestations had a significantly longer duration of illness.

The presence of extraintestinal manifestations was also significantly associated with smoking status, previous intestinal surgery, biologic therapy, and disease severity. No association was seen with age, gender, BMI, age at diagnosis, or type of inflammatory bowel disease, however. (Table 3)

Table 3. Comparison of Patients With and Without Extraintestinal Manifestations

Variable	**EIM Present (n=37)**	**EIM Absent (n=73)**	**p-value**
Age (years)	40.9 ± 11.8	37.4 ± 12.6	0.156
BMI (kg/m²)	24.5 ± 4.0	24.9 ± 4.2	0.641
Disease duration (years)	7.0 (5.0–10.0)	3.0 (2.0–6.0)	<0.001*
Age at diagnosis (years)	33.1 ± 10.9	33.6 ± 12.0	0.821
Gender			
Male	19 (51.4%)	43 (58.9%)	0.448
Female	18 (48.6%)	30 (41.1%)	
Ulcerative colitis	22 (59.5%)	49 (67.1%)	0.423
Crohn's disease	15 (40.5%)	24 (32.9%)	
Current smoker	14 (37.8%)	14 (19.2%)	0.034*
Previous intestinal surgery	12 (32.4%)	7 (9.6%)	0.003*
Biologic therapy	18 (48.6%)	13 (17.8%)	0.001*
Disease Severity			
Mild disease	4 (10.8%)	26 (35.6%)	<0.001*
Moderate disease	14 (37.8%)	35 (47.9%)	
Severe disease	19 (51.4%)	12 (16.4%)	
*Statistically significant ($p < 0.05$).			

Patients who had shorter disease duration or milder disease showed significantly fewer extraintestinal manifestations than patients with higher disease activity or longer disease duration >5 years.

These results showed that there was a strong correlation between the rates of extraintestinal manifestations and prolonged disease duration and disease severity. (Table 4)

Table 4. Association of Disease Duration and Disease Severity with Extraintestinal Manifestations

Variable	EIM Present n (%)	EIM Absent n (%)	p-value
Disease duration			<0.001*
<2 years	4 (10.8)	28 (38.4)	
2–5 years	8 (21.6)	23 (31.5)	
>5 years	25 (67.6)	22 (30.1)	
Disease severity			<0.001*
Mild	4 (10.8)	26 (35.6)	
Moderate	14 (37.8)	35 (47.9)	
Severe	19 (51.4)	12 (16.4)	

Multivariable binary logistic regression analysis revealed that after controlling for potential confounding factors, duration of disease >5 years, severe disease activity, current smoking, previous intestinal surgery, and biologic therapy were independent predictors of extraintestinal manifestations. Age, gender, and disease type did not show any statistically significant association. (Table 5)

Table 5. Binary Logistic Regression Analysis for Factors Associated with Extraintestinal Manifestations

Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.02 (0.99–1.05)	0.141	1.01 (0.98–1.05)	0.493
Male Gender	0.74 (0.34–1.61)	0.449	0.81 (0.33–1.97)	0.644
Smoking	2.56 (1.08–6.04)	0.033*	2.21 (1.01–5.17)	0.048*
Crohn's disease	1.39 (0.63–3.05)	0.416	1.31 (0.55–3.12)	0.539
Previous intestinal surgery	4.49 (1.57–12.80)	0.005*	3.12 (1.01–9.66)	0.047*
Biologic therapy	4.35 (1.84–10.27)	0.001*	2.54 (1.02–6.34)	0.044*
Disease duration (>5 years)	4.89 (2.02–11.85)	<0.001*	3.81 (1.52–9.54)	0.004*
Severe disease	5.76 (2.23–14.87)	<0.001*	4.68 (1.74–12.56)	0.002*
*Statistically significant ($p < 0.05$).				

DISCUSSION

The present study revealed that 33.6% of the patients with inflammatory bowel disease (IBD) had at least one extraintestinal manifestation (EIM). This prevalence was similar to that reported in the literature and demonstrates the significant systemic burden of IBD. In a recent systematic review and meta-analysis, Kilic et al. (2024) found a pooled prevalence of 24% for at least one joint manifestation, ocular, or skin manifestation within the IBD population, with a higher prevalence in Crohn's disease than in UC.[7] The differences in ethnicity, disease characteristics, study design, and hepatobiliary manifestations between the present study and others may explain the slightly greater prevalence seen in the present study. The most common extraintestinal manifestations observed in the present study were musculoskeletal manifestations, followed by dermatological, ocular, and hepatobiliary manifestations. These results corroborate those of the review by Faggiani et al. (2024), who found that peripheral arthritis and axial arthropathy were the most common EIMs due to similarities in inflammatory pathways between the intestinal mucosa and synovial tissue.[4] In the same way, Kilic et al. found that joint manifestations are the most common EIMs in both ulcerative colitis and Crohn's disease, and that ocular and skin manifestations are less common.[7] Peripheral arthritis was the most common single manifestation, whereas erythema nodosum, episcleritis, uveitis, and primary sclerosing cholangitis were less common. Similar results were noted by Idris et al. (2026) from Pakistan, where musculoskeletal, hepatobiliary, dermatological and ocular complaints were reported as the most prevalent symptoms.[16] Some similarities are observed between the two studies, which might be due to the shared genetic background, healthcare settings, and disease characteristics of the South Asian populations.Extraintestinal manifestations were significantly associated with the duration of disease in the current study. EIMs were significantly more common in patients with disease duration > 5 years compared with patients with lower disease duration. The results of this study are consistent with the one by Rogler et al. (2021), which indicated that chronic immune activation and progressive inflammatory burden raise the risk of systemic symptoms with time.[3] In a similar way, some of the studies in the meta-analysis performed by Kilic et al. demonstrated that the prevalence of EIMs was higher with the longer duration of the disease, but this was more or less pronounced among different populations.[7]

The present study also confirmed that there was a significant correlation between the severity of the disease and extraintestinal manifestations. The majority of patients with EIMs (more than 50%) were severely affected, and disease severity remained a significant predictor in multivariable logistic regression. The findings agree with the findings of Idris et al. (2026), who reported that the severity of ulcerative colitis was significantly associated with the presence of EIMs, but not with age and duration of disease.[16] In combination, these results highlight the idea that the gut can play a role in inflammatory complications of the body. In the current study, smoking was found to be an independent risk factor for

extraintestinal manifestations. Smoking is well known to be an important environmental trigger of immune dysregulation and chronic systemic inflammation and has been associated with the clinical course of IBD, especially Crohn's disease.[17] A similar study by Rogler et al. (2021) noted that smoking could act as a modifier of disease phenotype and severity, and that this may have an indirect role in the development of extraintestinal manifestations.[3] Extraintestinal manifestations were significantly more likely in patients with previous intestinal surgery. This association could mean that surgically treated patients have more aggressive or chronic disease and are more likely to be systemically involved. Similarly, Rogler et al. (2021) found that EIMs occur more often in patients with complex disease phenotypes who require intensive medical and/or surgical treatment.[12] In this study, biologic therapy was also related independently to the presence of extraintestinal manifestations. The finding does not have causal implications, as biologic agents are typically reserved for patients with moderate to severe disease or for patients who have already developed extraintestinal complications. This has been reported in recent literature, with biologic therapy being a marker for the severity of the disease and not an increased risk of EIMs. There were no significant associations between the presence of extraintestinal manifestations and age, gender, BMI, or type of inflammatory bowel disease. The present study results corroborate the study conducted by Idris et al. (2026) in Pakistan, who also found that there was no significant relationship between EIMs and age or gender.[16] Similarly, Kilic et al. conducted a systematic review and found that there was a great variability in the studies of demographic predictors, which indicates that disease-related factors might play a more significant role than demographic predictors.[7] Overall, the results of the present study mostly align with current international evidence showing that EIMs occur in about one-third of patients with IBD and that the most common pattern of EIMs is musculoskeletal involvement. In addition, the duration and severity of disease were the most significant factors associated with extraintestinal manifestations, suggesting that regular assessment and a multi-specialty approach are warranted in patients with long duration or severe IBD. The current study had a number of limitations. The first is that its cross-sectional design meant that causal relationships could not easily be drawn between disease duration, disease severity, and the extraintestinal manifestations. Secondly, it was a single tertiary care center study with a relatively small number of patients; thus, the results may not apply to all patients with inflammatory bowel disease. Third, from documented medical records and specialist consultation, some extraintestinal manifestations were identified, and this might have led to underreporting of mild or subclinical manifestations. Last, this study did not include long-term follow-up of extraintestinal manifestations or the impact of various treatments on the course of these manifestations.

CONCLUSION

Extraintestinal manifestations occurred in about one-third of patients with inflammatory bowel disease, and the most prevalent pattern of involvement was musculoskeletal. The presence of extraintestinal manifestations was significantly associated with longer disease duration and with higher disease severity, and was also a significant independent predictor after multivariable analysis. The findings highlight the need for regular screening for extraintestinal manifestations, especially in patients with chronic or complicated disease, to enable prompt multi-specialty treatment and enhance the patient's prognosis.

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