

# Prevalence of Extra Intestinal Manifestations in Inflammatory Bowel Disease and Associated Risk Factors

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## ABSTRACT

**Background and Aim:** Ulcerative colitis (UC) is a subtype of inflammatory bowel disease that can develop extra-intestinal manifestations (EIMs) in a subgroup of patients. There is a scarcity of data on the prevalence of extra-intestinal manifestations (EIMs) in inflammatory bowel disease and their risk factors analyses. The present study aimed to evaluate the prevalence of extra-intestinal manifestations in ulcer colitis and its associated risk factors.

**Methodology:** This prospective study was conducted on 334 inflammatory bowel disease patients who were followed for identification of EIMs associated risk factors in the Department of Medicine and Pulmonology, Ghulam Muhammad Medical College and Hospital (GMMCH)/ Civil Hospital, Sukkur for the duration of six months; from April 2021 to September 2021. All the patients above 16 years and who had ulcerative colitis and Crohn's disease (CD) were enrolled. Patient's demographic and clinical details such as gender, education, age, smoking history, diagnosis of EIMs, age at IBD, different IBDs, surgical, and treatment details were recorded.

**Results:** Out of 334 IBD patients, the prevalence of ulcerative colitis (UC) and Crohn's disease (CD) was 38.9% (n=130) and 61.1% (n=204) respectively. The overall mean age of UC and CD patients was 38.6±6.8 and 42.7±8.5 years respectively. Of the total 130 CD patients, the prevalence of arthritis, aphthous stomatitis, uveitis, erythema nodosum, ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis and psoriasis was 20.8% (n=27), 3.8% (n=5), 4.6% (n=6), 3.1% (n=4), 2.3% (n=3), 3.8% (n=5), and 1.5% (n=2) respectively. Out of 204 CD patients, the incidence of arthritis, aphthous stomatitis, uveitis, erythema nodosum, ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis, and psoriasis was 32.8% (n=67), 9.8% (n=20), 5.9% (n=12), 6.4% (n=13), 2% (n=4), 1% (n=2) and 2% (n=4) respectively. Risk factors for EIMs were identified using multiple logistic regression. In ulcerative colitis patients, no risk factors were identified.

**Conclusion:** Our study concluded that extra-intestinal manifestations are a major issue in ulcerative colitis and Crohn's disease patients. Moreover, the ongoing EIMs in Crohn's disease patients are significantly associated with inflammatory bowel disease positive family history, and active disease. Therapeutic management and diagnostic facilities can be improved with the determination of extra-intestinal manifestation prevalence and related risk factors.

**Keywords:** Crohn's Disease, Extra-intestinal Manifestation, Inflammatory Bowel Disease

## INTRODUCTION

Ulcerative colitis (UC) is a subtype of inflammatory bowel disease that can develop extra-intestinal manifestations (EIMs) in a subgroup of patients. Extra-intestinal manifestations (EIMs) mostly develop in inflammatory bowel disease [IBD] patients during the course of the disease. Ocular, musculoskeletal, and, mucocutaneous are the prevalent EIMs. Kidneys, biliary tract, lungs, and liver are other infrequently affected organs (1, 2). Additionally, certain abnormal conditions such as pancreatitis, thromboembolic events, cardiopulmonary disease, Cholelithiasis, anemia, osteopathy, and several autoimmune disorders are observed in inflammatory bowel disease (3-5). The incidence of extra-intestinal manifestation ranges from 16% to 40% based on multiple studies on EIMs (6, 7). Additional EIMs were developed with the occurrence of predisposed EIMs which might precede IBD diagnosis after intestinal resection (8). Inflammatory bowel disease activities are related to certain EIMs such as episcleritis, peripheral arthritis, aphthous stomatitis, and erythema nodosum; whereas others such as uveitis, pyoderma gangrenosum, ankylosing spondylitis,

and primary sclerosing cholangitis [PSC] present in a predominantly independent manner (9).

Inflammatory bowel disease (IBD) patients will experience extra-intestinal manifestations (EIMs) over the course of their lives. The morbidity and mortality caused by extra-intestinal manifestation are increased by ulcerative colitis and Crohn's disease (10, 11). Extra-intestinal manifestation is categorized into many groups; reactive manifestations such as erythema nodosum, peripheral arthritis, and aphthous ulcers and non-reactive manifestations such as primary sclerosing cholangitis (PSC), uveitis and spondylo-arthritis (12). The reported prevalence of group EIM in IBD ranges from 6% to 47% (13). The majority of EIMs patients have extensive colitis and positive family history of IBD (14). The current prospective study sought to determine the prevalence of EIMs in IBD patients as well as risk factors for the development of EIMs.

## METHODOLOGY

This prospective study was conducted on 334 inflammatory bowel disease patients who were followed for identification

of EIMs associated factors in the Department of Medicine and Pulmonology, Ghulam Muhammad Medical College and Hospital (GMMCH)/ Civil Hospital, Sukkur for the duration of six months from April 2021 to September 2021. All the patients above 16 years and who had ulcerative colitis and Crohn's disease (CD) were enrolled. Patient's demographic details such as gender, education, age, smoking history, and clinical details such as diagnosis of EIMs, age at IBD, different IBD, surgical, and treatment details were recorded. The extra-intestinal manifestations were referred to as "disorders associated with inflammatory bowel disease that appeared in areas other than the digestive tract". The peripheral pain in joints and detection of inflammation without active sign and motility restriction was referred to as Arthralgia. Based on clinical findings and swollen joints peripheral arthritis diagnosis was made on rheumatoid arthritis exclusion, connective tissue disease-related to arthritis, and osteoarthritis. Physical examination was used for the diagnosis of sacroiliitis and ankylosing spondylitis. Back pain, lower back and persisted stiffness showing positive response to anti-inflammatory non-steroidal drugs and magnetic resonance imaging or X-rays showing radiological changes. Patient's recall information assisted in diagnosis of extra-intestinal disease prior to inflammatory bowel disease based on chronological data. .

SPSS version 21 was used for data analysis. Descriptive statistics such as frequency and percentages were calculated based on chi-square and t-test for group

comparison. A two-sided test was performed with 0.05 as the level of significance.

**RESULTS**

Out of 334 IBD patients, the prevalence of ulcerative colitis (UC) and Crohn's disease (CD) was 38.9% (n=130) and 61.1% (n=204) respectively. The overall mean age of UC and CD patients was 38.6±6.8 and 42.7±8.5 years respectively. Of the total 130 CD patients, the prevalence of arthritis, aphthous stomatitis, uveitis, erythema nodosum, ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis, and psoriasis was 20.8% (n=27) , 3.8% (n=5) , 4.6% (n=6), 3.1% (n=4) , 2.3% (n=3) , 3.8% (n=5) , 3.8% (n=5) and 1.5% (n=2) respectively. Out of 204 CD patients, the incidence of arthritis, aphthous stomatitis, uveitis, erythema nodosum, ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis, and psoriasis was 32.8% (n=67) , 9.8% (n=20) , 5.9% (n=12) , 5.9% (n=12) , 6.4% (n=13), 2% (n=4) , 1% (n=2) and 2% (n=4) respectively. Risk factors for EIMs were identified using multiple logistic regression. In ulcerative colitis patients, no risk factors were identified. Demographic details of all the patients are shown in Table-I. The prevalence of CD and UC are depicted in Figure-1. Table-II and III demonstrate the prevalence and risk factors of IBD (ulcerative colitis and Crohn's disease). .

Table 1: Demographic details of patients (n=334)

| Parameters      | Total Patients (IBD n=334) | UC (n=130)            | CD (n=204)            | p-value |
|-----------------|----------------------------|-----------------------|-----------------------|---------|
| Gender (M/F)    | 189/145                    | 86 (66.2%)/44 (33.8%) | 145(71.1%)/59 (28.9%) | NS      |
| Age (mean± SD)  | 40.7±7.74                  | 38.6±6.8              | 42.7±8.5              | NS      |
| Smoking History |                            |                       |                       |         |
| Smokers         | 261 (78.1%)                | 92 (70.8%)            | 175 (85.8%)           | <0.001  |
| Non-smokers     | 73 (21.9%)                 | 38 (29.2%)            | 29 (14.2%)            |         |
| BMI (Kg/m2)     | 21.3±1.9                   | 21.2±1.8              | 21.4±1.9              | <0.0001 |
| Categorical BMI |                            |                       |                       |         |
| 18.5-25         | 334 (100%)                 | 130 (38.9%)           | 204 (61.1%)           | NS      |
| >25             | 0 (0%)                     | 0 (0%)                | 0 (0%)                |         |

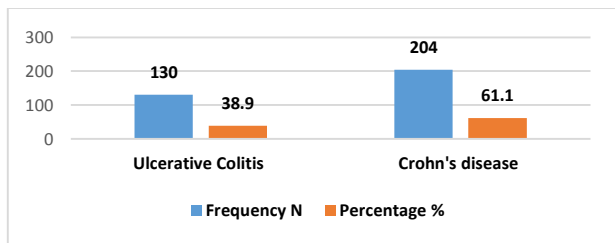


Figure 1: Prevalence of CD and UC (n=334)

Table 2: Prevalence of different extra-intestinal manifestations for UC disease patients

| Risk Factors                   | Frequency N | Percentage % |
|--------------------------------|-------------|--------------|
| Arthritis                      | 27          | 20.8         |
| Aphthous Stomatitis            | 5           | 3.8          |
| Uveitis                        | 6           | 4.6          |
| Erythema Nodosum,              | 4           | 3.1          |
| Ankylosing Spondylitis,        | 3           | 2.3          |
| Pyoderma Gangrenosum,          | 5           | 3.8          |
| Primary Sclerosing Cholangitis | 5           | 3.8          |
| Psoriasis                      | 2           | 1.5          |

Table 1: Prevalence of different extra-intestinal manifestations for Crohn's Disease disease patients

| Risk Factors                   | Frequency N | Percentage % |
|--------------------------------|-------------|--------------|
| Arthritis                      | 67          | 32.8         |
| Aphthous Stomatitis            | 20          | 9.8          |
| Uveitis                        | 12          | 5.9          |
| Erythema Nodosum               | 12          | 5.9          |
| Ankylosing Spondylitis         | 13          | 6.4          |
| Pyoderma Gangrenosum           | 4           | 2            |
| Primary Sclerosing Cholangitis | 2           | 1            |
| Psoriasis                      | 4           | 2            |

**DISCUSSION**

The present study evaluated the prevalence of extra-intestinal manifestations and associated risk factors in inflammatory bowel disease patients. The extra-intestinal manifestations were associated with demographic details such as female gender, younger age, environment, EIMs positive family history, smoking and clinical examination details such as CD diagnosis, IBD-related surgical history, extensive UC, tonsillectomy, and appendectomy. Gender distribution and extensive ulcerative colitis remained

significant factors in multivariate analysis. In ulcerative colitis patients, multiple EIMs were less frequently observed but in CD patients, the presence of EIMs was related to worsening of phenotype disease. The prevalence of EIMs in the study population was similar to the ones reported by previous studies conducted in Italy 40.6% (15), Switzerland 38.1% (16), Hungary 21.3% (17) and Canada 36% (18). Additionally, a European prospective study reported a 17% prevalence of EIMs (19).

Greenstein et al (20) found that 36% inflammatory bowel disease patients out of 700 patients developed EIMs. Jonathan et al observed that extraintestinal manifestations were common in both UC and CD (21). In previous studies it has been observed that those who suffer from Crohn's disease have a two fold increase in probability of having extra-intestinal symptoms as compared with those having ulcerative colitis. Nevertheless, vast distribution of inflammation in ulcerative colitis increases the risk of extra-intestinal manifestations (22). Similarly, Veloso et al. (23) observed a higher EIMs prevalence in Crohn's disease patients as compared with those having ulcerative colitis. Similarly, the present study also observed that EIMs have a higher incidence in Crohn's disease as compared to ulcerative colitis. Isene et al, reported that lower risk is developed in immune-mediation after first manifestation (22). Yet, two and three EIMs were presented in 8.1% and 3.2% respectively in patients who developed EIMs at median age and within a short span of time which remained lower (24).

Bernstein et al. (25) observed that uveitis, pyoderma gangrenosum, and ankylosing spondylitis had a higher prevalence (6.2%) among all other EIMs. However, in the present study it was observed that arthritis followed by aphthous stomatitis and uveitis were the most common EIMs. Variations in study design might be responsible for variation in the prevalence of different EIMs. The present study rates are significantly lower than those reported by a Turkish study (26).

The development of one EIM appears to increase the likelihood of the development of another EIM. An overlap of EIM with erythema nodosum, peripheral arthritis, and biliary tract and eye disease has been observed. Various studies reported that colonic disease had concomitant extra-intestinal manifestation in inflammatory bowel disease (7). A strong indication that EIM are linked to disease activity (27).

## CONCLUSION

Our study concluded that extra-intestinal manifestations are a major issue in ulcerative colitis and Crohn's disease patients. Also, the ongoing EIMs in Crohn's disease patients are significantly associated with inflammatory bowel disease positive family history and active disease. Therapeutic management and diagnostic facilities can be improved with determination of extra-intestinal manifestation prevalence and related risk factors.

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