

Prevalence of Classical Extraintestinal Manifestations among Inflammatory Bowel Disease Patients in Saudi Arabia: A Single Tertiary Center Experience

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Abstract

Background: Patients with inflammatory bowel disease (IBD) may also experience extraintestinal manifestations (EIMs), which can affect various organ systems, and their occurrence is based on disease activity.

Objectives: To determine the prevalence of EIMs and their most common types among IBD patients from Saudi Arabia.

Materials and Methods: This retrospective study included all IBD patients aged 14–80 years who visited the Gastroenterology and Hepatology clinics at King Fahad Medical City, Riyadh, between February 2017 and December 2022. The collected data included demographic characteristics, disease characteristics, EIMs, and treatment.

Results: The study included 578 IBD patients, of which 65 (11.2%) had at least one EIM, with primary sclerosing cholangitis (46.2%) and sacroiliitis (16.9%) being the most common. Patients with ulcerative colitis were more likely to have EIMs than those with Crohn's disease (15.1% vs. 9%; $P = 0.026$). Patients with ileocolonic (L3) Crohn's disease reported a higher prevalence of EIMs (7.5%) than those with other disease locations ($P = 0.012$), while in patients with ulcerative colitis, those with extensive colitis (E3) reported higher prevalence of EIMs (19.2%) ($P = 0.001$). Patients receiving 6 MP had a significantly high prevalence of EIMs ($P = 0.014$).

Conclusion: The prevalence of extraintestinal manifestations among IBD patients in Saudi Arabia is 11.2%. These findings suggest the need for clinicians to screen for EIMs and manage them early. Further research is needed to understand the mechanisms underlying EIMs for the development of more effective treatments.

Keywords: Crohn's disease, extraintestinal manifestations, inflammatory bowel disease, primary sclerosing cholangitis, sacroiliitis, Saudi Arabia, ulcerative colitis

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INTRODUCTION

The prevalence of inflammatory bowel disease (IBD) is significantly increasing worldwide and in Saudi Arabia, with variable trends.^[1,2] IBD is characterized by chronic, non-infectious inflammation of the gastrointestinal tract that may manifest as Crohn's disease (CD) or ulcerative colitis (UC).^[3] Common symptoms associated with IBD include fatigue, loss of appetite, weight loss, abdominal discomfort, diarrhea, and anemia.^[3,4] Additional complications of IBD, such as strictures and fistulas, are also seen, but mainly in patients with CD.^[4,5] IBD has been associated with extraintestinal manifestations (EIMs), which can affect any organ system but most commonly affects the musculoskeletal, rheumatological, dermatological, ophthalmic, and hepatobiliary systems.^[4,5] The severity, frequency, and occurrence of EIMs may also vary based on several variables, including disease activity.^[6]

The effects of EIMs can cause considerable morbidity among IBD patients, even more severe than the intestinal disease itself.^[4] It has been reported that 30%–50% of IBD patients have at least one EIM, with a much higher prevalence in patients with CD, females, smokers, and with a longer disease duration.^[7-10] Furthermore, the incidence of multiple EIMs in IBD patients is 25%.^[11] A study conducted in Riyadh, Saudi Arabia, reported an even higher EIM prevalence among pediatric IBD patients (32%), the majority with indeterminate colitis.^[12] In a South Korean study, frequent EIMs in IBD patients included rheumatoid arthritis, aphthous stomatitis, and osteoporosis.^[13]

EIMs can be particularly difficult to treat and have a wide-ranging impact on the quality of life of IBD patients.^[5] Thus, assessing the prevalence of EIMs in patients with IBD in Saudi Arabia is critical, due to the lack of local data. This study aimed to determine the prevalence of EIMs among patients with IBD in Saudi Arabia as well as identify the most common EIMs. In addition, the study also aimed to report associations between EIMs and demographic characteristics, disease characteristics, disease complications, and treatments.

METHODS

Study design, setting, and patients

This cross-sectional retrospective study included all adult IBD patients (age: 14–80 years) who visited the Gastroenterology and Hepatology clinics at King Fahad Medical City (KFMC), Riyadh, between February 2017 and December 2022. KFMC is a tertiary (referral) care hospital

that serves patients from all the regions of Kingdom of Saudi Arabia. Patients of all genders and nationalities were included in the study.

The study was conducted after obtaining approval from the Institutional Review Board at KFMC.

Variables

The International Classification of Diseases, Tenth Edition codes (ICD-10), was used for admission diagnoses. The collected data included demographic characteristics (such as age, gender, nationality, marital status, and smoking status), family history of IBD, age at diagnosis, anthropometric measurements, disease characteristics, EIMs, and treatment. Anthropometric measurements such as weight, height, and body mass index were taken from the DETECTO scale. The data collected on disease characteristics included the location and extent of CD using the Montreal classification. The occurrence of EIMs during the disease or before the diagnosis of IBD was also noted.

Treatments included 5-aminosalicylic acid (oral and rectal), systemic steroids, budesonide, azathioprine, mercaptopurine (6 MP), infliximab, adalimumab, vedolizumab, ustekinumab, tofacitinib, and upadacitinib.

Data analysis

All data were manually collected and recorded on Microsoft Excel spreadsheets for organization and clarity. SPSS version 28 was used for all statistical analyses. Descriptive statistics such as mean, median, and mode were used to describe the baseline characteristics of the study population. Mean and standard deviation were used to summarize continuous variables, while frequencies were used to summarize categorical variables. The prevalence of EIMs was calculated using the standard formula. The Chi-square and Fisher's exact tests were used to compare the observed results and determine the associations between the factors. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 600 patients' medical records with IBD diagnosis were initially retrieved. After excluding 22 records due to incomplete medical records, a total of 578 IBD patients were included in the study. Among these patients, 54% were males (312 patients) and 46% were females (266 patients). The average age of the patients was 32 (± 11) years. In terms of the type of IBD, 63.3% of the patients (366 patients) had CD and 36.7% (212 patients) had UC [Table 1].

Extraintestinal manifestations

A total of 65 patients (11.2%) had at least one EIM [Table 2]. The most common EIMs found were primary sclerosing cholangitis (46.2%), followed by sacroiliitis (16.9%), and venous thromboembolism (VTE) (9.2%).

The prevalence of EIMs was significantly higher in UC patients (15.1%) than in CD patients (9%) ($P = 0.026$). Among those with CD, patients with ileocolonic (L3) disease reported a higher prevalence of EIMs (7.5%) than those with other disease locations ($P = 0.012$). In contrast, among patients with UC, those with extensive colitis (E3) reported higher prevalence of EIMs (19.2%) ($P = 0.001$). The prevalence of EIMs according to disease behavior in CD patients showed that those with penetrating (B3) and perianal disease (p) reported the highest prevalence of EIMs (4.3% and 6.1%, respectively) ($P = 0.022$ and 0.05 , respectively) [Table 3].

In regard to treatment, most patients received azathioprine (39.6%) and infliximab (31.3%), but both were not significantly associated with EIMs ($P = 1$ and 0.571 , respectively). However, patients receiving 6 MP had a significantly higher prevalence of EIMs (7.7%; $P = 0.014$) [Table 4].

DISCUSSION

Our findings revealed that 11.2% of the patients included in the study had at least one EIM. This finding is consistent with previous studies that have reported EIMs in IBD patients to be between 6% and 47%, depending on the type of disease and study population.^[14,15]

Interestingly, our study found that the prevalence of EIMs was higher in UC patients than in CD patients (15.1% vs. 9%). In contrast to our findings, several previous studies report a higher prevalence of EIMs among CD patients compared with UC patients.^[11,16] The variations in EIMs prevalence could be attributed to variations in the study design and inclusion criteria; for example, some studies only included patients with an IBD diagnosis of >10 years.^[11] Additionally, the geographic location may also play a role in the variation of EIMs prevalences across different studies.^[11]

Our study also found that in CD patients, those with ileocolonic disease (L3) reported a higher prevalence of EIMs compared with other disease locations (7.5%). This finding is consistent with previous studies that have reported an increased prevalence of EIMs in CD patients with ileocolonic involvement.^[14,15] In addition, our study found that CD patients with penetrating (B3) and perianal

Table 1: Baseline characteristics of the patients with inflammatory bowel disease (N=578)

Characteristic	Value
Age (years), mean (\pm SD)	32.3 (\pm 11)
Age at diagnosis (years), mean (\pm SD)	24.9 (\pm 10)
Duration of IBD (years), mean (\pm SD)	7.5 (\pm 5.8)
Sex, n (%)	
Male	312 (54)
Female	266 (46)
Clinical diagnosis, n (%)	
CD	366 (63.3)
UC	212 (36.7)

IBD – Inflammatory bowel disease; SD – Standard deviation;
CD – Crohn's disease; UC – Ulcerative colitis

Table 2: Prevalence of extraintestinal manifestations (N=65)

Extraintestinal manifestations	n (%)
Hepatological	
Autoimmune hepatitis	3 (4.6)
Primary sclerosing cholangitis	30 (46.2)
Rheumatological	
Type I peripheral spondyloarthritis	5 (7.7)
Type II peripheral spondyloarthritis	9 (13.8)
Enthesitis	3 (4.6)
Dactylitis	0
Ankylosing spondylitis	5 (7.7)
Sacroiliitis	11 (16.9)
Dermatological	
Pyoderma gangrenosum	2 (3.1)
Erythema nodosum	1 (1.5)
Ophthalmological	
Uveitis	1 (1.5)
Miscellaneous	
Aphthous ulcer	4 (6.2)
Venous thromboembolism	6 (9.2)

disease (p) had the highest prevalence of EIMs (4.3% and 6.1%, respectively). This finding is in line with previous studies that have reported an increased prevalence of EIMs in CD patients with more severe disease behavior.^[15,17] On the other hand, our study found that in UC patients, those with extensive colitis (E3) had a higher prevalence of EIMs (19.2%). This finding is in line with previous studies that have reported a higher prevalence of EIMs in UC patients with more extensive colitis.^[14,15]

The reasons behind the high prevalence of EIMs among IBD patients and the differences observed based on disease location, behavior, and treatment are likely multifactorial. EIMs are characterized by the enteric flora playing a critical role in activating the immune system against bacterial antigens and the colonic mucosa based on an antigenic cross-reactivity process known as “antigen mimicry”.^[18] When bacteria translocate across the intestinal barrier, which is often permeable in IBD patients, an adaptive immune response is triggered.^[18] However, this immune response is unable to distinguish between bacterial epitopes and epitopes of joints or skin, attacking other systems in the body, and thus result in EIMs.^[18]

Table 3: Extraintestinal manifestations with respect to clinical diagnosis, disease location, disease extent, and disease behavior

Description	Non-EIM (513; 88.8%), n (%)	EIM (65; 11.2%), n (%)	Total (578; 100%), n (%)	P
Clinical diagnosis				
CD	333 (91.0)	33 (9.0)	366 (63.3)	0.026
UC	180 (84.9)	32 (15.1)	212 (36.7)	
CD location				
Ileal (L1)	51 (89.5)	6 (10.5)	57 (9.9)	0.856
Colonic (L3)	28 (87.5)	4 (12.5)	32 (5.5)	0.774
Ileocolonic (L3)	245 (92.5)	20 (7.5)	265 (45.8)	0.012
Upper GI (L4)	10 (90.9)	1 (9.1)	11 (1.9)	0.652
Extent of UC				
Proctitis (E1)	16 (100.0)	0	16 (2.8)	0.238
Left-sided colitis (E2)	47 (87.0)	7 (13.0)	54 (9.3)	0.675
Extensive colitis (E3)	105 (80.8)	25 (19.2)	130 (22.5)	0.001
Disease behavior				
Nonpenetrating and nonstricturing (B1)	44 (86.3)	7 (13.7)	51 (8.8)	0.557
Stricturing (B2) - inflammatory	52 (91.2)	5 (8.8)	57 (9.9)	0.534
Fibrostenotic	87 (88.8)	11 (11.2)	98 (17.0)	0.994
Penetrating (B3)	88 (95.7)	4 (4.3)	92 (15.9)	0.022
Perianal disease (P)	108 (93.9)	7 (6.1)	115 (19.9)	0.050

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

Table 4: Extraintestinal manifestations and IBD treatment

Treatment	Non-EIM (513; 88.8%), n (%)	EIM (65; 11.2%), n (%)	Total (578; 100%), n (%)	P
Oral 5-ASA	113 (22.0)	16 (24.6)	129 (22.3)	0.637
Rectal 5-ASA	54 (10.5)	11 (16.9)	65 (11.2)	0.124
Systemic steroid	7 (1.4)	1 (1.5)	8 (1.4)	1.000
Budesonide	10 (1.9)	1 (1.5)	11 (1.9)	1.000
Azathioprine	203 (39.6)	26 (40.0)	229 (39.6)	1.000
6 MP	9 (1.8)	5 (7.7)	14 (2.4)	0.014
Infliximab	163 (31.8)	18 (27.7)	181 (31.3)	0.571
Adalimumab	81 (15.8)	9 (13.8)	90 (15.6)	0.504
Vedolizumab	38 (7.4)	7 (10.8)	45 (7.8)	0.684
Ustekinumab	71 (13.8)	8 (12.3)	79 (13.7)	0.341
Tofacitinib	5 (1.0)	1 (1.5)	6 (1.0)	0.735
Upadacitinib	2 (0.4)	0	2 (0.3)	1.000

ASA – Aminosalicylic acid; MP – Mercaptopurine; EIM – Extraintestinal manifestation

Regarding the differences observed based on disease location and behavior, previous studies have shown that certain disease locations and behaviors in CD are associated with an increased risk of EIMs.^[19] For example, CD patients with ileocolonic (L3) disease, as observed in our study, have been shown to have a higher risk of developing EIMs such as arthralgia, uveitis, and erythema nodosum.^[19] Similarly, CD patients with penetrating (B3) and perianal disease (p), as also observed in our study, have been shown to have an increased risk of EIMs.^[19]

Our study found that patients receiving 6 MP had a significantly high prevalence of EIMs (7.7%) compared with patients receiving other IBD treatments. This finding is consistent with a study by Setshedi *et al.*, which reported that thiopurine therapy (including 6 MP and Azathioprine) was associated with an increased risk of EIMs in IBD patients.^[20] The association between 6 MP treatment and EIMs is supported by a study by Mowat *et al.*, which reported an increased incidence of skin cancer, lymphoproliferative disorders, and other malignancies in patients with IBD who

received thiopurine treatment.^[21] One possible explanation is that 6 MP is an immunosuppressant drug that can alter the immune system's response and increase the risk of infections and other EIMs. Moreover, a review by Axelrad *et al.* found that thiopurines, including 6 MP, were associated with an increased risk of hepatotoxicity and pancreatitis in patients with IBD.^[22] The underlying mechanism is poorly understood, but it may be related to the fact that thiopurines are metabolized by the liver and can accumulate in the hepatocytes, leading to damage.^[22]

The most common EIM in our study was primary sclerosing cholangitis, with a prevalence of 46.2%. This finding is consistent with previous studies that have reported an increased prevalence of primary sclerosing cholangitis in patients with IBD.^[23] One study by Karlsen *et al.* reported that most primary sclerosing cholangitis patients have IBD.^[24] The exact mechanism underlying the association between primary sclerosing cholangitis and IBD is not well understood, but it is thought to be related to shared genetic and environmental risk factors.^[24]

Sacroiliitis was the second most common EIM found in our study, with a prevalence of 16.9%. The association between IBD and sacroiliitis is well established, with previous studies reporting a prevalence of up to 25% in patients with IBD.^[17] The exact mechanism underlying the association between IBD and sacroiliitis is poorly understood, but it is thought to be related to a shared immunological basis and genetic susceptibility.^[17]

Finally, we found a 9.2% prevalence of VTE as an EIM in our study. The association between IBD and VTE is well documented, with previous studies reporting an increased risk of VTE in patients with IBD.^[25,26] The exact mechanism underlying the association between IBD and VTE is unclear, but it is thought to be related to a combination of inflammation, hypercoagulability, and endothelial dysfunction.^[25,26]

Limitations and recommendations

The retrospective nature of this study relied on previously collected medical records, so there is a lack of control over potential confounders and exposures. Consequently, we cannot determine with certainty the causal relationships between demographic factors and the prevalence of EIMs in the Saudi Arabian population. The inclusion of regression analysis could have been beneficial to explore the extent to which age, gender, education, or other factors may be related to the likelihood of experiencing EIMs among the Saudi population. Future research could address this limitation by including regression analysis to determine the extent to which these variables may influence the prevalence of EIMs in Saudi Arabia. Moreover, prospective studies with well-defined control over variables are required to better determine associations and potential causal relationships.

Further research is also needed to explore the underlying mechanisms behind the association between 6 MP treatment and EIMs, and to develop effective strategies for preventing and managing these manifestations. Our study highlights the need for a multidisciplinary approach to managing IBD, involving gastroenterologists, rheumatologists, and other specialists, as needed, to ensure comprehensive and optimal care for patients with this complex disease.

CONCLUSION

This study found that EIMs were present in a significant proportion of patients with IBD, with primary sclerosing cholangitis and sacroiliitis being the most common EIMs. The prevalence of EIMs was higher in patients with

UC compared to those with CD and varied depending on the location and behavior of the disease. Our results also showed that patients receiving 6 MP treatment had a significantly high prevalence of EIMs. These findings emphasize the importance of recognizing and monitoring EIMs in patients with IBD.

Ethical considerations

The study was approved by the Institutional Review Board at King Fahad Medical City, Riyadh, Saudi Arabia (Ref. no.: 22-377; date: 08-Nov-2022). Requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Author contributions

Conceptualization: A.Alotaibi, A.Allehibi, A.Almutawa, A.Alghamdi, N.A, A.Alqutub, A.Aleid, A.Alamr, B.I, M.Alahmari, S.Ahmad; Methodology:; A.A, H.Alhamidi, A.Alhubayshi, Ahmed Alghamdi; Data analysis: A.Alotaibi, H.Alhamidi, A.Alhubayshi, Ahmed Alghamdi; Writing—original draft preparation: A.A, H.Alhamidi, A.Alhubayshi, Y.Altannir, H.Albayyat, O.Alshaya, Ahmed Alghamdi; Writing – review and editing: A. Alotaibi, H.Alhamidi, A.Alhubayshi, Y.Altannir, Ahmed Alghamdi; Supervision: A.Allehibi, Ahmed Alghamdi, S.Alrajhi.

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Conflicts of interest

There are no conflicts of interest.

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